Official Title:	**A PHASE III, RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL OF OMALIZUMAB IN PATIENTS WITH CHRONIC RHINOSINUSITIS WITH NASAL POLYPS**
NCT Number:	**NCT03280550**
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PROTOCOL

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PROTOCOL NUMBER:	GA39688
VERSION NUMBER:	2
EUDRACT NUMBER:	2017-001724-22
IND NUMBER:	5369
TEST PRODUCT:	Omalizumab (IGE025)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE AMENDED:	Version 1: 2 June 2017 Version 2: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	11-Oct-2017 16:06:49

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol GA39688 has been amended to modify the study design according to the recommendations of the Voluntary Harmonization Procedure (VHP), the European-based process for obtaining a harmonized assessment of multinational clinical trial authorization (CTA) applications before the national process. Changes to the protocol are summarized below:

- The inclusion criteria have been updated to specify acceptable methods of contraception (Section 4.1.1).
- An additional exclusion criterion has been added to exclude patients with a history of myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack or a known history of a hypercoagulable disorder (Section 4.1.2).
- Four additional urine pregnancy tests have been added to the treatment period such that women of childbearing potential will have urine pregnancy testing every 4 weeks during the 24-week treatment period (Section 4.5.8, Appendix 1).
- Viral serologies for HIV, hepatitis B, and hepatitis C have been added during screening at Day -35 (Section 4.5.8, Appendix 1). Patients with a history of HIV, hepatitis B, and hepatitis C were excluded in the prior version of the protocol, and these exclusion criteria remain in the current version of the protocol.
- Additional specifications have been added to the section on the Management of Patients Who Experience Specific Adverse Events. While liver injury has not been described as a risk associated with omalizumab, this new section specifies how study drug should be managed for patients who experience drug induced liver injury (Section 5.1.4.2).
- Additional revisions have been made to the following statistical sections:
  - Section 6, Statistical Considerations and Analysis Plan
  - Section 6.1, Determination of Sample Size
  - Section 6.4, Efficacy Analyses
- The following statistical sections have been added:
  - Section 6.4.4, Subgroup Analyses
  - Section 6.4.5, Pooled Analyses
  - Section 6.8, Missing Data
  - Section 6.9, Unused and Spurious Data

This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 2:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 4.1.1: Inclusion Criteria

- 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).*
  - ~~Barrier methods must always be supplemented with the use of a spermicide~~
  - Women of childbearing potential must have a negative serum pregnancy test result during the screening period.

SECTION 4.1.2: Exclusion Criteria

- *History of myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack or a known history of a hypercoagulable disorder*

SECTION 4.5.8: Laboratory and Other Biological Samples

- Serum and urine pregnancy test
  - All women of childbearing potential must have a negative serum pregnancy test during the screening period, prior to initiation of study drug. Additionally, women should have a urine pregnancy test prior to the initiation of study drug, *every 4 weeks* during study treatment period, and at the safety follow-up visit, as indicated in Appendix 1. Urine pregnancy test results must be reviewed and confirmed to be negative before study drug administration. 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:

- *Viral serology (unless not permitted by local regulations or ethics committees): HIV, hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), hepatitis C (HCV) antibody*

SECTION 5.1.4.2: ***Management of Drug Induced Liver Injuries***
(NEW SECTION)

Liver injury has not been described as a risk associated with omalizumab. However, 1) if the patient's AST or ALT is >8× ULN, or 2) if the patient's ALT or AST >3× ULN and total bilirubin >2× 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.

SECTION 6: STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

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.*

SECTION 6.1: DETERMINATION OF SAMPLE SIZE

The sample size of 120 patients will provide at least 85% power to independently detect both a 0.56-point difference between treatment groups in change from baseline at Week 24 in the average daily NCS and a 1.50-point difference between treatment groups in change from baseline at Week 24 in NPS. [redacted]

TABLE 5: Summary of Studies Used for Determination of Sample Size

Table 5 has been revised to clarify the change in NCS at 16 weeks in the Bachert et al. 2016 study was the change in average NCS.

SECTION 6.4: EFFICACY ANALYSES

All hypothesis tests will be two-sided. Unless otherwise noted, all analyses of efficacy outcome measures will at a minimum be adjusted by geographic region through the use of a categorical variable and by baseline asthma comorbidity and aspirin sensitivity status. Adjustment by additional covariates, if any, will be described in the SAP.
~~Efficacy data on the co-primary and secondary endpoints from this study may be pooled with external data from another trial and analyzed in the Summary of Clinical Efficacy (SCE), details of which will be provided in a separate SAP for the SCE.~~

SECTION 6.4.4: *Subgroup Analyses* (NEW SECTION)

Exploratory subgroup analyses will be performed to evaluate the consistency of the primary analysis results across pre-specified subgroups defined by demographic and baseline characteristics. Further details on these subgroup analyses and any additional subgroups will be pre-specified in the SAP and finalized prior to data unblinding.
In addition to age, sex, and race, the following subgroups (at a minimum) will be analyzed with respect to the co-primary efficacy endpoints (change from baseline at Week -24 in NPS and change from baseline at Week -24 in NCS) using the same methods as specified for the co-primary endpoints:

- *Baseline comorbid asthma and aspirin sensitivity status (asthmatic and aspirin sensitive, asthmatic not aspirin sensitive, all other)*
- *Geographic region (North America, ex-North America)*
- *Baseline mometasone prescribed dose (daily dose of 400 μg, daily dose of 200 μg)*

If convergence problems with the statistical models arise due to a small number of patients per subgroup, the analysis may be simplified by combining some of the subgroups or by excluding baseline stratification variables from the model.

SECTION 6.4.5: *Pooled Analyses* (NEW SECTION)

Efficacy data on endpoints from this study may be pooled with external data from a replicate trial (GA39855). [redacted]

[redacted]

SECTION 6.8: *MISSING DATA* (NEW SECTION)

Unless otherwise noted, in the analysis of all continuous co-primary, secondary, and exploratory endpoints (NPS, NCS, loss of smell, anterior rhinorrhea, posterior rhinorrhea, TNSS, SNOT-22, UPSIT, EQ-5D-5L), missing values will not be explicitly imputed in the analyses, which will use a mixed-effect model repeated measurement (MMRM) model. The exception is for the co-primary endpoints NPS and NCS, for which missing values planned on or after the date of treatment failure will be imputed by the worst possible score of 8 for NPS and 3 for daily NCS. Patients without post-baseline endpoint data will not contribute to the MMRM model. Sensitivity analysis concerning missing data assumptions for all continuous co-primary and secondary efficacy endpoints meeting nominal statistical significance will be conducted (i.e., tipping point analysis). Details of these pre-specified sensitivity analyses will be provided in the SAP and finalized prior to data unblinding.

In the analysis of the following categorical secondary endpoints (for which a logistic regression model is specified) missing data from patients who discontinue the study prior to their Week -24 visit without having previously met the criteria for the event will be imputed as having the event:

- *Requirement of rescue treatment (systemic CS for ≥3 consecutive days) or having had surgery for nasal polyps through Week -24*
- *Requirement of rescue treatment (systemic CS for ≥3 consecutive days) through Week -24*
- *Having had surgery for nasal polyps through Week -24*

In the analysis of the following categorical secondary and exploratory endpoints (for which a logistic regression model is specified) missing data from patients who discontinue the study prior to Week -24 without having previously met the criteria for the event will be imputed as not having the event:

- *Reduction in the need for surgery by Week -24, as defined by an NPS of ≤4 (unilateral score of ≤2 on each side) and improvement in SNOT-22 score of ≥8.9*
- *Change from baseline at Week -24 in AQLQ of ≥0.5 (in patients with comorbid asthma only)*
- *Change from baseline at Week -24 in SNOT-22 of at least the minimal important difference (MID) (8.9 points).*

SECTION 6.9: *UNUSED AND SPURIOUS DATA* (NEW SECTION)

For the efficacy analysis of continuous co-primary, secondary, and exploratory endpoints for which an MMRM model is used, a single data point will be assigned to a

planned timepoint (e.g., Week 4, Week 8, Week 16, Week 24) 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 and finalized prior to unblinding.

Due to the nature of the data capture instruments (e.g., eCRF, eDiary, or tablet), spurious response data are not expected for PRO efficacy endpoints (i.e., NPS, NCS, SNOT-22, UPSIT, AQLQ, EQ-5D-5L). 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.

APPENDIX 1: Schedule of Activities

The schedule of activities has been revised to reflect the changes to the protocol.

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

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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:	**A PHASE III, RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL OF OMALIZUMAB IN PATIENTS WITH CHRONIC RHINOSINUSITIS WITH NASAL POLYPS**
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PHASE:	Phase III
INDICATION:	Chronic rhinosinusitis with nasal polyps
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

The purpose of this study is to determine the efficacy and safety of omalizumab compared with placebo in adult patients with CRSwNP who have had an inadequate response to standard-of-care treatments. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Efficacy Objective	Corresponding Co-Primary Endpoints
• To evaluate the efficacy of omalizumab compared with placebo	Co-primary endpoints: • Change from baseline at Week 24 in average daily nasal congestion score (NCS) • Change from baseline at Week 24 in nasal polyps score (NPS)
Secondary Efficacy Objective [a]	**Corresponding Endpoints**
• To evaluate the efficacy of omalizumab compared with placebo	• Change from baseline at Week 24 in the average daily total nasal symptom score (TNSS) • Change from baseline at Week 24 in the average daily sense of smell score • Change from baseline at Week 24 in the average daily posterior rhinorrhea score • Change from baseline at Week 24 in the average daily anterior rhinorrhea score • Change from baseline at Week 24 in patient-reported health-related quality of life as assessed by the total SNOT-22 • Change from baseline at Week 16 in the average daily NCS • Change from baseline at Week 16 in NPS

	• Change from baseline at Week 24 in sense of smell, as assessed by the UPSIT • Reduction in the need for surgery by Week 24, 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 24 • Requirement of rescue treatment (systemic CS for ≥ 3 consecutive days) through Week 24. • Having had surgery for nasal polyps through Week 24 • Change from baseline at Week 24 in AQLQ of ≥ 0.5 (in patients with comorbid asthma only)
Exploratory Efficacy Objective	**Corresponding Endpoint**
• To evaluate the efficacy of omalizumab compared with placebo	• Change from baseline at Week 24 in SNOT-22 of at least the MID (8.9 points).
• To evaluate health status utility scores compared with placebo	• Change from baseline at Week 24 as assessed by EQ-5D
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of omalizumab compared with placebo	• Incidence of adverse events • Incidence of serious adverse events • Incidence of adverse events leading to omalizumab/placebo discontinuation • Clinically significant change in laboratory values
Pharmacokinetic and Pharmacodynamic Objectives	**Corresponding Endpoint**
• To evaluate the pharmacokinetics and pharmacodynamics of omalizumab	• Serum concentration of omalizumab at specified timepoints outlined in the Schedule of Activities • Serum levels of total and free IgE at specific timepoints outlined in the Schedule of Activities

AQLQ = Asthma Quality of Life Questionnaire; CS = corticosteroid; MID = minimal important difference; NCS = nasal blockage/congestion score; NPS = nasal polyp score; SNOT-22 = Sino-Nasal Outcome Test-22; TNSS = total nasal symptom score; UPSIT = University of Pennsylvania Smell Identification Test.

[a] Order of endpoints presented here does not determine order in a sequential type I error control procedure. Details on type I error control procedures will be given in the Statistical Analysis Plan at a later date.

Study Design

Description of Study

This study is a Phase III, randomized, multicenter, double-blind, placebo-controlled, clinical trial that will be run in parallel with a replicate study, under Protocol GA39855.

The study consists of a 5-week screening/run-in period, a 24-week treatment period, and a 4-week study follow-up period. The 4-week follow-up period will be for all patients unless they enroll at Week 24 into another available sponsor-permitted study of omalizumab in nasal polyps.

The screening/run-in period will include two visits ("1st screening visit" at Day -35 and "2nd screening visit" at Day -7), during which patients will undergo video endoscopy to quantify the size of the polyps and assign a nasal polyps score (NPS) prior to baseline.

Beginning at Day -35 (1st screening visit), patients will be asked to standardize their nasal CS to a regimen of mometasone, 200 μg twice a day (400 μg total daily dosage). Patients deemed by the investigator to be intolerant to a BID regimen of mometasone may remain on a stable dosage of mometasone QD during the run-in period and throughout the duration of the treatment period (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 study.

After screening/run-in has been completed, eligible patients will be randomly allocated in a 1:1 ratio to receive double-blind treatment with omalizumab or placebo. Randomization will be stratified on comorbid asthma and aspirin sensitivity status at baseline (3 levels: asthmatic and aspirin sensitive, asthmatic not aspirin sensitive, all other) and geographic region (North America, ex-North America).

A modified version of the approved E.U. Summary of Product Characteristics (SmPC) omalizumab dosing table will be used; the SmPC has been modified to treat only the higher body weights reflective of the adult population being studied. The first dose of study drug will be administered on the same day as randomization ([Day 1, Week 0]). Dosing will be repeated every 2 or 4 weeks during a 24-week placebo–controlled treatment period.

Video nasal endoscopy will be performed at Day -35 (1st screening visit) and at baseline (Day -7), and at Weeks 4, 8, 16, and 24 (for a total of 6 endoscopies). Change from baseline in NPS at Week 24 will be used as a co-primary endpoint to evaluate the benefit of omalizumab, where the baseline measurement is performed at Day -7 (2nd screening visit) prior to randomization.

