PROTOCOL

TITLE:	**A MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO ASSESS THE IMPACT OF OMALIZUMAB ON EXERCISE CAPACITY, PHYSICAL ACTIVITY, AND SLEEP QUALITY IN PATIENTS WITH MODERATE TO SEVERE ALLERGIC ASTHMA**
PROTOCOL NUMBER:	ML41615
VERSION NUMBER:	3
EUDRACT NUMBER:	N/A
IND NUMBER:	N/A
NCT NUMBER:	NCT04195958
TEST PRODUCT:	Omalizumab (RO5489789)
MEDICAL MONITOR:	[redacted] Ph.D.
SPONSOR:	Genentech, Inc.
APPROVAL DATE:	See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
11-Dec-2020 00:09:55	Company Signatory	[redacted]

CONFIDENTIAL

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
1	6 September 2019
2	30 January 2020

PROTOCOL AMENDMENT, VERSION 3:
RATIONALE

Protocol ML41615 has primarily been amended to revise the study design from "randomized, double-blind, placebo-controlled" to an "open-label, single-arm" design to enhance enrollment. Changes to the protocol, along with a rationale for each change, are summarized below:

- The title of the study has been revised to reflect the change in the study design.
- Throughout the protocol the following revisions were made:
  - The following terms have been revised: "test" has been changed to "assess;" "efficacy" has been changed to "effect;" "randomization" has been changed to "enrolled" or "enrollment;" "study drug" has been changed to "omalizumab"
  - The following terms have been deleted: "double-blind," "blinded," "placebo," and "placebo-controlled" as well as text describing the placebo
  - The number of patients for enrollment was revised from 150 patients to 60 patients
  - The dose range for the study was revised from "75 mg to 375 mg" to "150 mg to 375 mg"
- The description of the study design and the study schema were revised to reflect the change in the study design (Section 3.1).
- The total length of the study was changed from "approximately 2 years" to "approximately 1.5 years" (Section 3.2).
- The inclusion criteria regarding asthma was clarified by removing "allergic" (Section 4.1.1).
- The inclusion criteria regarding perennial aeroallergen was clarified as follows "If no historical documentation is available, the skin test or in vitro reactivity to a perennial aeroallergen will need to be performed during screening" (Section 4.1.1).
- The inclusion criteria regarding history of variable airflow obstruction or hyper-responsiveness was clarified as follows "If no documented history is available, an assessment will need to be performed during screening" (Section 4.1.1).
- The exclusion criteria, regarding sleep disorders, was clarified by removing sleep apnea and adding "ongoing physicians treated" sleep disorder and "unrelated to asthma within 6 months prior to screening" (Section 4.1.2).
- Text concerning the method of treatment assignment and blinding was removed. Text concerning the patients enrolled under the randomized, double-blind, placebo-controlled study design was added (Section 4.2).
- During screening, the window for repeating the constant work rate (CWR) test was extended from +5 days to +10 days (Section 4.5.8).
- The description of how the sample size was determined has been updated (Section 6.1).

- The description of the efficacy analyses was revised to align with the revised study design (e.g., mixed-effect model repeated measurement (MMRM) model was changed to descriptive summary statistics) (Section 6.4).
- An interim analysis was added (Section 6.5.1).
- The number of sites was revised from 30−150 to 20−25 to accommodate the revised study design (Section 9.5).
- Appendix 1 has updated to reflect the updated screening period, the additional study treatment visits for patients on a 2-week dosing schedule, and the removal of ECGs and laboratory tests listed above.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in *Book Antiqua* italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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SPONSOR:	Genentech, Inc.

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 to the Sponsor or their designee. Contact details will be provided to the investigator prior to the study start. Please retain the original copy for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO ASSESS THE IMPACT OF OMALIZUMAB ON EXERCISE CAPACITY, PHYSICAL ACTIVITY, AND SLEEP QUALITY IN PATIENTS WITH MODERATE TO SEVERE ALLERGIC ASTHMA**
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NCT NUMBER:	NCT04195958
TEST PRODUCT:	Omalizumab (RO5489789)
PHASE:	IV
INDICATION:	Allergic Asthma
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will *assess* the *effect* of omalizumab on exercise capacity, physical activity, and sleep quality after 24 weeks of treatment in patients with moderate to severe allergic asthma. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Efficacy Objective

The primary efficacy objective is to *assess* the *effect* of omalizumab on the basis of the following endpoint:

- Change from baseline at Week 24 in endurance time (minutes) during cardiopulmonary exercise testing (CPET) at a constant work rate (CWR)

Secondary Efficacy Objectives

The secondary efficacy objective is to *assess* the *effect* of omalizumab on the basis of the following endpoints:

- Change from baseline at Week 24 in physical activity (min/day), as assessed by the physical activity and sleep monitor
- Change from baseline to Week 24 in dynamic hyperinflation at isotime, as measured by inspiratory capacity during CPET at a CWR
- Change from baseline at Week 24 in sleep efficiency, as assessed by the physical activity and sleep monitor

Exploratory Efficacy Objectives

The exploratory efficacy objective is to *assess* the *effect* of omalizumab on the basis of the following endpoints:

- Change from baseline at Week 24 in pre-bronchodilator FEV_1 (liters)
- Percent change from baseline at Week 24 in endurance time (minutes) during a CPET at a CWR
- Change from baseline at Week 24 in percent bronchoconstriction

- Change from baseline at Week 24 in min/day spent in sedentary, light, moderate or vigorous activity as assessed by the physical activity and sleep monitor
- Percent change from baseline to Week 24 of time/day spent in sedentary, light, moderate or vigorous activity as assessed by the physical activity and sleep monitor
- Change from baseline at Week 24 in energy expenditure (kcal/day) as assessed by the physical activity and sleep monitor
- Change from baseline at Week 24 in number of night-time awakenings as assessed by the physical activity and sleep monitor
- Change from baseline at Week 24 in wake after sleep onset (WASO) as assessed by the physical activity and sleep monitor
- Change from baseline at Week 24 in Asthma Daytime Symptom Diary (ADSD) score
- Change from baseline at Week 24 in Asthma Nighttime Symptom Diary (ANSD) score
- Clinician Global Impression of Change (CGIC) at Week 24

Safety Objectives

The safety objective for this study is to *assess* the safety of omalizumab on the basis of the following endpoints:

- Incidence of adverse events
- Incidence of serious adverse events
- Incidence of adverse events leading to discontinuation of omalizumab

Study Design

Description of Study

This study is a Phase IV, *open-label, single-arm*, multicenter study to *assess the effect* of omalizumab on exercise capacity, physical activity, and sleep quality in patients with moderate to severe allergic asthma.

The study will consist of a 4-week screening period, a 24-week treatment period, and a 4-week safety follow-up. Approximately *60* patients will be *enrolled, and* omalizumab will be dosed according to the approved United States Package Insert (USPI) dosing table.

Before performing any study specific tests or evaluations, written informed consent will be obtained for all patients.

During the screening period, patients will be evaluated to determine if they meet all eligibility criteria. Patients will be evaluated for their ability to perform required assessments that will take place during the study, including CPET using a cycle ergometer. Patients will *then* be assessed for adherence with their current asthma controller therapy, the degree of asthma control provided by their standard-of-care asthma medications and compliance with an eDiary, as well as a wrist-worn physical activity and sleep monitor. Patients will also be provided with information about the importance of regular physical activity to improve asthma control.

During the treatment period, at scheduled visits, exercise capacity will be assessed by CPET using a cycle ergometer. Additional measurements will include spirometry, questionnaires, adverse events, blood draws, rescue medication, and health care utilization. Physical activity and sleep will be assessed throughout the study using a wrist worn physical activity and sleep monitor.

Number of Patients

Approximately *60* patients with moderate-to-severe allergic asthma will be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age 18–65 years at time of signing Informed Consent Form
- Body mass index (BMI) of 18–35 kg/m^2

- Physician-diagnosed asthma for at least 12 months prior to screening
- Documented history of positive skin test or in vitro reactivity to a perennial aeroallergen

  If no historical documentation is available, the skin test or in vitro reactivity to a perennial aeroallergen will need to be performed during screening.
- Eligibility per the study drug–dosing table (serum IgE level ≥30 to ≤700 IU/mL and body weight ≥30 to ≤150 kg) and ability to be dosed per the USPI dosing table
- Able to comply with asthma control medication adherence, physical activity and sleep monitoring data collection, and eDiary requirements during screening period. Compliance will be assessed during the last 2 weeks prior to *study enrollment* and non-compliance is defined as:
  - Asthma control medication use <70% of the time during the 2 week period before *study enrollment*
  - Wearing the physical activity and sleep monitor less than approximately 80% of the time (approximately 90 hours during the day and approximately 44 hours at night) for each week during the 2 week period before *study enrollment*
  - Using the eDiary <5 out of 7 days for each week during the 2 week period before *study enrollment*
- Able to safely complete incremental exercise tolerance test at screening
- Able to comply with the study protocol for the duration of the study, in the investigator's judgment, including but not limited to:
  - Able and willing to use a wrist-worn activity and sleep monitor every day and night for the duration of the study
  - Able and willing to use eDiary device throughout the duration of the study
- Pre-bronchodilator FEV_1 of 40%–80% of predicted at screening
- Documented history of variable airflow obstruction or hyper-responsiveness within 12 months of study entry via **at least one** of the following criteria:
  - FEV_1 bronchodilator response ≥12% and ≥200 mL with up to 400 μg albuterol
  - Concentration of methacholine needed to produce a 20% decrease in FEV_1 from baseline (PC20 ≤8 mg/mL or PD20 ≤200 μg)
  - In patients with a forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) <70%, FEV1 variability should be ≥12% spontaneously (e.g., between clinic visits) or in response to oral corticosteroids

    If no documented history is available, an assessment will need to be performed during screening.
- On inhaled corticosteroids (ICS) therapy at a total daily dose ≥500 μg of fluticasone propionate or equivalent and at least one second controller (long-acting beta agonist [LABA], long-acting muscarinic antagonist [LAMA], leukotriene receptor antagonist [LTRA]) for ≥3 months prior to screening, with no changes within 4 weeks prior to screening or during the screening period and no anticipated changes in controller dosing regimens throughout the study
- Uncontrolled asthma during the screening period, defined as an Asthma Control Questionnaire 5 (ACQ5) ≥0.75 score and both of the following symptoms that are not controlled according to EPR (2007) and GINA (2019)
  - Night time awakening *due to asthma in the past 4 weeks*
  - *Activity limitations due to asthma in the past 4 weeks*
- Sleep disturbance due to asthma (e.g. cough, wheezing etc.) in the opinion of the investigator
- Medical Research Council Dyspnoea scale ≥2 at screening