After the treatment period ends (at Week 24), patients will be followed for 4 additional weeks as part of safety follow-up, unless they enroll at Week 24 into another available sponsor-permitted study of omalizumab in nasal polyps.

Number of Patients

A total of approximately 120 patients with CRSwNP whose disease remains inadequately controlled despite daily treatment with intranasal corticosteroid (CS) therapy will be enrolled.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age 18–75 years, inclusive, at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- NPS $\geq$ 5, with a unilateral score of $\geq$ 2 for each nostril, at screening (Day -35), and on Day -7 (as assessed by a central panel of independent central readers)
- SNOT-22 score $\geq$ 20 at screening (Day -35) and at randomization (Day 1)
- Treatment with nasal mometasone at least 200 μg per day, or equivalent daily dosing of another nasal CS, for at least 4 weeks before screening (Day -35)
- Treatment with nasal mometasone 200 μg twice a day (or once a day if intolerant to twice daily) during the run-in period with an adherence rate of at least 70%.
- Presence of nasal blockage/congestion with NCS $\geq$ 2 (1-week recall) at Day -35 and a weekly average at randomization of NCS $>$ 1 with at least one of the following symptoms prior to screening: nasal discharge (anterior/posterior nasal drip) and/or reduction or loss of smell
- Eligibility per the study drug–dosing table (serum IgE level $\geq$ 30 to $\leq$ 1500 IU/mL and body weight $\geq$ 30 to $\leq$ 150 kg) and ability to be dosed per the dosing table
- Willingness to maintain all background medications stable for the duration of the treatment and follow-up periods
- Willingness and ability to use electronic device to enter study-related information in electronic devices (electronic diary [eDiary]/electronic tablet [eTablet])

- Demonstration of at least 70% adherence to eDiary daily symptom assessment during run-in period, with fully completed entries on at least 4 days in the week prior to randomization
- 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 serum pregnancy test result during the screening period.

Exclusion Criteria

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

- Known history of anaphylaxis/hypersensitivity to omalizumab
- Treatment with investigational drugs within 12 weeks or 5 half-lives (whichever is longer) prior to screening (Day -35)
- Treatment with monoclonal antibodies (e.g., omalizumab, mepolizumab) for 6 months prior to screening (Day -35)
- Current treatment with leukotriene antagonists/modifiers, unless patient has been on stable dosing of such medication for at least 1 month prior to screening (Day -35)
- Treatment with non-steroid immunosuppressants (e.g., cyclosporine, methotrexate, azathioprine, mycophenolate, siroliumus, tacrolimus) within 2 months or 5 half-lives, whichever is longer, prior to screening (Day -35)
- Treatment with systemic corticosteroids (CS), except when used as treatment for nasal polyposis, within 2 months prior to screening (Day -35)
- Usage of systemic CS during the run-in period. Patients requiring systemic CS during run-in may be rescreened after completing systemic CS.
- Treatment with intranasal CS drops or CS–administering devices (e.g., OptiNose® device or stents) within 1 month prior to screening (Day -35) or during the run-in period
- History of nasal surgery (including polypectomy) within 6 months prior to screening
- History of sinus or nasal surgery modifying the structure of the nose such that assessment of NPS is not possible
- Uncontrolled epistaxis requiring surgical or procedural intervention, including nasal packing, within 2 months prior to screening
- Known or suspected diagnosis of cystic fibrosis, primary ciliary dyskinesia (e.g., Kartagener syndrome) or other dyskinetic ciliary syndromes, hypogammaglobulinemia or other immune deficiency syndrome, chronic granulomatous disease and granulomatous vasculitis, granulomatosis with polyangiitis (e.g., Wegener's Granulomatosis), or eosinophilic granulomatous with polyangiitis (EGPA) (e.g., Churg-Strauss syndrome)
- Presence of antrochoanal polyps
- Concomitant conditions that interfere with evaluation of primary endpoint:
  - Nasal septal deviation occluding one or both nostrils
  - Ongoing rhinitis medicamentosa
  - Acute sinusitis, nasal infection, or upper respiratory infection during the run-in period
  - Known or suspected invasive or expansive fungal rhinosinusitis

- Known HIV infection at screening
- Known acute and chronic infections with hepatitis C virus (HCV) and hepatitis B virus (HBV) at screening
- *History of myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack or a known history of a hypercoagulable disorder*
- Infection that meets any of the following criteria:
  - Resulted in hospital admission within 4 weeks prior to screening
  - Required treatment with intravenous or intramuscular antibiotics within 4 weeks prior to screening
  - Any active infection that required treatment with oral antibiotics within 2 weeks prior to screening
  - Active parasitic infection, including nematodes (e.g., Ascaris, Ancylostoma), platyhelminths (e.g., Schistosoma), or Listeria monocytogenes infection within 6 months prior to screening

  Note: Antibiotics are considered to include any antimicrobial therapy used to treat bacterial, fungal, parasitic, viral, or other infections.
- Active tuberculosis requiring treatment within 12 months prior to screening (Day -35)

  Patients who have completed treatment for tuberculosis at least 12 months prior to screening (Day -35) and have no evidence of recurrent disease are permitted.
- Initiation of or change in allergen immunotherapy within 3 months prior to screening (Day -35) or during the run-in period
- Initiation of or change in aspirin desensitization within 4 months prior to screening (Day -35) or during the run-in period
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 60 days after the last dose of omalizumab
- Current malignancy or history of malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix or non-melanoma skin carcinoma that has been treated or excised and is considered resolved
- Any serious medical condition (including but not limited to significant arrhythmia, uncontrolled hypertension, significant pulmonary disease other than asthma) or abnormality in clinical laboratory tests that precludes the patient's safe participation in and completion of the study
- History of alcohol, drug, or chemical abuse within 6 months of screening

End 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 at a maximum of 28 weeks after the last patient is randomized.

Length of Study

Each patient will be followed for up to 33 weeks (5-week screening/run-in period, 24-week treatment period, 4-week off-drug safety follow-up period). The 4-week follow-up period will be for all patients unless they enroll into another available sponsor-permitted study of omalizumab in nasal polyps.

Investigational Medicinal Products

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

Test Product (Investigational Drug)

Study drug will be administered subcutaneously to patients by qualified personnel who are not involved with conducting safety or efficacy evaluations 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.

Study drug 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) and body weight (kg) at Day -35. Assignment of the study drug 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.

Comparator

The placebo will be administered according to the same dose, route, and dosing regimen as omalizumab, shown above.

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 data from the 24-week treatment period may be performed after all patients have either completed the Week 24 visit or discontinued from the treatment period prematurely, and all data from the treatment period are in the database and have been cleaned and verified. Patients who discontinue early will not be replaced.

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

A total of approximately 120 patients will be enrolled in this study. Patients will be randomly allocated in a 1:1 ratio to receive treatment with omalizumab or placebo, in addition to intranasal steroids.

The sample size of 120 patients will provide at least 85% power to independently detect both a 0.56-point difference between treatment groups in change from baseline at Week 24 in the average daily NCS and a 1.50-point difference between treatment groups in change from baseline at Week 24 in NPS.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AERD	aspirin exacerbated respiratory disease
AQLQ	Asthma Quality of Life Questionnaire
ATE	arterial thrombotic events
BID	twice a day
CIU	chronic idiopathic urticarial
CRO	contract research organization
CRS	chronic rhinosinusitis
CRSwNP	chronic rhinosinusitis with nasal polyps
CS	corticosteroid
CSR	*Clinical Study Report*
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
FAS	full-analysis set
FDA	Food and Drug Administration
FESS	functional endoscopic sinus surgery
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
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 reponse system
LPLV	last patient, last visit
MID	*minimal important difference*
MMRM	mixed-effect model repeated measurement
NCS	nasal blockage/congestion score

NPS	nasal polyp score
PD	pharmacodynamic
PK	pharmacokinetic
PRO	patient-reported outcome
QD	once a day
QoL	quality of life
RBR	Research Biosample Repository
SAP	Statistical Analysis Plan
SC	subcutaneous
SCE	Summary of Clinical Efficacy
SD	standard deviation
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 et al. 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) with 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 a QoL that is considerably reduced in patients with CRSwNP, 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 kilodaltons 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 is currently approved by U.S. Food and Drug Administration (FDA) for allergic asthma and chronic idiopathic urticaria (CIU)/chronic spontaneous urticaria (CSU).

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

1.3 STUDY RATIONALE AND 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 (in 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; Boushey 2001; Holgate et al. 1998; Fick 1999; Jardieu and Fick 1999; Patalano 1999; 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 in Gevaert et al. 2013. Twenty-four patients (nasal polyp size ≥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 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.

Taken together, these studies provide evidence that anti-IgE therapy can be effective for patients with nasal polyps, particularly in those with large nasal polyps, suggesting that omalizumab therapy should be further evaluated in a large clinical trial for confirmation.

2. OBJECTIVES AND ENDPOINTS

The purpose of this study is to determine the efficacy and safety of omalizumab compared with placebo in adult patients with CRSwNP who have had an inadequate response to standard-of-care treatments. Specific objectives and corresponding endpoints for the study are outlined below.

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Co-Primary Endpoints
• To evaluate the efficacy of omalizumab compared with placebo	Co-primary endpoints: • Change from baseline at Week 24 in average daily nasal congestion score (NCS) • Change from baseline at Week 24 in nasal polyps score (NPS)
Secondary Efficacy Objective [a]	**Corresponding Endpoints**
• To evaluate the efficacy of omalizumab compared with placebo	• Change from baseline at Week 24 in the average daily total nasal symptom score (TNSS) • Change from baseline at Week 24 in the average daily sense of smell score • Change from baseline at Week 24 in the average daily posterior rhinorrhea score • Change from baseline at Week 24 in the average daily anterior rhinorrhea score • Change from baseline at Week 24 in patient-reported HRQoL as assessed by the total SNOT-22 • Change from baseline at Week 16 in the average daily NCS • Change from baseline at Week 16 in NPS • Change from baseline at Week 24 in sense of smell, as assessed by the UPSIT • Reduction in the need for surgery by Week 24, 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 24 • Requirement of rescue treatment (systemic CS for ≥ 3 consecutive days) through Week 24 • Having had surgery for nasal polyps through Week 24 • Change from baseline at Week 24 in AQLQ of ≥ 0.5 (in patients with comorbid asthma only)
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of omalizumab compared with placebo	• Change from baseline at Week 24 in SNOT-22 of at least the MID (8.9 points).
• To evaluate health status utility scores compared with placebo	• Change from baseline at Week 24 as assessed by EQ-5D-5L
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of omalizumab compared with placebo	• Incidence of adverse events • Incidence of serious adverse events • Incidence of adverse events leading to omalizumab/placebo discontinuation • Clinically significant change in laboratory values

Pharmacokinetic and Pharmacodynamic Objectives	Corresponding Endpoint
• To evaluate the pharmacokinetics and pharmacodynamics of omalizumab	• Serum concentration of omalizumab at specified timepoints outlined in Appendix 1 • Serum levels of total and free IgE at specified timepoints outlined in Appendix 1

AQLQ = Asthma Quality of Life Questionnaire; CS = corticosteroid; EQ-5D-5L = EuroQol 5-Dimension 5-Level Questionnaire; HRQoL = health-related quality of life; MID = minimal important difference; NCS = nasal blockage/congestion score; NPS = nasal polyp score; SNOT-22 = Sino-Nasal Outcome Test-22; TNSS = total nasal symptom score; UPSIT = University of Pennsylvania Smell Identification Test.

[a] Order of endpoints presented here does not determine order in a sequential type I error control procedure. Details on type I error control procedures will be given in the Statistical Analysis Plan at a later date.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This study is a Phase III, randomized, multicenter, double-blind, placebo-controlled, clinical trial that will be run in parallel with a replicate study, under Protocol GA39855. In this study (GA39688), a total of approximately 120 patients with CRSwNP whose disease remains inadequately controlled despite daily treatment with intranasal corticosteroid (CS) therapy will be enrolled.

Written informed consent for participation in the study must be obtained before performing any study-specific tests or evaluations. The 5-week screening/run-in period will include two visits (“1st screening visit” at Day -35 and “2nd screening visit” at Day -7) (see Figure 1). During the screening/run-in period, at both the 1st screening visit and 2nd screening visit, patients will undergo video endoscopy to quantify the size of the polyps and assign a nasal polyps score (NPS) prior to baseline. The final NPS will be determined by central readers based on the criteria presented below in Table 2 and in Appendix 3. The NPS ranges from 0–8 (0–4 on the left and 0–4 on the right).

Table 2 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

Note: 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 et al. 2013.

During the screening/run-in period, beginning at Day -35 (1st screening visit), patients will be asked to standardize their nasal CS to a regimen of mometasone, 200 μg twice a day (BID) (400 μg total daily dosage). Patients deemed by the investigator to be intolerant to a BID regimen of mometasone may remain on a stable dosage of mometasone once a day (QD) during the run-in period and throughout the duration of the treatment period (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 study. At Day -35 (1st screening visit), patients should receive appropriate training on proper self-administration of mometasone nasal spray.

Other assessments and activities occurring during the screening/run-in period are presented in Appendix 1.

If patients do not meet the inclusion criteria (e.g., development of an acute infection at the time of screening necessitating treatment with antibiotics), they may be eligible for re-screening up to two times, after discussion with a Medical Monitor. Additionally, if video endoscopy at Day -7 (2nd screening visit) is determined to be of insufficient quality to allow for scoring of NPS, patients may repeat nasal endoscopy if sufficient time remains to allow for central reading of that endoscopy prior to randomization; in such cases, before proceeding with repeat endoscopy, investigators should confirm that sufficient time does indeed remain for central reading of this endoscopy prior to randomization.

After screening/run-in has been completed, approximately 120 eligible patients will be randomly allocated in a 1:1 ratio to receive double-blind treatment with omalizumab or placebo. Randomization will be stratified on comorbid asthma and aspirin sensitivity status at baseline (see Section 4.2 for details) and geographic region (North America, ex-North America).

A modified version of the approved E.U. Summary of Product Characteristics (SmPC) omalizumab dosing table (Appendix 5) will be used; the SmPC has been modified to treat only the higher body weights reflective of the adult population being studied. The first dose of study drug will be administered on the same day as randomization ([Day 1, Week 0]). Dosing will be repeated every 2 or 4 weeks (Appendix 5) during a 24-week placebo–controlled treatment period.

Patients will remain on stable doses of intranasal CS therapy (mometasone nasal spray 200 μg BID as per Section 4.3.3) for the entire treatment period. Patients deemed by the investigator to be intolerant to a BID regimen of mometasone may remain on 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 the study.

Safety, efficacy, and patient-reported outcome (PRO) measurements will be assessed throughout the placebo-controlled treatment period, as detailed in the schedule of activities. The co-primary efficacy endpoints are changes from baseline in NPS and nasal blockage/congestion score (NCS) at Week 24.

Video nasal endoscopy will be performed at Day -35 (1st screening visit) and at baseline (Day -7), and at Weeks 4, 8, 16, and 24 (for a total of 6 endoscopies). Change from baseline in NPS at Week 24 will be used as a co-primary endpoint to evaluate the benefit of omalizumab, where the baseline measurement is performed at Day -7 (2nd screening visit) prior to randomization.

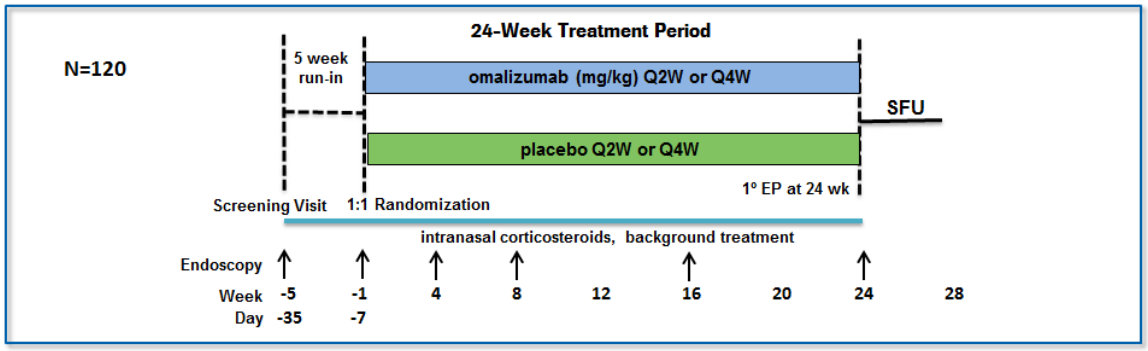
After the treatment period ends (at Week 24), patients will be followed for 4 additional weeks as part of safety follow-up (Appendix 1), unless they enroll at Week 24 into another available sponsor-permitted study of omalizumab in nasal polyps.

All patients who discontinue study drug early during the treatment period will be asked to continue the planned study assessments through Week 24 and then to complete a 4-week safety follow-up period. Patients who are unwilling or unable to continue with the planned assessments in the treatment period will instead complete a dosing-termination visit and then enter a 4–week safety follow-up period. Patients who require sinus surgery or require two or more courses of treatment with systemic CS for ≥3 consecutive days will discontinue study drug but continue in the study with assessments and treatments.

NCS will be calculated as an average of daily scores. Patients will complete an NCS assessment every morning (on a daily basis) via an electronic device, and change from baseline at Week 24 in the average daily NCS will be used as a co-primary endpoint to evaluate the benefit of omalizumab.

A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



1°EP = co-primary end point; Q2W = every 2 weeks; Q4W = every 4 weeks; SFU = safety follow-up; wk = week.

Note: All patients will be treated during the entire study with intranasal corticosteroids (mometasone nasal spray as per Section 4.3.4) as background therapy.

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 at a maximum of 28 weeks after the last patient is randomized.

Each patient will be followed for up to 33 weeks (5-week screening/run-in period, 24-week treatment period, 4-week safety follow-up period). The 4-week follow-up period will be for all patients unless they enroll into another available sponsor-permitted study of omalizumab in nasal polyps.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Omalizumab Dose and Schedule

Omalizumab will be dosed in this trial 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 5). 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 has been modified to remove lower patient weights because this trial will include only adult patients, whereas the asthma E.U. SmPC is also intended to treat pediatric patients. As with the E.U. SmPC, 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 (Appendix 5). In this trial, patient weights and IgE values used to determine study drug dosing will be based only on the Day -35 (1st screening visit) values.

3.3.2 Rationale for Patient Population

CRSwNP occurs in a subset of patients with 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 and by mucosal edema and albumin-containing pseudocysts with minimal extracellular matrix fibrosis (Huvenne et al. 2009; Mjosberg et al. 2011). 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, in association with increased mucus, and chemokines. 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 and, 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). Patients with and without a diagnosis of asthma will be eligible for this trial. During screening, it will be important to record in the eCRF any previous or current diagnosis of asthma. It is acknowledged that patients with more severe CRSwNP are more likely to have asthma. Previous trials with omalizumab in CRSwNP have generally focused on treating patients with a comorbid diagnosis of asthma, and there is less information about the efficacy in patients who do not have a diagnosis of asthma.

The target population for this study will include patients who have an inadequate response to standard of care. Standard of care for this study is defined as including at least 8 weeks of intranasal corticosteroids and may also include systemic/oral corticosteroids and/or surgery.

Patients who have required oral corticosteroids for treatment of their nasal polyposis will be eligible for this study. At the same time, requirement for systemic corticosteroids during the treatment period will be evidence of treatment failure, as detailed in Section 6.4.2. As such, clinical stability will be necessary at the time of randomization, and patients who have required oral/systemic corticosteroids during the run-in period will be required to complete their course of such corticosteroids and re-initiate the run-in and screening period prior to randomization.

The target population is defined based on currently available therapies that form the basis of standard of care for nasal polyps. These patients will have bilateral polyps with an NPS of ≥ 5, with a baseline Sino-Nasal Outcome Test-22 (SNOT-22) score of 20 or greater (indicating moderate to severe symptoms). Omalizumab will be evaluated in these patients as an add-on therapy to intranasal corticosteroids. Patients meeting these entry criteria (having large polyps obstructing their nasal passage and causing significant impairment to their QoL) represent a significant unmet medical need.

This CRSwNP target population is thought to exhibit type 2 inflammation in particular, with predominant expression of IL-13, IL-5, and some IL-4 (Wang et al. 2015). As discussed in Section 1.3, such patients with CRSwNP have marked local production of IgE antibodies, often in response to *Staphylococcus aureus*, which appears to be functional and involved in the regulation of chronic inflammation (Zhang et al. 2011). Furthermore, prior studies including a proof-of-concept study (Gevaert et al. 2013) demonstrated that omalizumab reduces nasal polyp size and symptoms in patients with CRSwNP. Therefore, by reducing circulating free IgE, preventing IgE cross-linking on the surface of mast cells and basophils, and interrupting the type 2 inflammatory cascade initiated by these events, omalizumab has the potential to offer significant clinical benefit for patients with CRSwNP and can very favourably address this significant unmet medical need in the target patient population.

3.3.3 Rationale for Control Group

The proposed design includes a placebo group to eliminate reporting and ascertainment biases in the data analysis. Patients in the placebo group will receive subcutaneous (SC) placebo injections at each treatment visit.

Per standard of care in clinical practice for this patient population, all patients regardless of the treatment group will remain on intranasal CS therapy (e.g., mometasone furoate nasal spray as specified in Section 4.3.4) throughout the study.

3.3.4 Rationale for Co-Primary Endpoint Selection

The two co-primary endpoints capture the important signs and symptoms of the disease and have regulatory precedence. The endpoints assess major clinical features of nasal polyps and were used as the basis for the registration of mometasone furoate monohydrate spray (NASONEX® USPI and E.U. SmPC for the treatment of nasal polyps). Of note, in the response from FDA dated 9 February 2017 (Reference ID: 4053742), the Agency noted that the selection of co-primary efficacy endpoints and proposed approach to consider patients who undergo surgery or use rescue medications to have experienced treatment failure (imputing with worst outcomes that are not in favor of the treatment) is reasonable.

3.3.5 Rationale for Choice of Stratification Factors

The similarity between the pathophysiology of asthma and CRSwNP suggests that asthma comorbidity and aspirin sensitivity status may be prognostic of nasal polyp size and nasal polyp symptoms (see Sections 1.1 and 1.3 for background). Stratification by asthma comorbidity status will minimize the chance of imbalance of this characteristic between treatment groups. Due to the subjective nature of the NCS and variability of medical practices by geographic region, the Sponsor anticipates that maintaining balance across geographic regions within the treatment groups will minimize the chance of biased estimation of the treatment effect. North America and ex–North America are

the factors chosen to maximize the similarity of culture and medical practice within these regions, balanced by the expected number of patients that will fall within a given strata.

3.3.6 Rationale for Patient-Reported Outcome Assessments

Change in nasal symptoms (i.e., patient-reported nasal congestion, sense of smell, anterior rhinorrhea, and posterior rhinorrhea) will provide important information to clinicians and patients regarding reduction in symptom burden. In fact, CRSwNP has been shown to have a negative impact on several aspects of QoL and has a greater impact on social functioning, than chronic heart failure, angina, or back pain (Gliklich and Metson 1995). Reduced symptom burden may improve patients' QoL and reduce economic burden of the disease (e.g., decreased work productivity) (Schalek 2011; Dietz de Loos et al. 2013; Chung et al. 2015).

The SNOT-22 will be employed to assess the impact of treatment on patient-reported symptoms and health-related quality of life (HRQoL). SNOT-22 was the recommended outcome tool by Fokkens et al. (2012) in their European position paper. This tool rates highly in terms of psychometric quality and has been used in a number of published studies performed in the European Union and the United States (Hopkins et al. 2006, 2009c; Kennedy et al. 2013; Yeolekar et al. 2013). Treatment benefit will be assessed by change from baseline at Week 24 in the SNOT-22 total score.

The University of Pennsylvania Smell Identification Test (UPSIT) is a standardized, 40-item “scratch-and-sniff” measure of olfactory function (Doty et al. 1984). It was developed using over 1,600 patients in a series of experiments designed to test the ability of the UPSIT to differentiate between patients with and without olfactory disorders. The UPSIT is widely used and is recommended by the BMJ Best Practice Guidelines (2015) to assess olfactory function in nasal polyps. The UPSIT will be employed to assess smell.

The four brief nasal symptom items will be completed by patients on a daily basis. Completion of these items is estimated to require <2 minutes each day. The SNOT-22 and UPSIT will be completed at a minimal number of study visits in order to reduce patient burden.

4. MATERIALS AND METHODS

4.1 PATIENTS

The study will enroll patients with difficult-to-treat CRSwNP. These will be patients with large bilateral nasal polyps that remain uncontrolled despite daily treatment with intranasal CS for at least 8 weeks, as demonstrated by an NPS score of ≥ 5.

Approximately 120 patients will be enrolled in this Phase III study at approximately 50–70 sites located globally.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age 18–75 years, inclusive, at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- NPS ≥ 5, with a unilateral score of ≥ 2 for each nostril (see Appendix 2), at screening (Day -35), and on Day -7 (as assessed by a central panel of independent central readers)
- SNOT-22 score ≥ 20 at screening (Day -35) and at randomization (Day 1)
- Treatment with nasal mometasone at least 200 μg per day, or equivalent daily dosing of another nasal CS, for at least 4 weeks before screening (Day -35)
- Treatment with nasal mometasone 200 μg BID (or QD if intolerant to twice daily) during the run-in period with an adherence rate of at least 70%.
- Presence of nasal blockage/congestion with NCS ≥ 2 (1-week recall) at Day -35 and a weekly average at randomization of NCS > 1 with at least one of the following symptoms prior to screening: nasal discharge (anterior/posterior nasal drip) and/or reduction or loss of smell
- Eligibility per the study drug–dosing table (serum IgE level ≥ 30 to ≤ 1500 IU/mL and body weight ≥ 30 to ≤ 150 kg) and ability to be dosed per the dosing table (see Appendix 5)
- Willingness to maintain all background medications stable for the duration of the treatment and follow-up periods
- Willingness and ability to use electronic device to enter study-related information in electronic devices (electronic diary [eDiary]/electronic tablet [eTablet])
- Demonstration of at least 70% adherence to eDiary daily symptom assessment during run-in period, with fully completed entries on at least 4 days in the week prior to randomization
- 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 serum pregnancy test result during the screening period.