- Impaired exercise capacity defined as VO2max % of predicted ≤80% of healthy volunteers (Koch et al. 2009) during the incremental exercise test at screening
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or to use adequate contraception during the treatment period and for 60 days after the final dose of study drug.
    - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
    - The following are examples of adequate contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and 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. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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
- Treatment with monoclonal antibodies (e.g., omalizumab, mepolizumab, dupilumab) for 6 months prior to screening
- Treatment with non-steroid immunosuppressants (e.g., cyclosporine, methotrexate, azathioprine, mycophenolate, sirolimus, tacrolimus) within 2 months or 5 half-lives, whichever is longer, prior to screening
- Asthma exacerbation, defined as new or increased asthma symptoms that require use of systemic corticosteroids for ≥3 days and/or hospitalization or emergency visit with systemic corticosteroid administration within 4 weeks prior to screening
- Intubation for respiratory failure due to asthma within 12 months prior to screening
- Maintenance oral corticosteroid therapy, defined as daily or alternate-day oral corticosteroid within 3 months prior to screening or during the screening period
- Treatment with systemic (oral, IV, or IM) corticosteroids within 4 weeks prior to screening or during the screening period for any reason, including an acute exacerbation event
- Inability to withhold short acting bronchodilators for a period up to 6 hours
- Isolated diagnosis of exercise induced asthma without chronic symptoms
- History of interstitial lung disease, COPD, or other clinically significant lung disease other than asthma
- Current participation or participation in the last 6 months in pulmonary rehabilitation prior to screening
- 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) or abnormality in clinical laboratory tests that precludes the patient's safe participation in and completion of the study in the opinion of the investigator

- Elevated IgE due to hyperimmunoglobulin E syndrome or allergic bronchopulmonary aspergillosis
- Unable to complete cardiopulmonary exercise testing and/or perform physical activity due to underlying cardiac, neurologic or orthopedic conditions
- *Ongoing physician-treated* sleep disorder *that is unrelated to asthma within 6 months prior to screening*
- Use of any prescription or over-the-counter sedative sleep medication for the duration of the study (e.g., zolpidem)
- Physician determination of patient lifestyle that can interfere with study endpoints, (e.g., rotating shifts, any prescription or over the counter medical cannabis, use of recreational drugs, etc.)
- Planned major surgery during the course of the study
- Current smoker or past smoker with >10 pack years
- Known HIV infection at screening
- Known acute or chronic infections with hepatitis C virus (HCV) and hepatitis B virus (HBV) at screening
- 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
  - Note: Antibiotics are considered to include any antimicrobial therapy used to treat bacterial, fungal, parasitic, viral, or other infections.
- Active parasitic infection, including nematodes (e.g., Ascaris, Ancylostoma), platyhelminths (e.g., Schistosoma), or Listeria monocytogenes infection within 6 months prior to screening
- Active tuberculosis requiring treatment within 12 months prior to screening
  - Patients who have completed treatment for tuberculosis at least 12 months prior to screening and have no evidence of recurrent disease are permitted.
- Initiation of or change in allergen immunotherapy within 3 months prior to screening.
- Initiation of or change in aspirin desensitization within 4 months prior to screening.
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 60 days after the last dose of omalizumab
  - Women of childbearing potential must have a negative serum pregnancy test result during the screening period.
- History of alcohol, drug, or chemical abuse within 6 months of screening

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 28 weeks after the last patient is *enrolled*.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately *1.5* years.

Investigational Medicinal Product

The investigational medicinal product (IMP) for this study is omalizumab. Omalizumab will be supplied by Genentech.

Test Product (Investigational Drug)

Omalizumab will be administered subcutaneously to patients by qualified personnel who are not involved with conducting safety or efficacy evaluations using a prefilled syringe. The

recommended injection sites are the upper arm and the front and middle of the thighs. Do not inject into moles, scars, bruises, or areas where the skin is tender, red, or hard, or if there are breaks in the skin. Choose a different injection site for each new injection at least 1 inch from the area used for the last injection. 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) and study drug may be administered every 2 or 4 weeks. Assignment of the *omalizumab* dose will be determined by using the study drug–dosing table. Based on the dosing required, some patients may need more than one injection. Do not administer more than one injection per injection site. The prefilled syringe is to be used for single use administration only.

Omalizumab 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. Before administration, set aside the study drug PFS carton unopened for at least 15–30 minutes so the syringe can warm up on its own to room temperature. For further details on drug handling, see the pharmacy manual.

After administration of omalizumab, patients should be observed 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 (see Appendix 2).

For additional details, see the pharmacy manual.

Statistical Methods

Primary Analysis

The primary analysis will *assess* the *effect of omalizumab* in the primary endpoint, change from baseline at Week 24 in endurance time (minutes).

Determination of Sample Size

The target sample size of 54 is based on feasibility.

The sample size was calculated based on data from Bonini 2019, which suggested that an improvement in the endurance time of at least 1 minute 40 seconds from baseline or >33% is clinically important. When the sample size is 54, a two-sided 95% confidence interval for the mean change from baseline will extend 1 minute 4 seconds from the observed mean change, assuming that the standard deviation is known to be 4 minutes and the confidence interval is based on the z-distribution (see table below). Assuming a 10% withdrawal rate, a sample size of 60 will be enrolled.

Confidence Intervals for Different Standard Deviations with Sample Size of 54

Standard Deviation	*95% Confidence Interval*
4 minutes	*(0 min 36 sec, 2 min 44 sec)*
5 minutes	*(0 min 20 sec, 3 min 0 sec)*
6 minutes	*(0 min 4 sec, 3 min 16 sec)*

Interim Analyses

The Sponsor may conduct interim analyses of efficacy/safety and no formal multiplicity adjustment will be performed. If performed, these interim analyses will not affect conduct of the study unless safety signals were identified. The decision to conduct such an interim analysis and its timing will be documented in the Sponsor's study master file prior to the conduct of the interim analysis.

The Clinical Study Report will also document that such an interim analysis occurred. The interim analysis, should it occur, will be performed by the Sponsor study team.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACQ5	Asthma Control Questionnaire 5
ADA	*anti-drug antibody*
ADSD	Asthma Daytime Symptom Diary
AE	*adverse event*
ANSD	Asthma Nighttime Symptom Diary
ATE	*arterial thrombotic event*
ATS/ERS	*American Thoracic Society/European Respiratory Society*
BMI	*body mass index*
BUN	*blood urea nitrogen*
CI	confidence interval
CGIC	Clinician Global Impression of Change
ClinRO	*Clinician-Reported Outcome*
COPD	*chronic* obstructive pulmonary disease
CPET	cardiopulmonary exercise testing
CSU/CIU	chronic spontaneous urticaria/chronic idiopathic urticaria
CRO	contract research organization
CWR	constant work rate
EC	Ethics Committee
ECG	*Electrocardiogram*
eCRF	electronic Case Report Form
EDC	electronic data capture
eDiary	*electronic Diary*
FDA	Food and Drug Administration
FEF_{25-75}	forced expiratory flow during the middle half of the forced vital capacity
FVC	forced vital capacity
FEV_1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
GETE	Global Evaluation of Treatment Effectiveness
HBV	*hepatitis B virus*
HCV	*hepatitis C virus*
HIPAA	Health Insurance Portability and Accountability Act
HIV	*human immunodeficiency virus*
IC	*inspiratory capacity*
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroids
iDMC	*independent Data Monitoring Committee*
IET	incremental exercise test
IgE	immunoglobulin E

Abbreviation	Definition
IM	*Intramuscular*
IMP	*investigational medicinal product*
IND	*Investigational New drug*
IRB	Institutional Review Board
IV	*Intravenous*
IWRS	*interactive voice or web-based response system*
LABA	long-acting beta agonist
LAMA	long-acting muscarinic antagonist
LDH	*lactate dehydrogenase*
LTRA	leukotriene receptor antagonist
LPLV	last patient, last visit
NCI CTCAE	*National Cancer Institute Common Terminology Criteria for Adverse Events*
NHLBI	National Heart, Lung, and Blood Institute of the National Institutes of Health
PRO	patient-reported outcome
RBC	*red blood cell*
SABA	*short*-acting β-agonist
SAMA	short-acting muscarinic antagonist
SAP	*Statistical Analysis Plan*
SD	*standard deviation*
SWFI	*Sterile Water for Injection*
ULN	*upper limit of normal*
USP	*United States Pharmacopeia*
USPI	*U. S.* Package Insert
WASO	wake after sleep onset
WBC	*White Blood Cell*

1. BACKGROUND

Omalizumab is an anti-IgE recombinant DNA-derived humanized monoclonal antibody designed to treat IgE-mediated inflammation by reducing the concentration of free IgE in blood by selectively binding to human IgE. Atopic patients respond immunologically to common, naturally occurring allergens by producing IgE antibodies. The IgE molecules circulate in the blood and bind tightly to the high affinity IgE binding receptor (FcεRI) on the surface of basophils and mast cells in the circulation and various tissues. Omalizumab selectively binds to human IgE at the same site as does the FcεRI (Schulman 2001).

The approved indications for omalizumab (Xolair®) are allergic asthma and chronic spontaneous urticaria/chronic idiopathic urticaria (CSU/CIU).

1.1 BACKGROUND ON ASTHMA

Asthma is a multifactorial chronic disease of the airways that involves a complex interaction of airflow obstruction, bronchial airway hyper-responsiveness and an underlying inflammation (NHLBI 2007). This interaction can be highly variable among patients and within patients over time, with distinct but overlapping patterns that reflect different aspects of the disease, such as intermittent versus persistent or acute versus chronic manifestations.

The causal role of IgE in allergic disease is well established (Johansson et al. 1967; Ishizaka et al. 1970). The allergic cascade is initiated when IgE, bound to high-affinity FcεRI receptors on the surface of basophils and mast cells, are cross-linked by allergen, resulting in the degranulation of these effector cells and the release of inflammatory mediators, such as histamine and leukotrienes. Epidemiologic studies have consistently shown that patients with asthma have elevated levels of IgE compared with nonasthmatic populations (Burrows 1989; Criqui 1990; Borish 2005). IgE antibodies have a relationship with asthma severity and the airway's early response to allergens through binding and signaling via high affinity IgE receptors (NHLBI 2003; Borish 2005).