4.1.2 Exclusion Criteria

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

- Known history of anaphylaxis/hypersensitivity to omalizumab
- Treatment with investigational drugs within 12 weeks or 5 half-lives (whichever is longer) prior to screening (Day -35)
- Treatment with monoclonal antibodies (e.g., omalizumab, mepolizumab) for 6 months prior to screening (Day -35)
- Current treatment with leukotriene antagonists/modifiers, unless patient has been on stable dosing of such medication for at least 1 month prior to screening (Day -35)
- Treatment with non-steroid immunosuppressants (e.g., cyclosporine, methotrexate, azathioprine, mycophenolate, siroliumus, tacrolimus) within 2 months or 5 half-lives, whichever is longer, prior to screening (Day -35)
- Treatment with systemic corticosteroids (CS), except when used as treatment for nasal polyposis, within 2 months prior to screening (Day -35)
- Usage of systemic CS during the run-in period. Patients requiring systemic CS during run-in may be rescreened after completing systemic CS.
- Treatment with intranasal CS drops or CS–administering devices (e.g., OptiNose® device or stents) within 1 month prior to screening (Day -35) or during the run-in period
- History of nasal surgery (including polypectomy) within 6 months prior to screening
- History of sinus or nasal surgery modifying the structure of the nose such that assessment of NPS is not possible
- Uncontrolled epistaxis requiring surgical or procedural intervention, including nasal packing, within 2 months prior to screening
- Known or suspected diagnosis of cystic fibrosis, primary ciliary dyskinesia (e.g., Kartagener syndrome) or other dyskinetic ciliary syndromes, hypogammaglobulinemia or other immune deficiency syndrome, chronic granulomatous disease and granulomatous vasculitis, granulomatosis with polyangiitis (e.g., Wegener's Granulomatosis), or eosinophilic granulomatous with polyangiitis (EGPA) (e.g., Churg-Strauss syndrome)
- Presence of antrochoanal polyps
- Concomitant conditions that interfere with evaluation of primary endpoint:
  - Nasal septal deviation occluding one or both nostrils
  - Ongoing rhinitis medicamentosa
  - Acute sinusitis, nasal infection, or upper respiratory infection during the run-in period
  - Known or suspected invasive or expansive fungal rhinosinusitis

- Known HIV infection at screening
- Known acute and chronic infections with hepatitis C virus (HCV) and hepatitis B virus (HBV) at screening
- *History of myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack or a known history of a hypercoagulable disorder*
- Infection that meets any of the following criteria:
  - Resulted in hospital admission within 4 weeks prior to screening
  - Required treatment with intravenous or intramuscular antibiotics within 4 weeks prior to screening
  - Any active infection that required treatment with oral antibiotics within 2 weeks prior to screening
  - Active parasitic infection, including nematodes (e.g., Ascaris, Ancylostoma), platyhelminths (e.g., Schistosoma), or Listeria monocytogenes infection within 6 months prior to screening

  Note: Antibiotics are considered to include any antimicrobial therapy used to treat bacterial, fungal, parasitic, viral, or other infections.
- Active tuberculosis requiring treatment within 12 months prior to screening (Day -35)

  Patients who have completed treatment for tuberculosis at least 12 months prior to screening (Day -35) and have no evidence of recurrent disease are permitted.
- Initiation of or change in allergen immunotherapy within 3 months prior to screening (Day -35) or during the run-in period
- Initiation of or change in aspirin desensitization within 4 months prior to screening (Day -35) or during the run-in period
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 60 days after the last dose of omalizumab
- Current malignancy or history of malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix or non-melanoma skin carcinoma that has been treated or excised and is considered resolved
- Any serious medical condition (including but not limited to significant arrhythmia, uncontrolled hypertension, significant pulmonary disease other than asthma) or abnormality in clinical laboratory tests that precludes the patient's safe participation in and completion of the study
- History of alcohol, drug, or chemical abuse within 6 months of screening

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

At the Day 1 visit, after verification of inclusion/exclusion criteria, patients will be randomized to receive either omalizumab or placebo at approximately a 1:1 ratio using an interactive Web-based response system (IWRS). Randomization will be stratified by

comorbid asthma and aspirin sensitivity status at baseline (3 levels: asthmatic and aspirin sensitive, asthmatic not aspirin sensitive, all other) and geographic region (North America, ex-North America).

The following individuals/groups will be blinded to treatment assignment throughout the study: patients, the designated evaluating physician(s) and study nurses, the central image readers, and the Sponsor and its agents. The following are exceptions to the blinding: IWRS service provider, unblinded pharmacist at the sites, and bioanalytical laboratory personnel. To minimize risk of potential bias arising from access to laboratory results that could potentially unblind treatment assignments (e.g., free IgE levels), access to these results will be restricted to the site and the sponsor until study completion. Treatment assignment may be unblinded to the personnel analyzing the data from the treatment period when all data through Week 24 are in the database and the data have been cleaned and verified.

Study drug supplies will be shipped blinded to each site. To minimize the risk of potential bias, study site personnel who are responsible for reconstituting and/or administering study drug will not be permitted to conduct any safety or efficacy evaluations. Each center will identify an individual (e.g., pharmacist) responsible for the reconstitution procedures. This individual will prepare the study drug for each patient prior to administration. An individual not involved with evaluating the patient must be identified to administer the study drug.

While pharmacokinetic (PK) samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK results for these patients are generally not needed for the safe conduct or proper interpretation of this study. Laboratories responsible for performing study drug PK assays will be unblinded to patients' treatment assignments to identify appropriate samples to be analyzed. PK samples from patients assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing).

As per local health authorities (HA) reporting requirements, the Sponsor will break the treatment code for all SUSARs (suspected unexpected serious adverse reactions). For more details on expedited reporting to HA, investigators, IRBs, and ethics committees, see Section 5.7. The internal study team will remain blinded to treatment assignment, and the patient may continue to receive treatment per protocol.

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IWRS). Treatment codes should not be broken except in emergency situations. If the investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and

provide an explanation for any premature unblinding (e.g., accidental unblinding or unblinding due to a serious adverse event).

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 and Placebo

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.

The placebo contains the same ingredients as the omalizumab formulation listed above, excluding omalizumab.

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. For information on the formulation, handling, and storage of mometasone furoate monohydrate nasal spray, see 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 regimens are 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 5.1.4.1.

4.3.2.1 Omalizumab and Placebo

Study drug will be administered subcutaneously to patients by qualified personnel who are not involved with conducting safety or efficacy evaluations 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.

Study drug 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) as specified in Appendix 1. Assignment of the study drug dose will be determined by using the study drug–dosing table (see Appendix 5). 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 take mometasone furoate nasal spray (e.g., Nasonex®) starting at Day -35 (1st screening visit) (two sprays/nostril, both nostrils, 50 μg/spray BID for a total daily dose of 400 μg) and remain on this medication at this dose throughout the study until Week 24. 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 the study.

Patients who have not been sufficiently adherent to mometasone during the run-in period, as specified in inclusion criteria and measured by eDiary (Section 4.1.1), will be prohibited from enrollment.

Patients will confirm daily mometasone use in the eDiary during the run-in period only. During the treatment period, patient adherence to prescribed mometasone regimen will be assessed by the investigator at clinic visits and recorded in the 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 using the IWRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any 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

Patients may be eligible to receive omalizumab as part of another available sponsor-permitted study of omalizumab in nasal polyps. The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

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

4.4 CONCOMITANT THERAPY

Concomitant therapy will consist 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

  These procedures, if performed will be considered rescue treatment and evidence of treatment failure. 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, cyclosporine, methotrexate, azathioprine, or mycophenolate and chronic use of systemic corticosteroids

  Acute courses of oral or systemic corticosteroids must be justified and reasons documented. Use of oral or systemic corticosteroids for ≥ 3 consecutive days will be considered rescue treatment and evidence of treatment failure. Patients who require two or more single courses of systemic corticosteroids for ≥ 3 consecutive days should discontinue study medication, although study assessments should continue. Should the patient elect to withdraw from study medication, the safety follow-up visits should be scheduled.
- Changes in allergen immunotherapy or initiation of new allergen immunotherapy within 3 months prior to screening and throughout the study
- Changes in aspirin desensitization therapy or initiation of new aspirin desensitization therapy within 4 months prior to screening and throughout the study
- 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 (SNOT-22, EQ-5D-5L, Asthma Quality of Life Questionnaire [AQLQ; for patients with comorbid asthma only]) 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 (including screening evaluations). 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 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history, reproductive status, and smoking history will be recorded at screening. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient prior to Day -35 (1st screening visit) will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

In particular, any history of anaphylaxis, cardiovascular disease, eosinophilic disease, inflammatory or autoimmune disease, parasitic disease, and diseases commonly associated with CRSwNP, including asthma, AERD, and fungal infections/allergies, should be recorded on the eCRF.

Demographic data to be collected will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at the 1st screening visit (Day -35) should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

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.

4.5.4 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, including administrations at Weeks 2,

6, 10, 14, 18, and 22 in patients receiving study drug every 2 weeks, as determined by screening IgE and weight.

4.5.5 CRSwNP History and Comorbidities

Specific clinical history and physical examination findings related to CRSwNP will be recorded at the 1st screening visit (Day -35). These will include the date of first diagnosis, number of prior surgeries, and the date and nature of the most recent surgical procedure.

The Medical History eCRF will collect specific information pertaining to diseases commonly associated with CRSwNP, including but not limited to asthma, allergic rhinitis, AERD, and allergic fungal rhinitis.

In addition, specific clinical history for the conditions listed below will be recorded at screening.

Asthma

Time since diagnosis, whether asthma is active or inactive, assessment of disease severity (mild, moderate, or severe), and dose and frequency of all asthma-targeted therapies (including but not limited to inhalers or oral medications) will be collected.

Aspirin-Exacerbated Respiratory Disease

Time since diagnosis, an assessment of disease severity (mild, moderate, or severe), and treatments given prior to the study will be collected.

Allergic Fungal Sinusitis

A history of sino-nasal fungal infections will be recorded on the eCRF. Any historic or ongoing treatments, including past surgeries, will be collected.

4.5.6 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 2 for nasal polyp scoring system and the nasal endoscopy site manual for more details).
- Nasal symptoms including NCS (see Section 4.5.10.2 and Appendix 3)
- SNOT-22 (see Section 4.5.10.2 and Appendix 4)
- UPSIT (see Section 4.5.10.3)

4.5.7 Physician Review 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. Sites should be especially vigilant in providing a reminder about importance of adherence at the Week 20 visit, 4 weeks before the assessment of the primary outcomes.

4.5.8 Laboratory and Other Biological Samples

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

- Serum and urine pregnancy test
  - All women of childbearing potential must have a negative serum pregnancy test during the screening period, prior to initiation of study drug. Additionally, women should have a urine pregnancy test prior to the initiation of study drug, *every 4 weeks* during study treatment period, and at the safety follow-up visit, as indicated in Appendix 1. Urine pregnancy test results must be reviewed and confirmed to be negative before study drug administration. 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.
- Stool ova and parasite evaluation

  This test should be conducted locally in patients who have risk factors for parasitic disease (e.g., living in an endemic area, travel to an endemic area within the last 6 months, chronic GI symptoms, or chronic immunosuppression) and an eosinophil count >2 times the upper limit of normal. This test should be conducted anytime during the screening period after the Day -35 eosinophil count results are available for applicable patients.

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

- Total IgE for study eligibility and dosing determination
- 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, alkaline phosphatase, ALT, AST, uric acid, LDH
- Coagulation: INR, aPTT, PT
- *Viral serology (unless not permitted by local regulations or ethics committees): HIV, hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), hepatitis C (HCV) antibody*

- Urinalysis, including but not limited to: dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)

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

- Serum samples for PK analysis. PK samples may also be used for additional drug level/anti-drug antibody (ADA) testing. PK 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 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 (see Section 4.5.11). Samples need to be drawn before administration of omalizumab.

4.5.9 Electrocardiograms

A single ECG recording will be obtained at the 1st screening (Day -35), as outlined in the schedule of activities (see Appendix 1). Lead placement should be as consistent as possible. The ECG recording must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety purposes, the investigator must review, sign, and date the ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QT interval corrected.

4.5.10 Patient-Reported Outcomes

PRO data will be collected to document the treatment benefit of omalizumab. The questionnaires, translated into the local language as appropriate, 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 electronic device (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. 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.

4.5.10.1 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, from screening through treatment period. The nasal symptom questions, which include NCS, are provided in Appendix 3.

4.5.10.2 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 4). 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.

4.5.10.3 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.

4.5.10.4 EuroQol 5-Dimension 5-Level Questionnaire

The EuroQol 5-Dimension 5-level Questionnaire (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 6). Patients will complete the EQ-5D-5L at specific visits as specified in the schedule of activities.

There are two components to the EuroQol EQ-5D-5L: a 5-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 modelling.

4.5.10.5 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 4 domains: activity limitations, symptoms, emotional function, and environmental stimuli. The AQLQ(S) has a recall specification of 2 weeks. Items are scored on a 7-point scale ranging from 1 (severe impairment) to 7 (no impairment). A copy of the AQLQ(S) is provided in Appendix 7. The AQLQ(S) will be administered at the randomization visit (Week 0), Week 16, and Week 24.

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 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 collected 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

4.5.11.2 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 4.5.11) will not be applicable at that site.

4.5.11.3 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 Chronic Rhinosinusitis with Nasal Polyps and related diseases:

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

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing (NGS), or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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).

4.5.11.4 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.

4.5.11.5 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.

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. 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 GA39688 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 GA39688.

4.5.11.7 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 post-marketing experience with omalizumab for the last 13 years. Omalizumab is marketed in over 90 countries for allergic asthma and 80 countries for chronic idiopathic urticaria (CIU)/chronic spontaneous urticaria (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 4.6.1).