It is estimated that the population-based proportion of asthma cases attributable to atopy is between 50% – 60% (Pearce 1999; Arbes 2007). Studies have confirmed that sensitization among susceptible populations to certain indoor allergens, such as house-dust mites, animal dander, and cockroaches, or, to a lesser extent, outdoor allergens, such as the fungus Alternaria or certain pollens (e.g., grass, ragweed), is a risk factor for developing asthma (NHLBI 2007). Data from longitudinal studies and prospective clinical trials indicate that between 60% – 82% of children with asthma and 48% of adults with asthma have at least 1 positive skin test (Ostergaard 1985; Lin 1995; Remes 1996).

It is estimated that approximately 55% – 60% of asthma patients have uncontrolled disease (Peters 2007; Stanford 2010). Analysis of data from the TENOR study

demonstrate that asthma exacerbations are frequent in patients with severe or difficult-to-treat asthma, notwithstanding treatment with multiple long-term asthma controllers, management by asthma specialists, and lung function of greater than 80% of predicted values (Zeiger 2009; Zeiger 2012).

1.2 BACKGROUND ON OMALIZUMAB

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

Omalizumab has demonstrated consistent effectiveness in patients previously inadequately controlled with standard asthma treatments. In two identical pivotal studies in severe allergic asthma patients receiving inhaled corticosteroids, omalizumab was superior to placebo in reducing asthma exacerbations and in inducing a clinically important improvement in daily symptom score and rescue medications (Busse et al. 2001; Solèr et al. 2001). In another study in severe allergic asthma patients receiving maintenance inhaled corticosteroids and a long acting beta2-agonist, omalizumab treatment resulted in the ability to reduce the dose of inhaled steroids compared to placebo and a greater proportion of patients on omalizumab were able to reduce their inhaled steroid use (Holgate et al. 2004). Subsequent additional studies confirmed the beneficial effects on asthma outcomes of omalizumab compared to placebo (Hanania et al. 2011; Humbert et al. 2005). Safety of omalizumab treatment has been evaluated in approximately 14,500 patients included in clinical studies (Phase I–III) for asthma and CSU/CIU. The most studied population, patients with moderate to severe allergic asthma, includes approximately 3500 patients from the double-blind, placebo-controlled studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The current standard of care for the management of moderate to severe asthma is the use of inhaled corticosteroids and a second controller medication. Despite these medications, a proportion of patients remains uncontrolled and will need additional medications, including biologics, to reduce the risk of asthma exacerbations and to control symptoms.

Patients with asthma are less physically active and are more sedentary than healthy controls (Lang, 2019; Cordova-Revera, 2018). Frequent routine exercise has been shown to improve quality of life, symptom control, and decrease in systemic inflammation in patients with asthma (Lang, 2019; Cordova-Revera, 2018). In addition, it has been shown that the average sleep duration per night is less in patients with asthma compared to controls (Yang et al. 2019). Sleep disturbance due to nocturnal asthma symptoms, including chest tightness, shortness of breath, cough, and/or wheezing may impact the ability to perform daily activities and quality of life. Increasing the capacity to perform physical activities and improving sleep duration and quality may improve overall health status (Agusti et al. 2016). Therefore, it is important for patients with asthma to

improve sleep to enable them to be more physically active and consequently have better asthma symptom control.

Currently, methods of assessing sleep quality and impairment of daily activities are often limited to patient reported outcomes (PRO). Omalizumab has shown improvement in asthma symptoms obtained by PROs, which include questions on sleep and limitations in daily activity (Busse, 2001, Solèr 2001). The limitation of these PROs is that they usually rely on the patient's recollection over a previous time period, which are based on patient's recall and can be limited to days or week in duration.

There is limited data available that objectively measures exercise capacity, the level of physical activity, and sleep quantity and quality upon treatment of asthma patients with any asthma treatment. A small study using omalizumab showed promising preliminary data using cardiopulmonary exercise testing (CPET) (Schaper 2011). Omalizumab improved the initially impaired exercise capacity and these improvements were associated with clinical response, as measured by Global Evaluation of Treatment Effectiveness (GETE).

The aim of this study is to extend these findings and objectively assess whether omalizumab can improve the patient's exercise capacity, physical activity and improve sleep quality. The ability to improve exercise capacity will be assessed by performing CPET at a constant work rate (CWR) on a cycle ergometer. CPET at a CWR is relatively independent from motivation and will provide information on whether omalizumab can improve the ability to perform exercise. Although limited information is available in patients with asthma, CPET at a CWR is a well-accepted method in patients with chronic obstructive pulmonary disease (COPD) in monitoring response to therapeutic interventions. CPET will be performed under close monitoring by trained and qualified personnel.

In addition to assessing exercise capacity, patients will be provided with a wrist-worn Physical activity and sleep monitor, which will capture physical activity levels and sleep data continuously over the duration of the study. The physical activity data will provide information on whether improved exercise capacity is translated into patients being more physically active. The sleep data will allow assessments of changes in sleep quality in the patient's natural environment and usual asthma triggers.

2. OBJECTIVES AND ENDPOINTS

This study will *assess* the *effect* of omalizumab on exercise capacity, physical activity, and sleep quality after 24 weeks of treatment in patients with moderate to severe allergic asthma. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective is to *assess* the *effect* of omalizumab on the basis of the following endpoint:

- Change from baseline at Week 24 in endurance time (minutes) during a CPET at a CWR

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objective is to *assess* the *effect* of omalizumab on the basis of the following endpoints:

- Change from baseline at Week 24 in physical activity (min/day), as assessed by the physical activity and sleep monitor
- Change from baseline to Week 24 in dynamic hyperinflation at isotime, as measured by inspiratory capacity during CPET at a CWR
- Change from baseline at Week 24 in sleep efficiency, as assessed by the physical activity and sleep monitor

2.1.3 Exploratory Efficacy Objectives

The exploratory efficacy objective is to *assess* the *effect* of omalizumab on the basis of the following endpoints:

- Change from baseline at Week 24 in pre-bronchodilator FEV_1 (liters)
- Percent change from baseline at Week 24 in endurance time (minutes) during a CPET at a CWR
- Change from baseline at Week 24 in percent bronchoconstriction
- Change from baseline at Week 24 in min/day spent in sedentary, light, moderate or vigorous activity as assessed by the physical activity and sleep monitor
- Percent change from baseline to Week 24 of time/day spent in sedentary, light, moderate or vigorous activity as assessed by the physical activity and sleep monitor
- Change from baseline at Week 24 in energy expenditure (kcal/day) as assessed by the physical activity and sleep monitor
- Change from baseline at Week 24 in number of night-time awakenings as assessed by the physical activity and sleep monitor
- Change from baseline at Week 24 in wake after sleep onset (WASO) as assessed by the physical activity and sleep monitor
- Change from baseline at Week 24 in Asthma Daytime Symptom Diary (ADSD) score
- Change from baseline at Week 24 in Asthma Nighttime Symptom Diary (ANSD) score
- Clinician Global Impression of Change (CGIC) at Week 24

2.2 SAFETY OBJECTIVES

The safety objective for this study is to *assess* the safety of omalizumab on the basis of the following endpoints:

- Incidence of adverse events
- Incidence of serious adverse events
- Incidence of adverse events leading to discontinuation of omalizumab

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This study is a Phase IV, *open-label, single-arm*, multicenter study to *assess the effect* of omalizumab on exercise capacity, physical activity, and sleep quality in patients with moderate to severe allergic asthma.

The study will consist of a 4-week screening period, a 24-week treatment period, and a 4-week safety follow-up. Approximately *60* patients will be *enrolled, and* omalizumab will be dosed according to the approved United States Package Insert (USPI) dosing table.

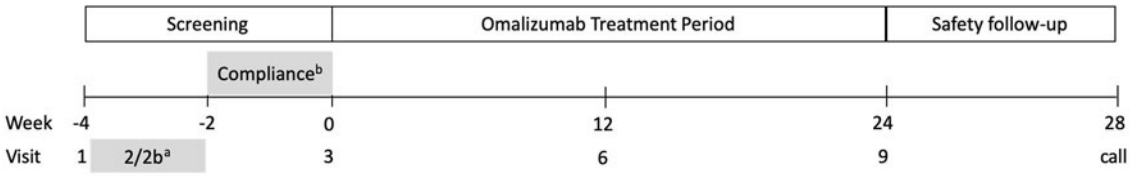
Before performing any study specific tests or evaluations, written informed consent will be obtained for all patients.

During the screening period, patients will be evaluated to determine if they meet all eligibility criteria. Patients will be evaluated for their ability to perform required assessments that will take place during the study, including CPET using a cycle ergometer. Patients will *then* be assessed for adherence with their current asthma controller therapy, the degree of asthma control provided by their standard-of-care asthma medications and compliance with an eDiary, as well as a wrist-worn physical activity and sleep monitor. Patients will also be provided with information about the importance of regular physical activity to improve asthma control.

During the treatment period, at scheduled visits, exercise capacity will be assessed by CPET using a cycle ergometer. Additional measurements will include spirometry, questionnaires, adverse events, blood draws, rescue medication, and health care utilization. Physical activity and sleep will be assessed throughout the study using a wrist worn physical activity and sleep monitor.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



Note: Visit 3 is the enrollment visit. Patients will enroll in the study, perform all baseline assessments, and receive omalizumab. A patient may screen fail at Visit 3 due to non-compliance with the physical activity and sleep monitor and/or eDiary.

[a] Visits 2 and 2b are flexible visits and can be performed any time after Visit 1 and before Week -2.

[b] Patients will need to use the eDiary and wear the physical activity and sleep monitor to assess compliance with the devices.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 28 weeks after the last patient is *enrolled*.

Each patient will be followed approximately 32 weeks (4-week screening period, 24-week treatment period, 4-week safety follow-up period).

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately *1.5* years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Xolair Dose and Schedule

Dosing of omalizumab will be according to the approved USPI. Omalizumab will be administered from *150* mg to 375 mg by subcutaneous injection every 2 or 4 weeks. The dose (mg) and dosing frequency will be determined by serum total IgE level (IU/mL), measured before the start of study treatment, and by body weight (kg).