5.1.1 Safety and Data Monitoring

All safety events will be closely monitored by the study team. The sponsor followed the U.S. Food and Drug Administration (FDA) guidance (FDA 2006; https://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm) 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 3-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) and whether the reported anaphylaxis event is causally related to blinded 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 post-marketing spontaneous reports. Anaphylactic reactions were rare in clinical trials (0.1%) and estimated as 0.2% from post-marketing 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 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 3 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 patients 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 pre-existing 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 the EXCELS revealed the rate of ATEs per 1000 patient years was 7.52 (115/15286 patient years) for omalizumab-treated patients and 5.12 (51/9963 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 anti-drug antibodies [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× ULN, or 2) if the patient's ALT or AST >3× ULN and total bilirubin >2× 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 9)
- 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 and 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 28). 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 3 will be used for assessing severity of adverse events.

Table 3 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 4):

- 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 4 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 9) 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., alkaline phosphatase and bilirubin 5 × 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 5.3.5.6) 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, 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 pre-existing 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 pre-existing 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 pre-existing 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 Institutional Review Board or Ethics Committee (IRB/EC).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information (Primary)

Medical Monitor: [redacted], M.D.
[redacted] Medical Monitor

Telephone No. (24/7) North America: [redacted]

Telephone No. (24/7) Europe: [redacted]

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 safety follow-up period (Week 28). 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 electronic data capture (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 data from the 24-week treatment period may be performed after all patients have either completed the Week 24 visit or discontinued from the treatment period prematurely, and all data from the treatment period are in the database and have been cleaned and verified. Patients who discontinue early will not be replaced.

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.

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.*

Detailed specifications of the statistical methods will be described in the Statistical Analysis Plan (SAP). The SAP will be reviewed by health authorities and finalized prior

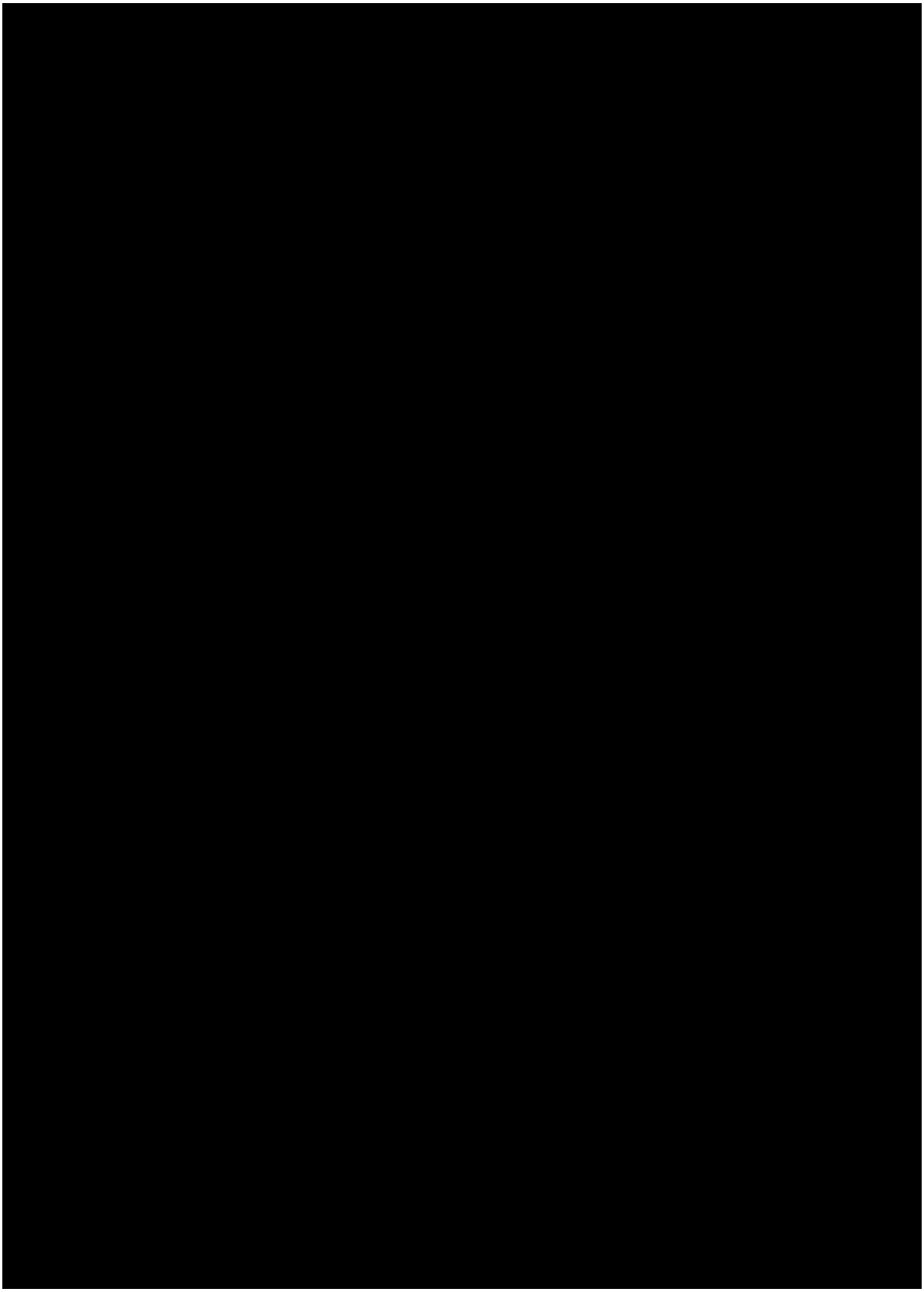
to database lock. To allow for incorporation of health authority input, the statistical methods in the SAP may differ from and will supersede those described in this document.

6.1 DETERMINATION OF SAMPLE SIZE

A total of approximately 120 patients will be enrolled in this study. Patients will be randomly allocated in a 1:1 ratio to receive treatment with omalizumab or placebo, in addition to intranasal steroids.

The sample size of 120 patients will provide at least 85% power to independently detect both a 0.56-point difference between treatment groups in change from baseline at Week 24 in the average daily NCS and a 1.50-point difference between treatment groups in change from baseline at Week 24 in NPS. [redacted]

The sample size of n = 102 patients will provide approximately 92% power to detect a 0.56-point treatment group difference in change from baseline at Week 24 in NCS (SD = 0.83) and approximately 93% power to detect a 1.50-point treatment group difference in change from baseline at Week 24 in NPS (SD=2.2), for an overall power of approximately 85% ($0.93 \times 0.92 > 0.85$). [redacted]



6.2 SUMMARIES OF CONDUCT OF STUDY

Descriptive statistics will be used to evaluate the conduct of the study. The number of patients randomized will be tabulated by country, study site, and treatment arm in all patients with data. Patient disposition (the number of patients randomized, treated, and completing each study period) will be tabulated by treatment arm 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.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics, such as age, sex, race/ethnicity, NPS, NCS, sense of smell, anterior rhinorrhea, posterior rhinorrhea, UPSIT, and SNOT-22 will be summarized with descriptive statistics by treatment arm in all patients with data. Baseline disease characteristics will be defined as the last measurement (or average in the case of daily nasal symptom scores) prior to randomization. Exposure to study drug (number of study drug treatments and duration of treatment) will be summarized by treatment arm in all patients with data.

6.4 EFFICACY ANALYSES

There are two distinct and equally important estimands of interest in this trial. The first estimand is the treatment group difference in mean change from baseline at Week 24 in NPS in patients with CRwNP, where the need for rescue medication or nasal polypectomy is accounted for as an unfavorable (worst) outcome. The second estimand is the treatment group difference in mean change from baseline at Week 24 in the average daily NCS in patients with CRwNP, where the need for rescue medication or nasal polypectomy is accounted for as an unfavorable (worst) outcome.

Hypothesis testing for all efficacy endpoints will be conducted in the full-analysis set (FAS). The FAS will include all randomized patients who received at least one dose of study drug grouped according to the treatment assigned at randomization.

The study level type-1 error for the family of primary and select secondary efficacy hypotheses will be controlled at $\alpha = 0.05$. Details for the type-1 error control procedures for the co-primary endpoints are provided below, while further type-1 error control procedures for secondary efficacy endpoints will be provided in the SAP.

All hypothesis tests will be two-sided. Unless otherwise noted, all analyses of efficacy outcome measures will at a minimum be adjusted by geographic region through the use of a categorical variable and by baseline asthma comorbidity and aspirin sensitivity status. Adjustment by additional covariates, if any, will be described in the SAP.

Treatment Failure and Missing Data

In NPS, NCS, and nasal symptoms analyses, a patient is considered to have experienced treatment failure if they initiate rescue treatment (i.e., use of systemic CS for ≥ 3 consecutive days or nasal polypectomy) at any point during the interval between randomization and their Week 24 visit inclusive. Unless otherwise noted, handling of missing data, treatment failure, and handling of observed data post-treatment failure will be detailed in the SAP.

6.4.1 Co-primary Efficacy Endpoints

As NCS and NPS are co-primary endpoints, both null hypotheses for NCS and NPS need to be rejected for the study to be deemed positive. The primary analysis will separately test the null hypotheses that no treatment group difference exists in each of the co-primary endpoints:

- Change from baseline at Week 24 in NPS in the FAS
- Change from baseline at Week 24 in the average daily NCS in the FAS

Because both NCS and NPS hypotheses need to be rejected to demonstrate efficacy of omalizumab in patients with CRSwNP, there is no adjustment for multiple endpoints and each will be tested at the two-sided $\alpha = 0.05$ level.

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 2; Gevaert et al. 2013) by a central panel of independent sinus surgeons who are blinded to treatment assignment. 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 2). NPS will be assessed during screening at Day -35 and Day -7 and post-randomization on Weeks 4, 8, 16, and 24. Baseline NPS is defined as the last measurement performed before the first dose of study drug. The absolute change from baseline NPS values will be defined as the NPS at the timepoint minus the

NPS at baseline. The absolute change from baseline in NPS will be summarized by treatment arm and timepoint.

Treatment group comparisons of absolute change from baseline at Week 24 in NPS between treatment groups will be assessed using a mixed-effect model repeated measurement (MMRM) model. The model will use absolute change from baseline as the response variable and will be adjusted for the covariates mentioned in Section 6.4, as well as timepoint (Weeks 4, 8, 16, and 24), baseline NPS, treatment by timepoint interaction, and baseline NPS by timepoint interaction. Further details about the model and additional covariates, if any, will be described in the SAP. Point estimates, 95% confidence intervals, and p-values for the treatment effect (omalizumab vs. placebo) on absolute change from baseline in NPS will be calculated on the basis of the model for all post-baseline study visits, including Week 24, using appropriate contrasts.

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 3; Fairley et al. 1993) every morning through Week 24 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. For each patient and monthly post-baseline assessment study visit (i.e., Weeks 4, 8, 12, 16, 20, and 24), the post-baseline 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. Through ongoing monitoring of eDiary compliance, we will aim to obtain at least 4 of the 7 days of data for NCS in any given week.

Treatment group comparisons of absolute change from baseline at Week 24 in NCS between treatment groups will be assessed using a MMRM model. The model will use absolute change from baseline as the response variable and will be adjusted for the covariates mentioned in Section 6.4, as well as timepoint (Weeks 4, 8, 12, 16, 20, and 24), baseline NCS, treatment by time point interaction, and baseline NCS by timepoint interaction. Further details about the model and additional covariates will be described in the SAP. Point estimates, 95% confidence intervals, and p-values for the treatment effect (omalizumab vs. placebo) on absolute change from baseline in NCS will be calculated on the basis of the model for all post-baseline study visits, including Week 24, using appropriate contrasts.

Handling of Treatment Failure and Missing Data

In patients classified as having experienced treatment (i.e., use of systemic CS for $\geq$3 consecutive days or nasal polypectomy), the worst possible score of 8 for NPS and 3 for average daily NCS will be imputed for all timepoints on or after the initiation of rescue medication or nasal polypectomy. Sensitivity analysis concerning missing data assumptions for all efficacy endpoints meeting nominal significance will be conducted (i.e., tipping point analysis) and details will be provided in the SAP.

6.4.2 Secondary Efficacy Endpoints

Change from Baseline at Week 24 in Nasal Symptoms

In addition to nasal congestion, the following patient-reported nasal symptom scores will be measured every morning: loss of smell, posterior rhinorrhea, and anterior rhinorrhea. Each symptom is scored on the integer scale ranging from 0 [not at all] to 3 [severe]. The treatment group difference in absolute change from baseline at Week 24 in each of the daily nasal symptom scores will be estimated using separate MMRM models with absolute change from baseline as the response variable and adjusted for timepoint (Weeks 4, 8, 12, 16, 20, and 24), baseline covariates as described in Section 6.4, as well as the respective nasal symptom score at baseline. The TNSS, a composite of nasal congestion, loss of smell, and rhinorrhea, will be analyzed separately using the same methods. Further details, including the calculation of TNSS, will be described in the SAP.

Change from Baseline at Week 24 in Sino-Nasal Outcome Test-22

The SNOT-22, a disease-specific HRQoL measure, has a range 0–110 (lower score indicating less disease and better HRQoL). The treatment group difference in absolute change from baseline at Week 24 in SNOT-22 will be estimated using an MMRM model with absolute change from baseline as the response variable, adjusted for timepoint (Weeks 4, 8, 16, and 24), baseline covariates as described in Section 6.4, as well as baseline SNOT-22. Further details will be described in the SAP.

Change from Baseline at Week 16 in Nasal Congestion Score

The MMRM model used for the primary analysis of absolute change from baseline at Week 24 in average daily NCS will be used to estimate the treatment group difference in absolute change from baseline at Week 16 in NCS.