3.3.2 Rationale for Patient Population

The study population includes patients with moderate to severe asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled despite daily use of inhaled corticosteroids and a second controller. As the study aims to *assess* changes in exercise capacity, physical activity, and sleep, patients must demonstrate evidence of impaired exercise capacity, sleep disturbance due to asthma, and interference with daily activities. The patient population will include patients who are willing and able to perform physical activity. Therefore, patients with cardiac, neurologic, or orthopedic conditions and patients who are unable to safely complete CPET or who are not able or willing to wear a physical activity and sleep monitor for the duration of the study will be excluded from the study. Patients with

ongoing physician treated sleep disorders *that are unrelated to asthma*, will also not be eligible to participate in the study.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately *60* patients with moderate-to-severe allergic asthma will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age 18–65 years at time of signing Informed Consent Form
- Body mass index (BMI) of 18–35 kg/m^2
- Physician-diagnosed asthma for at least 12 months prior to screening
- Documented history of positive skin test or in vitro reactivity to a perennial aeroallergen

  If no historical documentation is available, the skin test or in vitro reactivity to a perennial aeroallergen will need to be performed during screening.
- Eligibility per the study drug–dosing table (serum IgE level ≥30 to ≤700 IU/mL and body weight ≥30 to ≤150 kg) and ability to be dosed per the USPI dosing table
- Able to comply with asthma control medication adherence, physical activity and sleep monitoring data collection, and eDiary requirements during screening period. Compliance will be assessed during the last 2 weeks prior to *study enrollment* and non-compliance is defined as:
  - Asthma control medication use <70% of the time during the 2 week period before *study enrollment*
  - Wearing the physical activity and sleep monitor less than approximately 80% of the time (approximately 90 hours during the day and approximately 44 hours at night) for each week during the 2 week period before *study enrollment*)
  - Using the eDiary <5 out of 7 days for each week during the 2 week period before *study enrollment*
- Able to safely complete incremental exercise tolerance at screening
- Able to comply with the study protocol for the duration of the study, in the investigator's judgment, including but not limited to:
  - Able and willing to use a wrist-worn physical activity and sleep monitor every day and night for the duration of the study
  - Able and willing to use eDiary device throughout the duration of the study
- Pre-bronchodilator FEV_1 of 40%–80% of predicted at screening

- Documented history of variable airflow obstruction or hyper-responsiveness within 12 months of study entry via <u>at least one</u> of the following criteria:
  - FEV1 bronchodilator response ≥12% and ≥200 mL with up to 400 μg albuterol
  - Concentration of methacholine needed to produce a 20% decrease in FEV1 from baseline (PC20 ≤8 mg/mL or PD20 ≤200 μg)
  - In patients with a forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) <70%, FEV1 variability should be ≥12% spontaneously (e.g., between clinic visits) or in response to oral corticosteroids

    If no documented history is available, an assessment will need to be performed during screening.
- On inhaled corticosteroid (ICS) therapy at a total daily dose ≥500 μg of fluticasone propionate or equivalent and at least one second controller (long-acting beta agonist [LABA], long-acting muscarinic antagonist [LAMA], leukotriene receptor antagonist [LTRA]) for ≥3 months prior to screening, with no changes within 4 weeks prior to screening or during the screening period and no anticipated changes in controller dosing regimens throughout the study
- Uncontrolled asthma during the screening period, defined as an Asthma Control Questionnaire 5 (ACQ5) ≥0.75 score and both of the following symptoms that are not controlled according to EPR (2007) and GINA (2019)
  - Night time awakening *due to asthma in the past 4 weeks*
  - *Activity limitations due to asthma in the past 4 weeks*
- Sleep disturbance due to asthma (e.g., cough, wheezing, etc.) in the opinion of the investigator
- Medical Research Council Dyspnoea scale ≥2 at screening
- Impaired exercise capacity defined as VO_2max % of predicted ≤80% of healthy volunteers (Koch et al. 2009) during the incremental exercise test at screening
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or to use adequate contraception during the treatment period and for 60 days after the final dose of study drug.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  The following are examples of adequate contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with spermicide; and cap, diaphragm, or sponge with spermicide.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and 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.
If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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
- Treatment with monoclonal antibodies (e.g., omalizumab, mepolizumab, dupilumab) for 6 months prior to screening
- Treatment with non-steroid immunosuppressants (e.g., cyclosporine, methotrexate, azathioprine, mycophenolate, sirolimus, tacrolimus) within 2 months or 5 half-lives, whichever is longer, prior to screening
- Asthma exacerbation, defined as new or increased asthma symptoms that require use of systemic corticosteroids for ≥3 days and/or hospitalization or emergency visit with systemic corticosteroid administration within 4 weeks prior to screening
- Intubation for respiratory failure due to asthma within 12 months prior to screening
- Maintenance oral corticosteroid therapy, defined as daily or alternate-day oral corticosteroid within 3 months prior to screening or during the screening period
- Treatment with systemic (oral, IV, or IM) corticosteroids within 4 weeks prior to screening or during the screening period for any reason, including an acute exacerbation event
- Inability to withhold short acting bronchodilators for a period up to 6 hours
- Isolated diagnosis of exercise induced asthma without chronic symptoms
- History of interstitial lung disease, COPD, or other clinically significant lung disease other than asthma
- Current participation or participation in the last 6 months in pulmonary rehabilitation prior to screening
- 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) or abnormality in clinical laboratory tests that precludes the patient's safe participation in and completion of the study in the opinion of the investigator
- Elevated IgE due to hyperimmunoglobulin E syndrome or allergic bronchopulmonary aspergillosis
- Unable to complete cardiopulmonary exercise testing and/or perform physical activity due to underlying cardiac, neurologic or orthopedic conditions
- *Ongoing physician-treated* sleep disorder *that is unrelated to asthma within 6 months prior to screening*
- Use of any prescription or over-the-counter sedative sleep medication for the duration of the study (e.g., zolpidem)
- Physician determination of patient lifestyle that can interfere with study endpoints, (e.g., rotating shifts, any prescription or over the counter medical cannabis, use of recreational drugs, etc.)
- Planned major surgery during the course of the study
- Current smoker or past smoker with >10 pack years
- Known HIV infection at screening
- Known acute or chronic infections with hepatitis C virus (HCV) and hepatitis B virus (HBV) at screening
- 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
  - Note: Antibiotics are considered to include any antimicrobial therapy used to treat bacterial, fungal, parasitic, viral, or other infections.
- Active parasitic infection, including nematodes (e.g., Ascaris, Ancylostoma), platyhelminths (e.g., Schistosoma), or Listeria monocytogenes infection within 6 months prior to screening
- Active tuberculosis requiring treatment within 12 months prior to screening

  Patients who have completed treatment for tuberculosis at least 12 months prior to screening and have no evidence of recurrent disease are permitted.
- Initiation of or change in allergen immunotherapy within 3 months prior to screening.
- Initiation of or change in aspirin desensitization within 4 months prior to screening.
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 60 days after the last dose of omalizumab

Women of childbearing potential must have a negative serum pregnancy test result during the screening period.

- History of alcohol, drug, or chemical abuse within 6 months of screening

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label, single-arm study.

4.2.1 *Patient ID* Assignment

After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number from an interactive voice or web-based response system (IWRS*)* at *Visit 3.*

4.2.2 *Patients Enrolled Under the Double-Blind, Placebo-Controlled Protocol*

Patients who have been enrolled under the double-blind, placebo-controlled protocol (i.e., Version 1 or Version 2) can continue in the open-label study if they choose. Study drug assignments will be unblinded, and patients who were assigned to the omalizumab arm will continue per schedule. Patients who were assigned to the placebo arm will need to restart at Visit 3/baseline. Before enrolling patients previously receiving placebo, please contact the medical monitor. After enrollment follow the study schedule through the treatment and safety period.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

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

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Omalizumab

Omalizumab will be supplied by the sponsor. Omalizumab is a sterile, preservative-free, clear to slightly opalescent and colorless to pale brownish-yellow solution for subcutaneous injection. Omalizumab is provided as prefilled single use syringe and is available in two doses. The prefilled syringes are for single use and should not be re-used or tampered with.

Each 75 mg prefilled syringe delivers 75 mg omalizumab in 0.5 mL and contains L-arginine hydrochloride (21.05 mg), L-histidine (0.68 mg), L-histidine hydrochloride monohydrate (1.17 mg), and polysorbate 20 (0.2 mg) in Sterile Water for Injection (SWFI), United States Pharmacopeia (USP).

Each 150 mg prefilled syringe delivers 150 mg omalizumab in 1 mL and contains L-arginine hydrochloride (42.1 mg), L-histidine (1.37 mg), L-histidine hydrochloride monohydrate (2.34 mg), and polysorbate 20 (0.4 mg) in SWFI, USP.

The removable needle cap of Xolair solution for injection in pre-filled syringe contains a derivative of natural rubber latex. Although no natural rubber latex is detected in the removable needle cap, the safe use of Xolair solution for injection in pre-filled syringe in latex-sensitive individuals has not been studied.

For additional details, see the pharmacy manual and the Omalizumab Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.3.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Dose modifications or interruptions are not permitted during the study. Cases of omalizumab accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.13.

4.3.2.1 Omalizumab

Study drug will be administered subcutaneously to patients by qualified personnel who are not involved with conducting safety or efficacy evaluations using a prefilled syringe. The recommended injection sites are the upper arm and the front and middle of the thighs. Do not inject into moles, scars, bruises, or areas where the skin is tender, red, or hard, or if there are breaks in the skin. Choose a different injection site for each new injection at least 1 inch from the area used for the last injection. 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) and study drug may be administered every 2 or 4 weeks. Assignment of the study drug dose will be determined by using the study drug–dosing table (see Appendix 8). Based on the dosing required, some patients may need more than one injection. Do not administer more than one injection per injection site. The prefilled syringe is to be used for single use 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. Before administration, set aside the study drug PFS carton unopened for at least 15–30 minutes so the syringe can warm up on its own to room temperature. For further details on drug handling, see the pharmacy manual.

After administration of omalizumab, patients should be observed 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 (see Appendix 2).