Change from Baseline at Week 16 in Nasal Polyp Score

The MMRM model used for the primary analysis of absolute change from baseline at Week 24 in NPS will be used to estimate the treatment group difference in absolute change from baseline at Week 16 in NPS.

Change from Baseline at Week 24 in University of Pennsylvania Smell Identification Test

The UPSIT is a 40-question instrument that measures an individual's ability to detect odors and ranges from 0–40. The treatment group difference in absolute change from baseline at Week 24 in UPSIT will be estimated using MMRM model with absolute change from baseline as the response variable and adjusted for timepoint (Weeks 4, 8, 16, and 24) baseline covariates as described in Section 6.4 as well as baseline UPSIT. Further details will be described in the SAP.

Reduction in the Need for Surgery at Week 24

A reduced need for surgery by Week 24 is defined by a reduction in NPS to ≤ 4 (unilateral score of ≤ 2 on each side) and with improvement from baseline at Week 24 in

SNOT-22 score of ≥ 8.9 without treatment failure. The treatment group difference in proportion of patients at Week 24 with a reduced need for surgery will be estimated using a logistic regression model analysis adjusted for baseline covariates as described in Section 6.4, as well as baseline NPS and SNOT-22. Further details will be described in the SAP.

Requirement of Rescue Treatment through Week 24

Requiring rescue treatment is defined here as having taken systemic CS for ≥ 3 consecutive days or having had sinus surgery for nasal polyps at any point between randomization and Week 24 inclusive. The treatment group difference in proportion of patients requiring rescue treatment will be estimated using a logistic regression model analysis adjusted for baseline covariates as described in Section 6.4. Similarly, requirement of systemic CS and sinus surgery will be analyzed separately. Further details will be described in the SAP.

Change from Baseline at Week 24 in Asthma Quality of Life Questionnaire of ≥ 0.5 Points

The AQLQ is a 32-item measure of asthma-related QoL with a total score ranging from 1 to 7; a higher score indicates a better QoL. The treatment group difference in proportion of patients with comorbid asthma with a change from baseline at Week 24 in AQLQ score of ≥ 0.5 points will be estimated using a logistic regression model analysis adjusted for baseline covariates as described in Section 6.4, as well as baseline AQLQ. Further details will be described in the SAP.

6.4.3 Exploratory Efficacy Endpoints

Details on analysis of exploratory efficacy endpoints will be provided in the SAP.

6.4.4 *Subgroup Analyses*

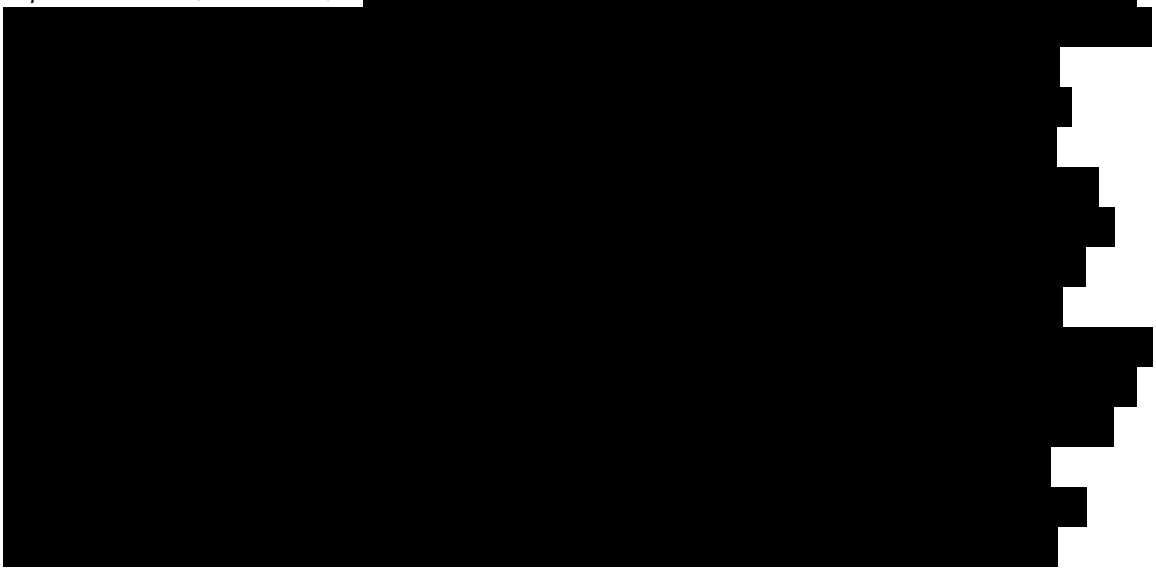
Exploratory subgroup analyses will be performed to evaluate the consistency of the primary analysis results across pre-specified subgroups defined by demographic and baseline characteristics. Further details on these subgroup analyses and any additional subgroups will be pre-specified in the SAP and finalized prior to data unblinding. In addition to age, sex, and race, the following subgroups (at a minimum) will be analyzed with respect to the co-primary efficacy endpoints (change from baseline at Week -24 in NPS and change from baseline at Week -24 in NCS) using the same methods as specified for the co-primary endpoints:

- *Baseline comorbid asthma and aspirin sensitivity status (asthmatic and aspirin sensitive, asthmatic not aspirin sensitive, all other)*
- *Geographic region (North America, ex-North America)*
- *Baseline mometasone prescribed dose (daily dose of 400 μg, daily dose of 200 μg)*

If convergence problems with the statistical models arise due to a small number of patients per subgroup, the analysis may be simplified by combining some of the subgroups or by excluding baseline stratification variables from the model.

6.4.5 ***Pooled Analyses***

Efficacy data on endpoints from this study may be pooled with external data from a replicate trial (GA39855). [redacted]



6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received. Safety summaries will be presented by treatment group for all treated patients.

Safety will be assessed through the summary of adverse events, laboratory test results, and vital signs.

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. In addition, separate summaries will be generated for serious adverse events, deaths, adverse event of special interest, and adverse events leading to discontinuation of study drug.

Vital Signs

Vital signs (pulse rate, systolic and diastolic blood pressure while the patient is in a seated position) will be summarized by descriptive statistics by timepoint.

Clinical Laboratory Evaluations

Clinical laboratory data (serum chemistry, hematology evaluations including CBC with differential and platelet counts, and urinalysis values) will be summarized by descriptive statistics by timepoint.

6.6 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Serum omalizumab and total and free IgE concentrations will be measured predose (C_{min}) and at Weeks 16 and 24 during the treatment period, and at Week 28 during the safety follow-up period according to the schedule of activities (see Appendix 1). These concentrations will be summarized using descriptive statistics (mean, SD, coefficient of variation, median, minimum, and maximum) by treatment group and timepoint based on the safety analysis population.

Additional PK analyses will be conducted as appropriate.

6.7 INTERIM ANALYSIS

There are no planned interim efficacy analyses.

6.8 *MISSING DATA*

Unless otherwise noted, in the analysis of all continuous co-primary, secondary, and exploratory endpoints (NPS, NCS, loss of smell, anterior rhinorrhea, posterior rhinorrhea, TNSS, SNOT-22, UPSIT, EQ-5D-5L), missing values will not be explicitly imputed in the analyses, which will use a mixed-effect model repeated measurement (MMRM) model. The exception is for the co-primary endpoints NPS and NCS, for which missing values planned on or after the date of treatment failure will be imputed by the worst possible score of 8 for NPS and 3 for daily NCS. Patients without post-baseline endpoint data will not contribute to the MMRM model. Sensitivity analysis concerning missing data assumptions for all continuous co-primary and secondary efficacy endpoints meeting nominal statistical significance will be conducted (i.e., tipping point analysis). Details of these pre-specified sensitivity analyses will be provided in the SAP and finalized prior to data unblinding.

In the analysis of the following categorical secondary endpoints (for which a logistic regression model is specified) missing data from patients who discontinue the study prior to their Week -24 visit without having previously met the criteria for the event will be imputed as having the event:

- *Requirement of rescue treatment (systemic CS for ≥3 consecutive days) or having had surgery for nasal polyps through Week -24*
- *Requirement of rescue treatment (systemic CS for ≥3 consecutive days) through Week -24*
- *Having had surgery for nasal polyps through Week -24*

In the analysis of the following categorical secondary and exploratory endpoints (for which a logistic regression model is specified) missing data from patients who discontinue the study prior to Week -24 without having previously met the criteria for the event will be imputed as not having the event:

- *Reduction in the need for surgery by Week -24, as defined by an NPS of ≤4 (unilateral score of ≤2 on each side) and improvement in SNOT-22 score of ≥8.9*
- *Change from baseline at Week -24 in AQLQ of ≥0.5 (in patients with comorbid asthma only)*
- *Change from baseline at Week -24 in SNOT-22 of at least the minimal important difference (MID) (8.9 points).*

6.9 *UNUSED AND SPURIOUS DATA*

For the efficacy analysis of continuous co-primary, secondary, and exploratory endpoints for which an MMRM model is used, a single data point will be assigned to a planned timepoint (e.g., Week 4, Week 8, Week 16, Week 24) 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 and finalized prior to unblinding.

Due to the nature of the data capture instruments (e.g., eCRF, eDiary, or tablet), spurious response data are not expected for PRO efficacy endpoints (i.e., NPS, NCS, SNOT-22, UPSIT, AQLQ, EQ-5D-5L). 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 PRO data (i.e., the UPSIT) will be collected on paper. The data from the UPSIT will be 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 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 50–70 sites globally will participate to enroll approximately 120 patients. 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 analyses), as specified in Section 4.5. 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

	Screening/ Run-In Period		Treatment [a]													SFU [b]	UV	Dosing Term./ Early Term.
Day (Window)	-35	-7 (± 5)	1 (-5/+7) [c]	14 (± 3)	28 (± 3)	42 (± 3)	56 (± 3)	70 (± 3)	84 (± 3)	98 (± 3)	112 (± 3)	126 (± 3)	140 (± 3)	154 (± 3)	168 (± 3)	196 (± 3)		
Visit/Week [d]	V1	V2	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W28		
Informed consent	x																	
Demographic data	x																	
Medical history	x																	
Vital Signs (BP, pulse)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight, height	x																	
Physical examination	x																	
Limited physical examination		x	x		x		x		x		x		x		x	x	x	x
ECG	x																	
IWRS randomization			x															
Study drug admin. [a]			x	x	x	x	x	x	x	x	x	x	x	x				

Appendix 1 Schedule of Activities (cont.)

	Screening/ Run-In Period		Treatment [a]													SFU [b]	UV	Dosing Term./ Early Term.
Day (Window)	-35	-7 (± 5)	1 (-5/+7) [c]	14 (± 3)	28 (± 3)	42 (± 3)	56 (± 3)	70 (± 3)	84 (± 3)	98 (± 3)	112 (± 3)	126 (± 3)	140 (± 3)	154 (± 3)	168 (± 3)	196 (± 3)		
Visit/Week	V1	V2	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W28		
Patient-reported nasal CS usage (eDiary) [e]	<<——>>																	
Nasal symptoms (eDiary) [f]	<<————————————————————————————————————>>																	
Adverse events			<<————————————————————————————————————>>															
Concomitant medications			<<————————————————————————————————————>>															
Video endoscopy, NPS [g]	x	x			x [h]		x [h]				x [h]				x [h]			
UPSIT			x				x				x				x			
Patient-Reported Outcomes																		
EQ-5D-5L			x								x				x			
SNOT-22	x		x		x		x				x				x			
AQLQ [i]			x								x				x			

Appendix 1 Schedule of Activities (cont.)

	Screening /Run-In Period		Treatment [a]													SFU [b]	UV	Dosing Term./ Early Term.
Day (Window)	-35	-7 (± 5)	1 (-5/+7) [c]	14 (± 3)	28 (± 3)	42 (± 3)	56 (± 3)	70 (± 3)	84 (± 3)	98 (± 3)	112 (± 3)	126 (± 3)	140 (± 3)	154 (± 3)	168 (± 3)	196 (± 3)		
Visit/Week	V1	V2	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W28		
Laboratory Tests																		
Urine pregnancy test [j]		x	x		*x*		*x*		*x*		x		*x*		x	x		x
Serum pregnancy test [j]	x																	
PK [k]			x								x				x	x		x
Total IgE [l, m]	x [l]		x								x				x	x		x
Free IgE [m]			x								x				x	x		x
Hematology [n]	x		x								x				x	x		x
Chemistry [o]	x		x												x	x		x
Coagulation [p]	x																	
Viral serology [q]	*x*																	
Urinalysis [r]	x																	
Stool ova and parasite [s]		x																
Optional DNA [t]			x															

Appendix 1 Schedule of Activities (cont.)

ADA = anti-drug antibody; AQLQ = Asthma Quality of Life Questionnaire; BID = twice a day; BP = blood pressure; CS = corticosteroid; d = day; eDiary = electronic diary; EQ-5D-5L = EuroQol 5-Dimension 5-Level Questionnaire; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; IWRS = interactive web-based response system; NCS = nasal blockage/congestion score; NPS = nasal polyp score; PK = pharmacokinetic; Q2W = every 2 weeks; RBR = Roche Biosample Repository; SNOT-22 = Sino-Nasal Outcome Test-22; SFU = safety follow-up; Term. = termination; UPSIT = University of Pennsylvania Smell Identification Test; UV = unplanned visit; W = week.

Notes: Cells shaded in gray pertain to patients on Q2W dosing schedule only.

[a] Patients requiring omalizumab dosing every 2 weeks, based on IgE levels and weight as in dosing table (see Appendix 5), will return to clinic every 2 weeks for study drug administration between baseline and Week 22. Vital signs (blood pressure and pulse rate) should be assessed prior to all study drug administration, including administration at Weeks 2, 6, 10, 14, 18, and 22 in patients receiving study drug every 2 weeks.

[b] 4-week safety follow-up period for patients unless they enroll at Week 24 into another available sponsor-permitted study of omalizumab in nasal polyps.

[c] Baseline/Day 1 visit should be targeted for 7 days after the Day -7 visit but may occur as late as 14 days after the Day -7 visit.

[d] The 1st screening visit at Day -35 is defined as Visit 1 (V1) and the 2nd screening visit at Day -7 is defined as Visit 2 (V2). Thereafter, because some patients will require visits every 2 weeks and other patients every 4 weeks (depending on frequency of study drug administration), all remaining visits are referenced by their timing in relationship to baseline (e.g., Week 0 [W0], Week 2 [W2], Week 4 [W4]).

[e] 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.

[f] Patients will be instructed to complete the questions in their eDiary in the morning, within approximately 1 hour of awakening. NCS (1-week recall) at Day -35 used for inclusion criteria will be collected via the EDC system.

[g] Video endoscopy will be read centrally.

[h] 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.

[i] AQLQ assessed only in patients with asthma

[j] For women of childbearing potential

[k] PK samples should be obtained prior to study drug administration. Residual PK samples will be stored and may be used for further PK analysis and/or ADA analysis. See Section 4.5.8 for further details.

[l] Dosing of omalizumab should be based on IgE and weight levels from Day -35, and patients must meet criteria for dosing based on dosing table in Appendix 5 using the IgE value from Day -35. Exceptions to the specific timing of IgE measurement may be made for cases in which there are problems with sample processing (e.g., sample destroyed in shipment requiring repeat phlebotomy).

[m] Total IgE and free IgE samples need to be drawn before study drug administration. Residual samples will be stored and may be used for specific IgE testing. See Section 4.5.8 for further details.

Appendix 1 Schedule of Activities (cont.)

[n] Hematology, including: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)

[o] Chemistry panel (serum or plasma), including: sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, LDH

[p] Coagulation: INR, aPTT, PT

[q] *Viral serology: HIV, HBsAg, total HBcAb, HCV antibody. Viral serology will not be assessed if prohibited by local regulations or ethics committees.*

[r] Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)

[s] Stool ova and parasite examination should be performed on Day -7 in patients with an eosinophil count > 2 times the upper limit of normal on Day -35 and risk factors for parasitic disease, as per Section 4.5.8. Stool ova and parasite examination will be performed by a local laboratory.

[t] Optional DNA collection for donation to RBR. These samples will only be collected from patients who give specific consent for his or her samples to be stored for optional exploratory research

Appendix 2
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

Note: 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 et al. 2013.

Appendix 3
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 4
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 how you feel using this scale: ➔	**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 the 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 5
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 5
Omalizumab Dosing Table for Nasal Polyps (cont.)

Table 2 Blinded Study Drug Dosing Schedule (Number of Injections and Total Injection Volumes)

Dose (mg)	Number of Vials (mL)	Number of Injections	Total Volume Injected (mL) [a]
75	1	1	0.6
150	1	1	1.2
225	2	2	1.8
300	2	2	2.4
375	3	3	3.0
450	3	3	3.6
525	4	4	4.2
600	4	4	4.8

[a] 1.2 mL maximum delivered volume per vial.

Appendix 6 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 ❑

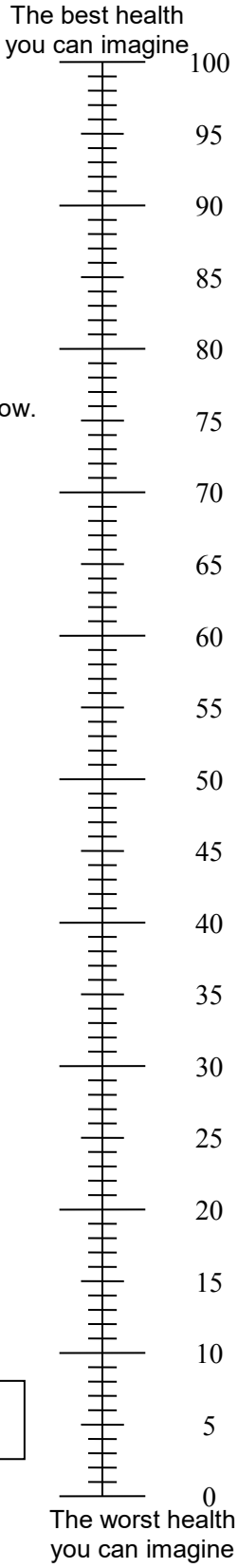
ANXIETY/DEPRESSION

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 6 EuroQol 5-Dimension 5-Level Questionnaire (cont.)

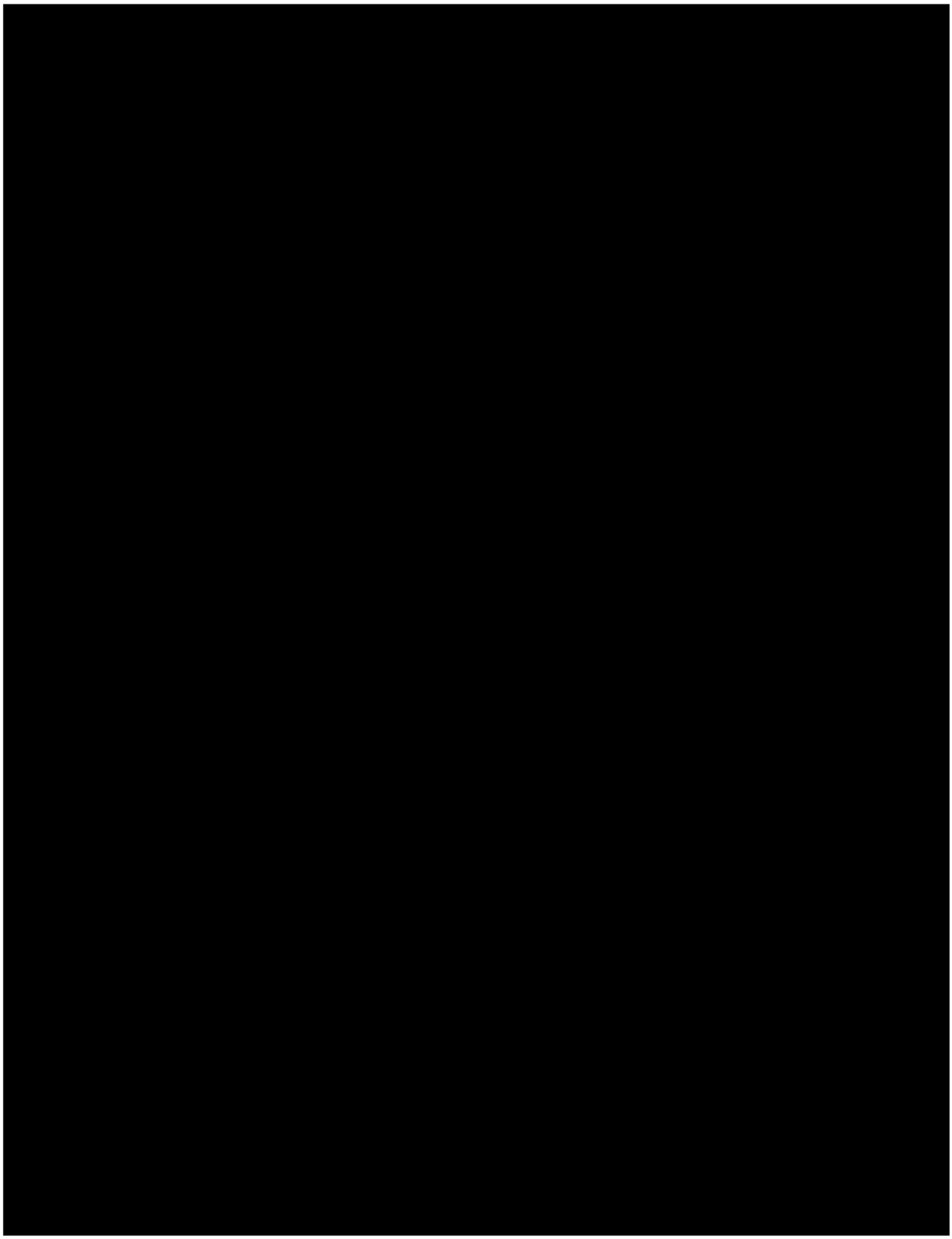
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the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