For additional details, see the pharmacy manual

4.3.3 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 IMPs supplied by the Sponsor using the IWRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

4.3.4 Continued Access to Omalizumab

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide omalizumab to patients who have completed the study. The Sponsor may evaluate whether to continue providing omalizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

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

4.4 CONCOMITANT THERAPY

All medications used for the treatment of asthma should be recorded on the appropriate electronic Case Report Form (eCRF). Other medications (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 Week -4 (first screening visit) should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Required Asthma Controller Therapy

All patients will continue their asthma controller therapy as recommended in asthma guidelines (EPR3 2007; GINA 2019). Required asthma controller therapy for this study includes daily ICS therapy (500–2000 μg/day of fluticasone propionate DPI or equivalent; refer to Appendix 9) and at least one of the following second controller

medications: LABA, LTRA, or LAMA. Refer to Section 4.4.4 for additional details regarding ICS and second controller therapy.

4.4.2 Short-Acting Rescue Therapy

It is expected that the majority of patients will be using short-acting B-agonist (SABA) or short-acting muscarinic antagonist (SAMA) therapy for symptoms of uncontrolled asthma per existing treatment guidelines. Combination SABA or SAMA inhalers (e.g., albuterol/ipratropium) are also permitted. Short-acting rescue therapy must be administered via the patient's prescribed inhaler or nebulizer. Any short-acting therapy that is prescribed as asthma rescue medication over the course of the study or administered during hospitalization or an emergency department, urgent care visit, or urgent unscheduled office visit should be documented on the appropriate eCRF. Restrictions on the timing of administration of SABA or SAMA therapy relative to spirometry measurements and CPET are described in Section 4.4.4.

4.4.3 Systemic Corticosteroid Use

Patients who require any systemic corticosteroids (oral, IV, or IM) within 4 weeks prior to screening or during the screening period will not be eligible for the study (see Section 4.1.2). The use of systemic corticosteroids is permitted for acute patient management after $enrollment$. Corticosteroids used for treatment of asthma should be documented on the appropriate eCRF. Whereas systemic corticosteroids should not be used other than for asthma exacerbation, in the event that they are used to treat other medical conditions, this should be documented on the Concomitant Medications eCRF.

4.4.4 Medication Use Prior to Spirometry Measurements and CPET

At specified timepoints during the study, patients will undergo pre-bronchodilator spirometry and CPET measurements in the clinic. Bronchodilator use is prohibited within a specified window prior to these measurements as follows:

- Twice-daily LABA and LAMA: prohibited within 12 hours prior to spirometry and CPET
- Once-daily LABA and LAMA: prohibited within 24 hours prior to spirometry and CPET
- SABA or SAMA: prohibited within 6 hours prior to spirometry and CPET

4.4.5 Permitted Therapy

The following asthma medications are permitted with the following instructions in Table 1.

Table 1 Permitted Asthma Medications

Medication	Restrictions [a]
ICS therapy	No changes in ICS therapy within 4 weeks prior to Visit 1/screening and throughout the study
LABAs LTRAs LAMAs	No changes in dose or initiation of therapy within 4 weeks prior to Visit 1/screening and throughout the study
Allergen immunotherapy	No changes in allergen immunotherapy or initiation of new allergen immunotherapy within 3 months prior to Visit 1/screening and throughout the study

ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist.

[a] The Medical Monitor should be consulted in cases of uncertainty.

4.4.6 Prohibited Therapy

The following medications are prohibited with the instructions in Table 2.

Table 2 Prohibited Asthma Medications

Medication	Restrictions [a]
Maintenance corticosteroids (e.g., daily or every other day oral therapy)	Prohibited within 3 months prior to Visit 1/screening and throughout the study
Zileuton	Prohibited within 4 weeks prior to Visit 1/screening and throughout the study
Immunomodulatory or immunosuppressive therapy (other than monoclonal antibodies or corticosteroids [see separate exclusion])	Prohibited within 3 months or 5 drug half-lives prior to Visit 1/screening (whichever is longer) and throughout the study
Licensed or investigational [b] monoclonal antibodies for asthma or any other indication	Prohibited within 6 months or 5 drug half-lives prior to Visit 1/screening (whichever is longer) and throughout the study
Any other investigational drug not described above (including investigational use of a formulation of an approved drug) [b]	Prohibited within 4 weeks or 5 drug half-lives prior to Visit 1/screening (whichever is longer) and throughout the study
Pulmonary rehabilitation	Prohibited for 6 months prior to Visit 1/screening and throughout the study
Any prescription or over-the-counter sedative sleep medication (e.g., zolpidem).	Prohibited from Visit 1/screening throughout the study

[a] The Medical Monitor should be consulted in cases of uncertainty.

[b] Patients participating in a clinical trial that has not been unblinded should be assumed to have received the active drug.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

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 local laboratory test values are acceptable.

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly.

If a patient is having an acute asthma exacerbation event or has a respiratory infection at the time of a scheduled study visit, the CPET and spirometry visit should be scheduled at the next 4-week visit (e.g., if an exacerbation happens at Visit 6, the patient should be scheduled for CPET and spirometry at Visit 7).

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 all patients (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.

Patients who fail screening are allowed to be rescreened once, at the discretion of the investigator.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including, but not limited to, clinically significant diseases, surgeries, cancer history, reproductive status, and smoking history will be recorded at screening. In addition, all asthma and other medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient prior to Visit 1 (first screening visit) will be recorded. At the time of each follow-up physical examination, an interval medical history will be obtained and any changes in medications and allergies will be recorded.

In particular, any history of anaphylaxis, cardiovascular disease, neurological disease, orthopedic conditions, inflammatory or autoimmune disease, and parasitic disease will 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 physical examination, performed at the first screening visit 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.

At subsequent visits, as outlined in the schedule of assessments in Appendix 1 (or as clinically indicated), physical examinations should be performed 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 respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and body temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Height and Weight

Height and weight will be measured at visits according to the schedule of assessments. Weight will be determined to the nearest 0.1 kg. For body weight measurements, the patient should wear street clothes, without shoes, outerwear, or accessories.

4.5.6 Spirometry

Spirometry, including the procedure for bronchodilator testing if needed, will be conducted as per the study pulmonary function testing manual, which is based on the American Thoracic Society/European Respiratory Society (ATS/ERS) Consensus Statement “Standardisation of Spirometry” (Graham et al. 2019). The manual will include information on equipment, procedures, patient instructions, and precautions. Existing spirometry equipment and capabilities will be assessed at all sites. Training on equipment use, system calibration, and data storage and transfer will be provided.

4.5.6.1 Pre-Bronchodilator Spirometry

Pre-bronchodilator spirometry evaluations should ideally be performed in the morning, before use of bronchodilators. Every attempt should be made to perform spirometry approximately at the same time of the day throughout the study for each patient. Asthma therapies that may affect spirometry must be withheld until pre-bronchodilator spirometry measurements are completed. Patients must be made aware that

bronchodilator use is prohibited within a specified window prior to each clinic visit at which spirometry will be performed as follows:

- Twice-daily LABA and twice-daily LAMA: prohibited within 12 hours prior to spirometry
- Once-daily LABA and once-daily LAMA: prohibited within 24 hours prior to spirometry
- SABA or SAMA: prohibited within 6 hours prior to spirometry

If a patient arrives for a study visit having used a bronchodilator within the time window defined above for each medication, spirometry should be rescheduled to the next 4-week visit. All assessments that do not require bronchodilator withholding should be performed as scheduled.

Spirometric assessments will include FEV_1, FVC, percentage of predicted values for FEV_1 and FVC, FEV_1 to FVC ratio, and average expiratory flow during the middle portion of the expiration (FEF_{25-75}). The percentage of predicted values for FEV_1 FVC and FEF_{25-75} will be derived from the Global Lung Function Initiative (Quanjer et al. 2012). Each test procedure requires that three valid spirometry maneuvers be performed within 1 hour. An acceptable session must also meet ATS/ERS repeatability criteria for FEV_1 and FVC (Graham et al. 2019). The highest FEV_1 and FVC values from the set of three accepted maneuvers will be recorded. Other parameters will be taken from the accepted maneuver with the highest sum of FEV_1 and FVC. A hard-copy report of the spirometry results will be maintained in the patient's medical record.

4.5.7 Asthma Exacerbations

At each study visit, the investigator will ask directed questions to assess whether the patient experienced any protocol-defined asthma exacerbations since the last study visit. An asthma exacerbation is defined as new or increased asthma symptoms (including wheeze, cough, dyspnea, chest tightness, and/or night-time awakening due to these symptoms) that lead to treatment with systemic corticosteroids or to hospitalization. Treatment with systemic corticosteroids is defined as treatment with oral, IV, or IM corticosteroids for at least 3 days or an emergency department visit with at least one dose of IV or IM corticosteroids. An asthma exacerbation must be reported as an adverse event (or serious adverse event as applicable) as per Section 5.2. Sites should update the appropriate eCRF with all medications used for treatment of the asthma exacerbation.

4.5.8 Cardiopulmonary Exercise Testing

CPET will be performed on an electromagnetically braked cycle ergometer. Patients will perform the exercise while breathing through a mouthpiece with nose clip in place. Ventilation and gas exchange will be measured breath-by-breath by a metabolic cart. Heart rate will be assessed via the ECG. Arterial oxygen saturation will be estimated by

pulse oximetry. CPET will be performed under close monitoring of trained and qualified personnel.

At the second screening visit *(Visit 2a),* patients will perform an incremental exercise test (IET) to the limit of tolerance. Recordings will be made for 3 minutes at rest, 3 minutes during unloaded pedaling and then at continuously increasing work rate (on a ramp-like fashion) until unable to maintain pedaling rate or intolerable shortness of breath despite standardized encouragement.

At screening Visit 2b, a CWR testing at 80% of the peak work rate (determined by the IET) will be performed to tolerance. This will identify an individualized work rate that the patient can tolerate for 3–8 minutes. *The procedure will be as follows:* After 3 minutes of rest, the work rate will be increased abruptly to 80% of the work rate tolerated in the incremental test. Patients will continue to exercise at this work rate until unable to maintain pedaling rate or intolerable shortness of breath despite standardized encouragement. If the tolerated time falls outside the 3–8 minute window, a repeat of the CWR testing will need to be performed, after work rate adjustment. Visit 2b is a flexible visit and may be a series of visits depending on the preference of the patient and study site. A maximum of three CWR tests (one initial and two adjusted) may need to be performed during screening. *The window may be extended by +10 days accumulatively to complete the CWR.* Patients who fail to achieve a CWR with an endurance time between 3–8 minutes within three attempts will not qualify for the study. At the discretion of the investigator, the patient may rescreen once. If two tests are performed on the same day, the time between the tests needs to be at least 90 minutes to allow for recovery. If a SABA or SAMA rescue medication is used during or after CWR testing, the patient will need to perform the adjusted work-rate test on a separate day.

At the baseline visit (*enrollment* visit/*Visit 3*), testing of the individualized CWR that is established during screening will be performed to tolerance and will be the baseline endurance time. The CWR testing will be repeated at Week 12 and Week 24 to assess change in endurance time. During the CWR test, dynamic hyperinflation will be measured by serial inspiratory capacity (IC) maneuvers. After the CWR test, serial spirometry will be performed to assess bronchoconstriction and recovery from bronchoconstriction.

All CPET evaluations should be performed after resting ECG and spirometry. Every attempt should be made to perform CPET approximately at the same time of day throughout the study for each patient.

Asthma therapies that may affect CPET must be withheld until CPET measurements are completed as follows:

- Twice-daily LABA and twice-daily LAMA: prohibited within 12 hours prior to CPET
- Once-daily LABA and once-daily LAMA: prohibited within 24 hours prior to CPET
- SABA or SAMA: prohibited within 6 hours prior to CPET

If a patient arrives for a study visit having used a bronchodilator within the time window defined above for each medication, CPET should be rescheduled to the next 4-week visit. All assessments that do not require bronchodilator withholding should be performed as scheduled.

Details for IET and CWR testing are provided in a separate *CPET laboratory* manual.

4.5.9 Wrist-Worn Physical Activity and Sleep Monitor

At the second screening visit *(Visit 2b),* a wrist-worn physical activity and sleep monitor will be provided to patients who meet inclusion and exclusion criteria requirements.

Physical activity and sleep data will be collected from patients continuously via a wrist-worn accelerometer (physical activity and sleep monitor). The physical activity and sleep monitor will be worn day and night, from the moment the patient receives the monitor, on the patient's non-dominant wrist for the entire duration of the study. The study will utilize the CentrePoint Insight Watch (Actigraph Corp, USA) as the activity and sleep monitor, which was selected due to its high accuracy, long battery life, excellent form-factor (e.g., ease and comfort of use) and clinically validated algorithms for measuring the relevant physical-activity and sleep-based endpoints. The watch collects raw accelerometry data in m/s^2 in 3-dimensions and transmits wirelessly via 3G cellular network to Actigraph's cloud-based servers. The raw physical activity and sleep data is processed for analyses using Actigraph's ActiLife software to determine the endpoints as described in this protocol using algorithms such as those detailed in Staudenmayer et al. (2015). All data collected by the watch will be uploaded passively to a hub at the patient's home. The data is anonymous and patients will not be able to view their individual data during the course of the study.

All patients will also be provided with information about the importance of regular physical activity to improve asthma control, and provided with a tip sheet 'Being Active When You Have Asthma (exercise is medicine) from the American College of Sports Medicine.

4.5.10 Laboratory Assessments

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, performed at the site, prior to the initiation of study drug, every 4 weeks during study treatment period, 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 before giving study drug.

- Total IgE for study eligibility and dosing determination
- Standard hematology panel, may include but is 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), may include but is 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

4.5.11 Clinical Outcome Assessments

4.5.11.1 Assessments Completed by the Patient at Home

At the screening Visit 2b patients who meet inclusion and exclusion criteria requirements will receive an eDiary device that will be used for documenting asthma controller medication use, answering questions related to asthma symptoms, nighttime awakenings due to asthma, activity limitations and use of short-acting rescue therapy.

Patients will be given instructions on how to use the eDiary device and how to complete the eDiary assessments:

- Patients should complete their diaries in a quiet area with minimal distractions and disruptions.
- Patients should answer questions to the best of their ability; there are no right or wrong answers.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

Details of each home assessment are detailed below.

Morning and Evening Asthma Diaries

The daily diary comprises morning items (Asthma Nighttime Symptom Score [ANSD], rescue medication since going to bed and nighttime awakenings due to asthma symptoms, to be completed when patients wake up) and evening items (Asthma Daytime Symptom Score [ADSD], rescue medication use since getting up in the morning and activity limitations during the day to be completed before bedtime). Patients will complete daily diary questions on the eDiary twice a day for 2 weeks before the baseline visit (*enrollment* visit), for 2 weeks before the Week 12, and for 2 weeks before the Week 24. Rescue medication use will need to be entered throughout the study every day that the patient uses rescue medication. The eDiary will remind patients when it is time to complete their diary through text and sound alerts.

Sites must report to sponsor within 10 business days after experiencing or receiving any *reported* issues with the use of the eDiary.

A copy of morning and evening diaries are provided in Appendix 4 and Appendix 5.

4.5.11.2 Clinical Outcome Assessments Completed During Site Visits

Patient-reported outcome (PRO) and clinician-reported outcome (ClinRO) instruments will be completed to support understanding of treatment benefit of omalizumab as measured by physical activity and sleep quality assessments.

PRO data will be collected through use of Asthma Control Questionnaire 5 (ACQ5) and ClinRO data will be collected through assessment of the patient's Urgent Asthma-Related Health Care Utilization and Clinician Global Impression of Change (CGIC).

The ACQ5 will be completed in its entirety by the patient. The urgent asthma-related health care utilization assessment and CGIC will be completed by the investigator as described below. All instruments will be administered at specified timepoints during the study, as outlined in Appendix 1.

Site-completed instruments should be administered as outlined below:

- ACQ5 will 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' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 5 minutes at each administration time.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

Site staff should review the completed ACQ5 and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank

The ACQ5, Urgent Asthma-Related Healthcare Resource Utilization assessment, and CGIC will be recorded on the official, dedicated eCRF.

Details of assessments to be completed at the sites are detailed below.

Asthma Control Questionnaire 5

Asthma control, as measured by the ACQ5 (Juniper et al. 1999) will be assessed by asking patients to recall their experience with asthma during the previous week. The ACQ5 consists of five questions related to symptoms (i.e., nighttime awakening, asthma symptoms upon awakening in the morning, activity limitation, shortness of breath, and wheezing frequency). The items are scored on a scale ranging from 0 (totally controlled) to 6 (extremely poorly controlled). The items are equally weighted. The ACQ5 is scored as the mean of the five symptom-related items. The ACQ5 has strong measurement properties for use in both clinical practice and clinical trials. The ACQ5 is part of the eligibility criteria and will be administered at the screening, baseline (*enrollment*), Week 12 and Week 24 Visits.

A copy of the ACQ5 is provided in Appendix 6.

Clinician Global Impression of Change

The CGIC is a single-item assessment of the clinician's impression of a patient's change in asthma symptoms since beginning the 24-week treatment period (Visit 3). Change in asthma symptoms is rated on a 7-point scale ranging from "very much worse" to "very much improved." The CGIC is completed by the investigator and takes less than 1 minute to complete. The CGIC will be completed at Weeks 12 and 24.

A copy of the CGIC is provided in Appendix 7.

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 determination that treatment discontinuation is in the best interest of the patient

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 *the* remaining study assessments.

Patients who do not wish to continue with study assessments will be asked to return to the clinic for a dosing termination visit within 4 weeks after the last dose of study treatment. *The patient will bring the eDiary and physical activity and sleep monitor. The dosing termination visit may be performed virtual if needed in which case the eDiary and physical activity and sleep monitor will need to be shipped to the site. The patient will* subsequently receive a phone call as safety follow-up 4 weeks after their dosing termination visit.

4.6.2 Patient Discontinuation from the 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 patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- 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
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation 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 with omalizumab 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 (GCP)
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

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 or subsequent injection although some occurred beyond 2 hours. Omalizumab has also been investigated in patients with chronic idiopathic urticaria, seasonal allergic rhinitis, perennial allergic rhinitis, atopic dermatitis, nasal polyps, 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 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 or discontinuation *are* provided appropriately (see Section 4.6).

5.1.1 Safety and Data Monitoring

All safety events will be closely monitored by the study team. The sponsor followed the U.S. 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, the established safety record of omalizumab, and the outcomes being examined.

5.1.2 Anaphylaxis Adjudication Committee

All potential anaphylaxis cases reported by investigators to the Sponsor will be subsequently submitted for adjudication to a 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, Appendix 3) and whether the reported anaphylaxis event is causally related to *omalizumab*. 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 post-marketing 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 granulomatosis with polyangiitis (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 manifested by 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).

Final results from the EXCELS study revealed an increased ATE rate in the omalizumab cohort as compared to the non-omalizumab cohort, with a hazard ratio of 1.32 (95% CI: 0.91, 1.91) when adjusted for confounders and risks factors. The results from the EXCELS study 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. In a new analysis of pooled clinical trials of ≥8 weeks duration, the rate of ATE per 1000 patient years was 2.69 (5/1856 patient years) for omalizumab-treated patients and 2.38 (4/1680 patient years) for placebo patients.

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. In the clinical trials for asthma and CSU/CIU, out of the 23,498 samples tested, only 5 samples were confirmed to be ADA positive in the confirmatory assay. However, 2 of the 4 samples tested positive had been collected prior to omalizumab administration. In both cases, the post-dose samples of these subjects were negative. Importantly, the 3 ADA-positive cases following omalizumab administration were not associated with any serious adverse events.

5.1.3.8 Parasitic Infections

IgE may be involved in the immunological response to some infections. In patients at chronic high risk of helminth infection, a placebo-controlled trial in allergic patients showed a slight increase in infection rate with omalizumab, although the course, severity, and response to treatment of infection were unaltered. The helminth infection

rate in the overall clinical program, which was not designed to detect such infections, was less than 1 in 1,000 patients. However, caution may be warranted in patients at high risk of helminth infection, in particular when traveling to areas where helminthic infections are endemic. If patients do not respond to recommended anti-helminth treatment, discontinuation of omalizumab should be considered.

5.1.4 Management of Patients Who Experience Specific Adverse Events

5.1.4.1 Dose Modifications and Treatment Interruption

Dose modification and/or treatment interruption is not 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 5.4.