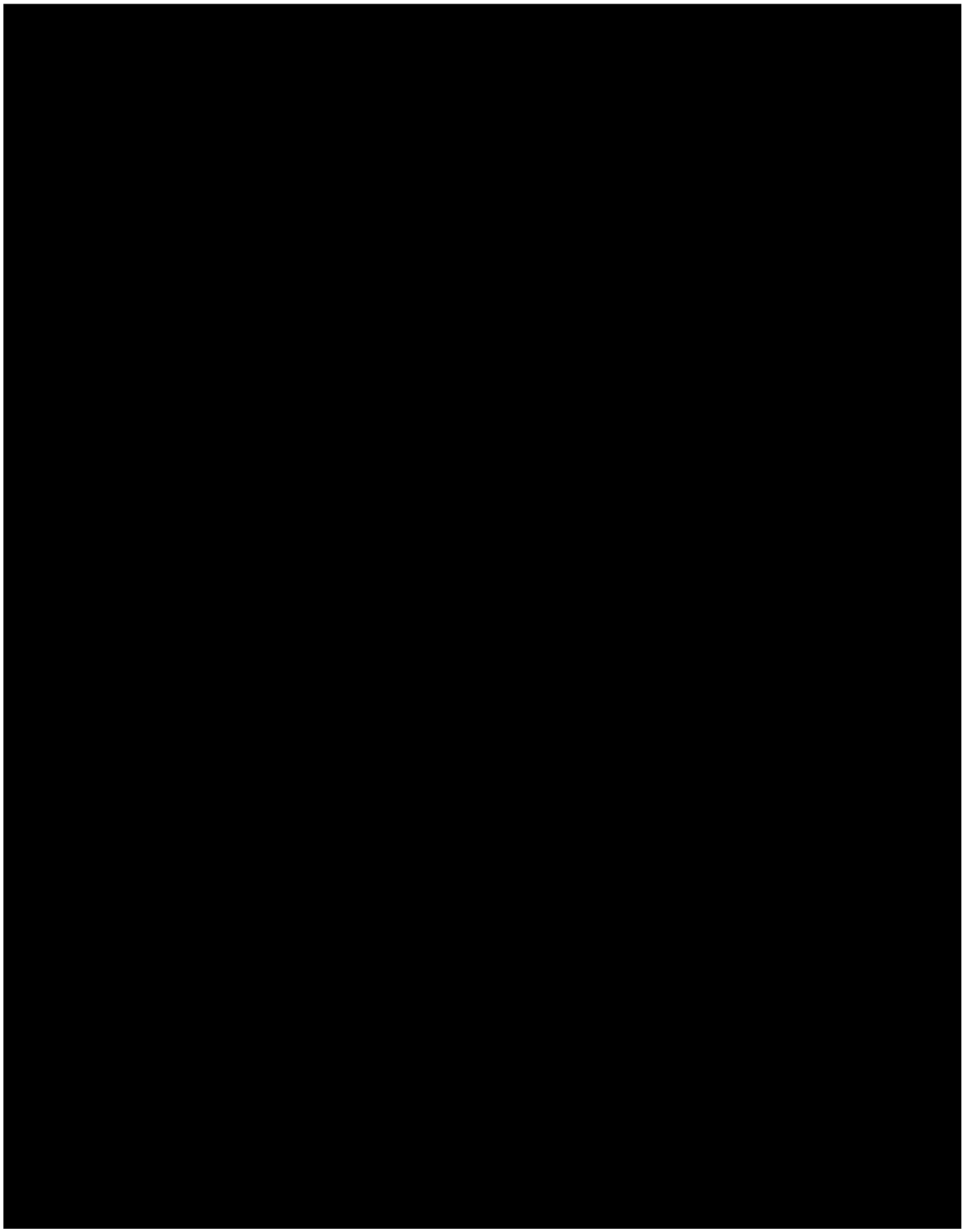
YOUR HEALTH TODAY = ☐

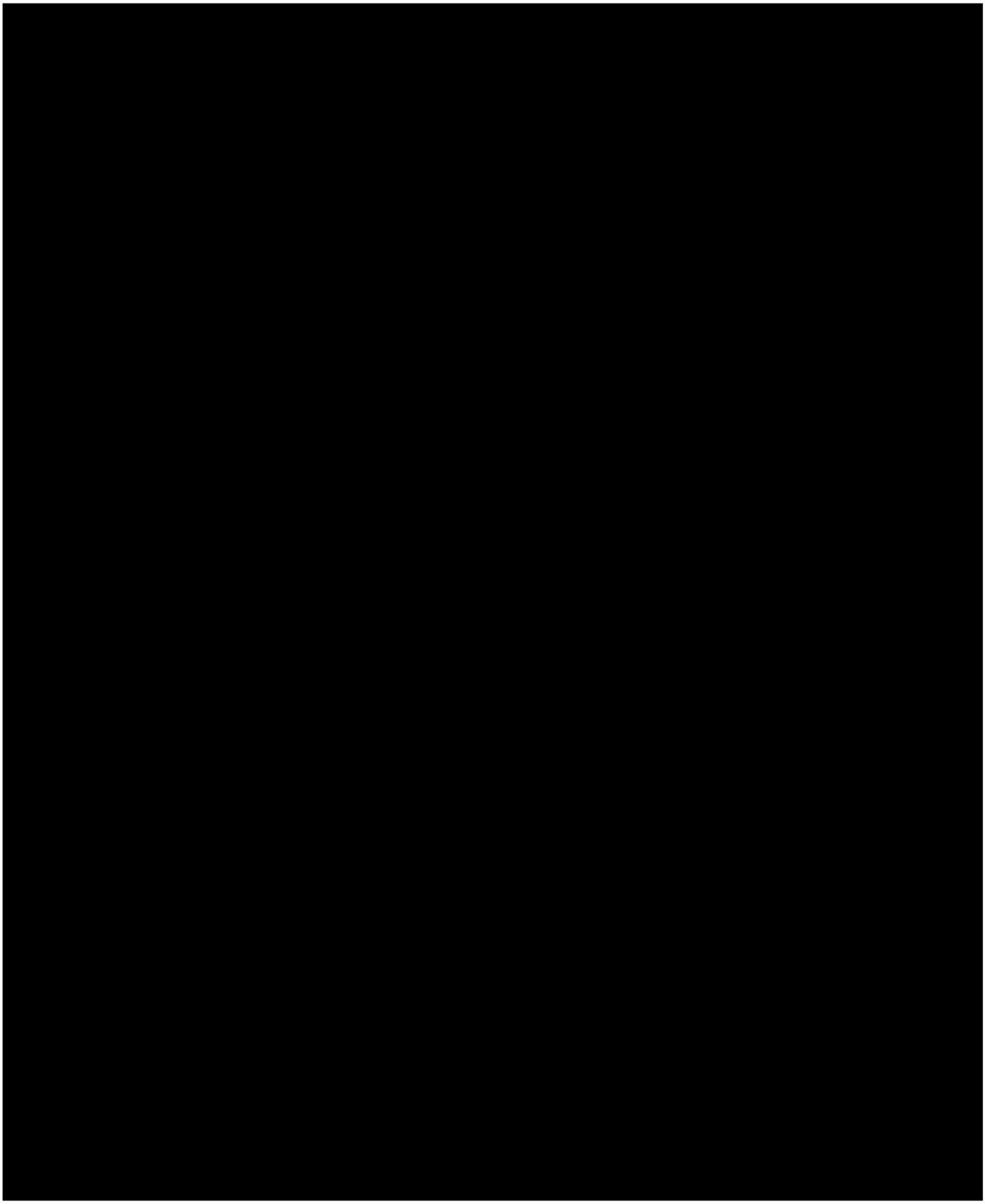


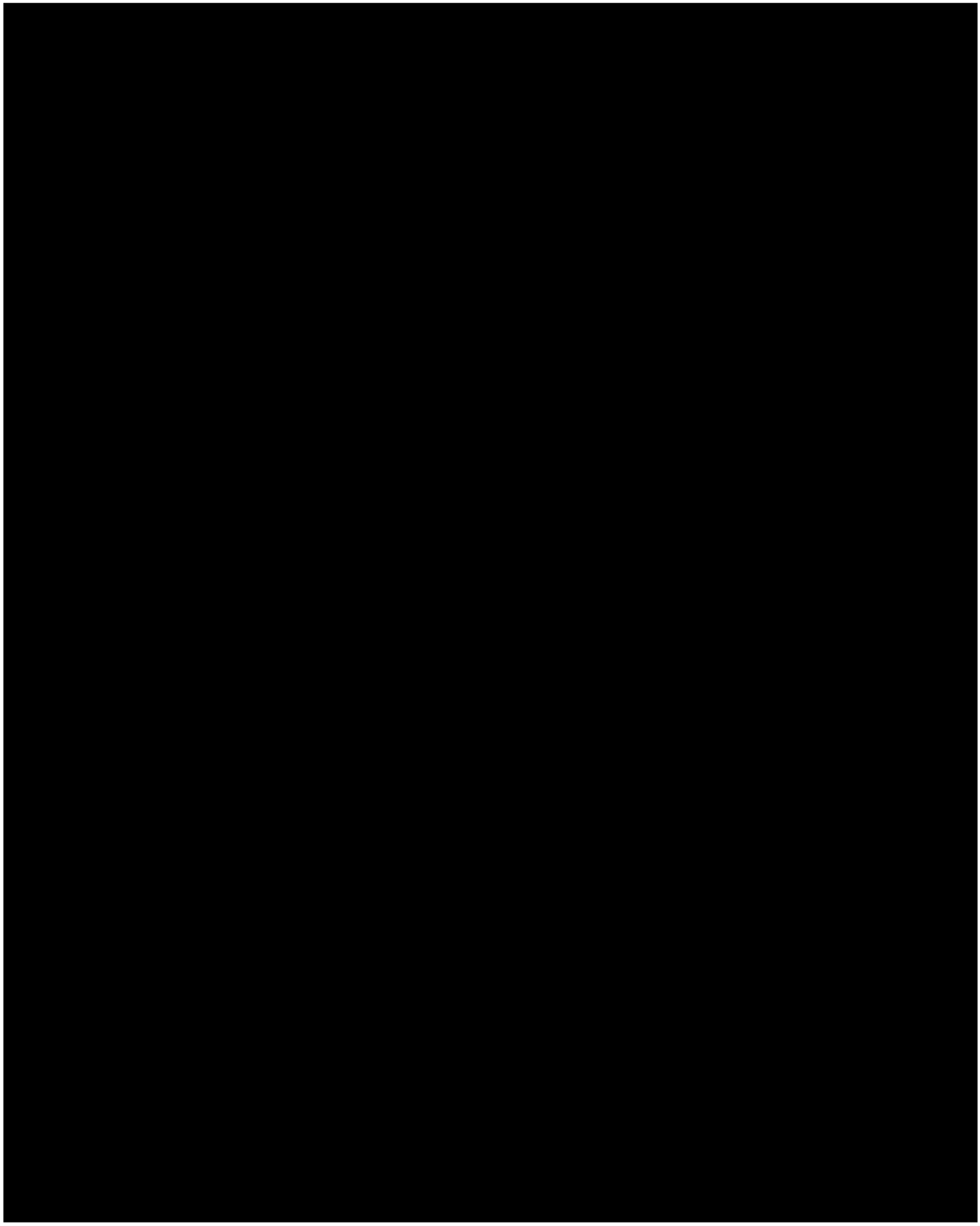
NOTE: This is an example of the content; formatting may be adjusted for adaptation to the tablet electronic patient-reported outcome device.

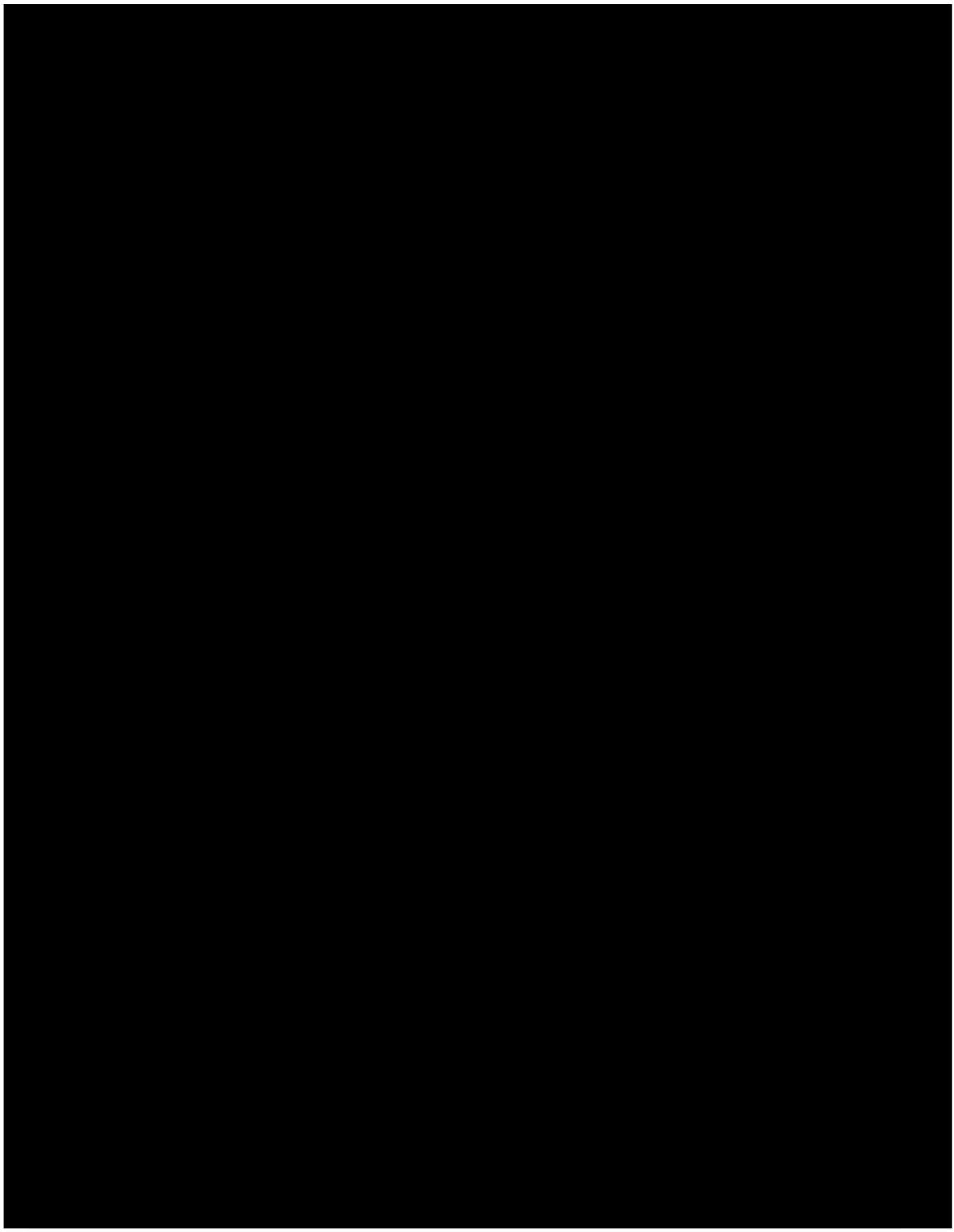
Appendix 7 Asthma Quality of Life Questionnaire











[redacted]

Appendix 8 Study Drug Preparation and Administration

An unblinded pharmacist or other qualified designated individual will prepare the study drug (omalizumab or placebo) injection as outlined below. Study drug for subcutaneous (SC) administration should be prepared using Sterile Water for Injection (SWFI), USP only.

To minimize the risk of potential bias, study site personnel who are responsible for reconstituting and/or administering study drug will not be permitted to conduct any safety or efficacy evaluations. An individual not involved with evaluating the patient must be identified to administer the study drug.

Study drug is for single use only and contains no preservatives. The solution should be used for SC administration within 8 hours following reconstitution when stored in the vial at 2°C–8°C (36°F–46°F), or within 4 hours of reconstitution when stored at room temperature.

The lyophilized product will take 15–20 minutes to dissolve. The fully reconstituted product will appear clear or slightly opalescent and may have a few small bubbles or foam around the edge of the vial. The reconstituted product is somewhat viscous; in order to obtain the full 1.2 mL dose, ALL OF THE PRODUCT MUST BE WITHDRAWN from the vial before expelling any air or excess solution from the syringe.

Administration

1. Draw 1.4 mL SWFI, USP into a 3-cc syringe equipped with a 1-inch, 18-gauge needle.
2. Place the vial upright on a flat surface and, using standard aseptic technique, insert the needle and inject the SWFI directly onto the product.
3. Keeping the vial upright, gently swirl the upright vial for approximately 1 minute to evenly wet the powder. Do not shake.
4. Gently swirl the vial for 5–10 seconds approximately every 5 minutes in order to dissolve any remaining solids. Vials typically take 10–20 minutes to solubilize. Longer reconstitution times may be required. Continue to swirl the vial occasionally during this time to aid in solubilization. There should be no visible gel-like particles in the solution. Do not use if foreign particles are present. Note: It is acceptable to have small bubbles or foam around the edge of the vial. Do not use if the contents of the vial do not dissolve completely in 40 minutes.
5. Invert the vial for 15 seconds to allow the solution to drain toward the stopper. Using a new 3-cc syringe equipped with a 1-inch, 18-gauge needle, insert the needle into the inverted vial. Position the needle tip at the very bottom of the solution in the vial stopper when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel to remove all of the solution from the inverted vial.
6. Replace the 18-gauge needle with a 25-gauge needle for SC administration.

Appendix 8 Study Drug Preparation and Administration(cont.)

7. Expel air, large bubbles, and any excess solution to obtain the required 0.6–1.2 mL dose. A thin layer of small bubbles may remain at the top of the solution in the syringe. Because the solution is slightly viscous, the injection may take 5–10 seconds to administer.
8. A vial delivers 1.2 mL (150 mg) of study drug. For a 75-mg dose, draw up all contents of the vial and dispel the contents of the syringe until only 0.6 mL of the contents remains in the syringe.
9. Cap the syringe. Label the syringe with the patient number, kit number details (Kit 1 or 2), and protocol number (GA39688). The syringe is now ready for use.

Appendix 9 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