5.2.1 Adverse Events

According to the ICH guideline for GCP, 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) (see Sections 5.3.5.10 and 5.3.5.11 for more information)
- 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., screening invasive procedures such as biopsies)

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 [NCI CTCAE]; 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 3)
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8)
- Suspected transmission of an infectious agent by the study drug, as defined below

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6. The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

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

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in 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 (see Appendix 3) 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., 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., treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

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

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

5.3.5.8 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.3) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.9 Deaths

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

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

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

5.3.5.10 Preexisting Medical Conditions

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

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

5.3.5.11 Lack of Efficacy or Worsening of Asthma

Medical occurrences or symptoms of deterioration that are anticipated as part of asthma 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 asthma on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of asthma).

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 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 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately 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). For omalizumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with omalizumab, regardless of whether they result in an adverse event, should be recorded on the eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.

- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

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)
- Medical device complaints (see Section 5.4.4 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information 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 the Institutional Review Board/ Ethics Committee (IRB/EC).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor contact information:

Medical Monitor: [redacted], M.D.

Telephone No.: [redacted]

Alternate Genentech Medical Monitor contact information:

Medical Monitor: [redacted], Ph.D.

Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk (1-888-835-2555) will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week.

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, serious adverse 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 Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper form 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 final dose of study drug. A paper 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

A spontaneous 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).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity 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). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

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).

5.4.4 Reporting Requirements for Medical Device Complaints

In this study, the prefilled syringe and the physical activity and sleep monitor (CentrePoint Insight Watch) are considered medical devices.

For the prefilled syringe, the investigator must report all complaints to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

For complaints and adverse events associated with the CentrePoint Insight Watch, the investigator must report all complaints to the sponsor who will forward the complaint to the manufacturer. The manufacturer will report all AEs according to the regulatory requirements for reporting of medical device-related adverse events (21 CFR 803).

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 (see Section 4.3.1) if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- Omalizumab Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The analysis of complete data from the 24-week treatment period and 4 week safety follow-up period will be performed when all patients have either completed the study or discontinued the study early, all data from the study are in the database, and the database is cleaned and locked.

Detailed specifications of the statistical methods will be described in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

The target sample size of 54 is based on feasibility.

The sample size was calculated based on data from Bonini 2019, which suggested that an improvement in the endurance time of at least 1 minute 40 seconds from baseline or >33% is clinically important. When the sample size is 54, a two-sided 95% confidence interval for the mean change from baseline will extend 1 minute 4 seconds from the observed mean change, assuming that the standard deviation is known to be 4 minutes and the confidence interval is based on the z-distribution (see Table 5). Assuming a 10% withdrawal rate, a sample size of 60 will be enrolled.

Table 5 Confidence Intervals for Different Standard Deviations with Sample Size of 54

Standard Deviation	*95% Confidence Interval*
4 minutes	*(0 min 36 sec, 2 min 44 sec)*
5 minutes	*(0 min 20 sec, 3 min 0 sec)*
6 minutes	*(0 min 4 sec, 3 min 16 sec)*

6.2 SUMMARIES OF CONDUCT OF STUDY

Descriptive statistics will be used to evaluate the conduct of the study. The number of patients *enrolled* will be tabulated by study site in all patients with data. Patient disposition (the number of patients *enrolled*, treated, and completed) will be tabulated in all patients with data. Premature study drug discontinuation and study discontinuation, as well as reasons for discontinuations, will be summarized.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics, such as age, sex, race/ethnicity, baseline endurance time and other baseline variables used for efficacy endpoints will be summarized with descriptive statistics in all patients with data. Baseline disease characteristics will be defined as the last measurement prior to *enrollment*. Exposure to *omalizumab* (number of *omalizumab* treatments and duration of treatment) will be summarized in all patients with data.

6.4 EFFICACY ANALYSES

The primary efficacy analysis population will consist of all *omalizumab treated* patients, who have both baseline and at least one post-baseline assessment at Week 12 or Week 24 *and received any dose of omalizumab*.

Change from baseline at Week 24 in the primary endpoint will be summarized descriptively.

Details of the efficacy analyses will be provided in the SAP.

6.4.1 Primary Efficacy Endpoint

The primary analysis will *assess* the *effect of omalizumab* in the primary endpoint, change from baseline at Week 24 in endurance time (minutes).

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Change from baseline at Week 24 in physical activity (min/day)
- Change from baseline to Week 24 in dynamic hyperinflation at isotime, as measured by inspiratory capacity during CPET at a CWR
- Change from baseline at Week 24 in sleep efficiency

For each patient, physical activity and sleep efficiency at baseline, Week 12 and Week 24 will be calculated as the average of the daily moving time and average of daily sleep efficiency during 14 days prior to the baseline visit (*enrollment* visit), Week 12 visit and Week 24 visit.

Each secondary efficacy endpoint will be *summarized descriptively*.

6.4.3 Exploratory Efficacy Endpoints

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

6.5 SAFETY ANALYSES

The safety analysis population will consist of all *enrolled* patients who received *any* dose of study drug. Safety summaries will be presented 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.

6.5.1 Planned Interim Analyses

The Sponsor may conduct interim analyses of efficacy/safety. The decision to conduct such an interim analysis and its timing will be documented in the Sponsor's study master file prior to the conduct of the interim analysis.

The Clinical Study Report will also document that such an interim analysis occurred. The interim analysis, should it occur, will be performed by the Sponsor study team.

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 or contract research organization (CRO) will request data clarification from the sites, which the sites will resolve electronically in the EDC system. Local laboratory data will be sent to sites and results will be entered into the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the 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.

Spirometry and CPET data will be securely transmitted from sites to a central spirometry/CPET core lab. Quality control will be conducted to ensure data integrity of each record and all data points are acceptable and correct. Data will be securely maintained and subsequently securely transferred to the Sponsor.

Physical activity and sleep monitor data will be automatically captured and securely transmitted from each device to a cloud-based server maintained by the digital device vendor. The digital device data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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 that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC PATIENT REPORTED OUTCOME DATA

eDiary data will be collected through the use of an electronic device provided by a vendor. 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 from devices will be transmitted to a secured centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only via a secure web portal. Only identified and trained site users may view the data, and their actions will become part of the audit trail. The Sponsor will manage data quality and discrepant data through the secured web portal and all actions will become part of the 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.

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 that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

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, patient-reported outcomes, 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 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, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 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.

Genentech will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the applicable 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) and applicable local, regional, and national laws.

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 language that may be used by some of the participating patients as their primary way of communication. 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 submission. The final IRB–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-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB policy. 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.

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

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB. Investigators are also responsible for promptly informing the IRB of any protocol amendments (see Section 9.7).

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. 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, 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.

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.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

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 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 GCP 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 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial

processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed.

9.4 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 to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Genentech, Inc. The Sponsor will be responsible for clinical operations management, data management, and medical monitoring.

Approximately *20-25* sites in the US will participate in this study and are expected to enroll approximately *60* patients. Enrollment will occur through an IWRS.

An anaphylaxis adjudication committee will be employed to assess whether a reported anaphylaxis event is a true anaphylaxis event (based on Sampson's criteria) and whether the reported anaphylaxis event is causally related to *omalizumab*. Further details will be provided in the Anaphylaxis Adjudication Charter.

9.6 DISSEMINATION 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, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

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.

9.7 PROTOCOL AMENDMENTS

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

Approval must be obtained from the IRB 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).

10. REFERENCES

Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. European Respiratory Journal. European Respiratory Society; 2016 Feb;47(2):410–9.

Arbes SJ Jr, Gergen PJ, Vaughn B, Zeldin DC. Asthma cases attributable to atopy: results from the Third National Health and Nutrition Examination Survey. J Allergy Clin Immunol 2007;120:1139 – 45.

Bonini M, Di Paolo M, Bagnasco D, et al. Minimal clinically important difference for asthma endpoints: an expert consensus report. Eur Respir Rev. 2020 Jun 3; 29(156):190137

Borish L, Chipps B, Deniz Y, Gujrathi S, Zheng B, Dolan CM, TENOR Study Group. Total serum IgE levels in a large cohort of patients with severe or difficult-to-treat asthma. Annals of Allergy, Asthma & Immunology. 2005 Sep 1;95(3):247-53.

Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. New England Journal of Medicine. 1989 Feb 2;320(5):271–7.

Busse WW. Anti-immunoglobulin E (omalizumab) therapy in allergic asthma. Am J Respir Crit Care Med 2001;164(8 Pt 2): S12e7.

Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. Journal of Allergy and Clinical Immunology. 2001 Aug;108(2):184–90.

Casaburi R. Factors determining constant work rate exercise tolerance in COPD and their role in dictating the minimal clinically important difference in response to interventions. COPD. 2005;2(1):131-6.

Casaburi R, Kukafka D, Cooper CB, Witek Jr TJ, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest. 2005;127(3):809–17.

Cordova-Rivera L, Gibson PG, Gardiner PA, Powell H, McDonald VM. Physical Activity and Exercise Capacity in Severe Asthma: Key Clinical Associations. J Allergy Clin Immunol Pract. 2018 Jun;6(3):814–22

Criqui MH, Seibles J, Hamburger RN, et al. Epidemiology of immunoglobulin E levels in a defined population. Ann Allergy 1990;64:308–313.

National AE, Prevention P. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. The Journal of allergy and clinical immunology. 2007 Nov;120(5 Suppl):S94.

Food and Drug Administration. Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees. U.S. Department of Health

and Human Services (2006) OMB Control No. 0910-0581 Expiration Date: 12/31/2018.

Global Strategy for Asthma Management and Prevention (GINA). Global strategy for asthma management and prevention. Updated 2019

Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. Am J Respir Crit Care Med. 2019;200(8):e70-88.

Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Ann Intern Med. 2011 Apr 15;154(9):573–82.

Holgate ST, Chuchalin AG, Hebert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. Clinical & Experimental Allergy2004; Apr;34(4):632–8.

Humbert M, Beasley R, Ayres, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy. 2005 Mar;60(3):309–16.

Ishizaka K, Tomioka H, Ishizaka T. Mechanisms of passive sensitization: I. Presence of IgE and IgG molecules on human leukocytes. The Journal of Immunology. 1970 Dec 1;105(6):1459-67.

Johansson SG, Bennich H. Immunological studies of an atypical (myeloma) immunoglobulin. Immunology. 1967;13:381-94.

Juniper EF, Buist AS, Cox FM, et al. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest 1999;115:1265–70.

Kim HL, Leigh RL, Becker A. Omalizumab: practical considerations regarding the risk of anaphylaxis. Allergy Asthma Clin Immunol 2010;6:32

Koch B, Schaper C, Ittermann T, et al. Reference values for cardiopulmonary exercise testing in healthy volunteers: the SHIP study. Eur Respir J 2009;33(2):389e97

Lang JE. The impact of exercise on asthma. Current Opinion in Allergy and Clinical Immunology. 2019 Apr;19(2):118–25.

Limb SL, Starke PR, Lee CE, et al. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. J Allergy Clin Immunol 2007;120:1378–81.

Lin FJ, Wong D, Chan-Yeung M. Immediate skin reactivity in adult asthmatic patients. Ann Allergy Asthma Immunol 1995;74:398–404.

National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program Expert Panel Report: Guidelines for the diagnosis and management of

asthma. Update on selected topics 2002. Bethesda (MD); June 2003. Report No.: 02 – 5074.

National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. Full Report 2007. Bethesda, MD: National Institutes of Health/National Heart, Lung, and Blood Institute; 2007. Publication no. 97–4051.

Ostergaard PA. Exogenous allergic asthma in children. Ugeskrift for laeger. 1985 Feb;147(7):603–6.

Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? Thorax 1999;54:268–72.

Peters SP, Jones CA, Haselkorn T, Mink DR, Valacer DJ, Weiss ST. Real-world evaluation of asthma control and treatment (REACT): Findings from a national Web-based survey. J Allergy Clin Immunol 2007;119:1454 – 61.

Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. European Respiratory Journal. 2012 Dec;40(6):1324–43.

Remes ST, Korppi M. Asthma and atopy in schoolchildren in a defined population. Acta Paediatrica. 1996 Aug;85(8):965-70.

Schulman ES. Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. Am J Respir Crit Care Med 2001;164:S6–11.

Schäper C, Gläser S, Felix SB, et al. Omalizumab treatment and exercise capacity in severe asthmatics - results from a pilot study. Respiratory Medicine. 2011 Jan;105(1):3–7.

Solèr M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur Respir J. 2001 Aug;18(2):254–61.

Stanford RH, Gilsenan AW, Ziemiecki R, Zhou X, Lincourt WR, Ortega H. Predictors of uncontrolled asthma in adult and pediatric patients: analysis of the Asthma Control Characteristics and Prevalence Survey Studies (ACCESS). J Asthma 2010;47:257–62.

Staudenmayer J, He S, Hickey A, et al. Methods to estimate aspects of physical activity and sedentary behavior from high-frequency wrist accelerometer measurements. J. Appl Physiology 2015; 119:396–403.

XOLAIR (omalizumab) Summary of product characteristics, Genentech Inc. 2003 [cited 17 October 2016]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000606/WC500057298.pdf

Yang G, Han Y-Y, Sun T, et al. Sleep Duration, Current Asthma, and Lung Function in a Nationwide Study of U.S. Adults. American Journal of Respiratory and Critical Care Medicine. 2019 Jun 21.

Zeiger RS, Chipps BE, Haselkorn T, et al. Comparison of asthma exacerbations in pediatric and adult patients with severe or difficult-to-treat asthma. J Allergy Clin Immunol 2009;124:1106–8.

Zeiger RS, Yegin A, Simons FE, et al. Evaluation of the National Heart, Lung, and Blood Institute guidelines impairment domain for classifying asthma control and predicting asthma exacerbations. Ann Allergy Asthma Immunol 2012;108: 81–7.

Appendix 1
Schedule of Activities

	Screening			Treatment													Safety Follow-Up	Dosing/ Early Term. Visit
Day (±5 days)	-28 to -14			0	14	28	42	56	70	84	98	112	126	140	154	168		
Week	-4 to -2			0	2	4	6	8	10	12	14	16	18	20	22	24	28	NA
Visit	1	2 [a]	2b [b]	3 [c]	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	telephone call	NA
Informed consent [d]	x																	
Inclusion/exclusion criteria	x	x	x	x														
Enrollment				x														
Omalizumab administration [e]				x	x	x	*X*	x	x	x	x	x	x	x	x			
Demographics	x																	
Medical and asthma history [f]	x																	
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs	x			x		x		x		x		x		x		x		x
Weight [g]	x	x [g]	x [g]	x		x		x		x		x		x		x		x
Height	x																	
Physical examination [h]	x			x						x						x		x
ACQ5	x			x						x						x		
CGIC										x						x		
Pre-bronchodilator spirometry [i]		x		x						x						x		x
CPET (IET) [j, k]		x																

Appendix 1: Schedule of Activities

	Screening			Treatment													Safety Follow-Up	Dosing/ Early Term. Visit
Day (±5 days)	-28 to -14			0	14	28	42	56	70	84	98	112	126	140	154	168		
Week	-4 to -2			0	2	4	6	8	10	12	14	16	18	20	22	24	28	NA
Visit	1	2 [a]	2b [b]	3 [c]	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	telephone call	NA
CPET (CWR) [k]			x [l]	x						x [m]						x [m]		x [n]
Distribution of eDiary, physical activity/sleep monitor [o]			x															
Collection of eDiary, physical activity/sleep monitor				x [p]												x		x
Morning and Evening Asthma Diaries [q]				x						x						x		
Physical activity/sleep monitoring [r]				x	x	x	x	x	x	x	x	x	x	x	x	x		
Total IgE [s]	x																	
Hematology	x			x						x						x		x
Chemistry	x			x												x		x
Pregnancy test [t]	x [u]			x		x		x		x		x		x				
Adverse events [v]	x [v]	x [v]	x [v]	x [v]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Health Care Utilization	x	x	x	x		x		x		x		x		x		x	x	x
Rescue medication				x	x	x	x	x	x	x	x	x	x	x	x	x		x

ACQ5=Asthma Control Questionnaire 5; ADSD= Asthma Daytime Symptom Diary; ANSD= Asthma Nighttime Symptom Diary; CGIC=clinician global impression of change; CPET=cardiopulmonary exercise testing; IET=incremental exercise testing; CWR=Constant Work Rate; eCRF=electronic Case Report Form; LABA=long-acting beta agonist; LAMA=long-acting muscarinic antagonist; NA=not applicable; SABA=short-acting beta agonist; SAMA= short-acting muscarinic antagonist; Term.=Termination; USPI=United States Package Insert.

Appendix 1: Schedule of Activities

Notes: All assessments should be performed within ±5 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] The second screening visit will be completed for patients who meet all screening criteria from Visit 1.

[b] The purpose of the visit is to establish the CWR that will be used during the study. Visit 2b is a flexible visit and may be a series of visits depending on the preference of the patient and study site. Up to three visits may be scheduled within the -4 to -2 week. *If more than 1 visit is needed for Visit 2b, the* window *may* be extended *up to 10* days *accumulatively*.

[c] Visit 3 should be scheduled at least 14 (+5 days) days after Visit 2b to ensure sufficient time to assess compliance with medication, eDiary use, and wearing of the physical activity and sleep monitor.

[d] Written informed consent for participation in the study must be obtained before performing any study-specific tests or evaluations.

[e] *Omalizumab* administration will be per approved USPI dosing schedule and may be every 2 or 4 weeks. The last dose for patients who receive *omalizumab* every 4 weeks will be at Week 20 and patients who receive *omalizumab* every 2 weeks will be at Week 22.

[f] Medical history will include clinically significant diseases and surgeries, smoking history, and medication allergies. In particular, sites should record whether the patient has any history of anaphylaxis, cancer, cardiovascular disease, eosinophilic disease, inflammatory or autoimmune disease, and parasitic disease.

[g] If the clinical site and CPET site are separate sites, weight (without shoes) will be captured at the clinical site and provided to the CPET site, except at Visits 2 and 2b where the weight can be captured by the CPET site.

[h] A physical examination, performed at the first screening visit 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. At subsequent visits (or as clinically indicated), physical examinations should be performed as clinically indicated.

[i] Pre-bronchodilator spirometry needs to be performed before taking any bronchodilators for specific time periods:

- Twice-daily LABA and twice-daily LAMA: prohibited within 12 hours prior to spirometry
- Once-daily LABA and once-daily LAMA: prohibited within 24 hours prior to spirometry
- SABA or SAMA: prohibited within 6 hours prior to spirometry

[j] If an upper respiratory infection or exacerbation occurred, the visit needs to be postponed until the resolution of the event and the patient is stable.

[k] CPET needs to be performed after spirometry. Bronchodilators will need to be withheld for specific time periods:

- Twice-daily LABA and twice-daily LAMA: prohibited within 12 hours prior to CPET
- Once-daily LABA and once-daily LAMA: prohibited within 24 hours prior to CPET
- SABA or SAMA: prohibited within 6 hours prior to CPET

[l] A CWR test, determined as 80% of the peak rate during the IET, will be performed to identify an individualized work rate that can be tolerated for 3–8 minutes. If the CWR tolerated time falls outside the 3–8 *minute* window, a repeat of the constant work rate testing will need to be performed after work rate adjustment. Up to three CWR tests (one initial and two adjusted) may be performed during screening. Patients who fail to

achieve a CWR with an endurance time between 3–8 minutes will not qualify for the study. At the discretion of the investigator, the patient may rescreen once.
If two tests are performed on the same day, the time between the tests needs to be at least 90 minutes to allow for recovery. If a SABA or SAMA rescue medication is used during or after CWR testing, the patient will need to perform the adjusted work rate test on a separate day.

[m] If CPET CWR cannot be performed (e.g., due to patient not withholding bronchodilators, upper respiratory infection, exacerbation), the assessment should be done at the next monthly visit. The event has to be resolved and the patient needs to be stable.

[n] A patient who discontinues the study early may be asked to perform a final CPET CWR test. This is voluntary and can only be performed if there are no safety risks.

[o] The eDiary and the physical activity and sleep monitor will be distributed at the screening visit at which the CWR is successfully completed (CWR that results in endurance time between 3–8 minutes). Compliance with the eDiary and the physical activity and sleep monitor will be assessed during the 2 weeks prior to *enrollment (Day -14-0)*.

[p] If a patient screen fails, the eDiary device and the physical activity and sleep monitor will be collected at the baseline visit (*enrollment* visit).

[q] The morning asthma and evening asthma diaries are to be completed on an eDiary daily in the morning and evening during the 2 weeks before the baseline/*enrollment* visit and 2 weeks before the Week 12 and Week 24 visits only. The three measures completed in the morning are: ANSD, overnight rescue medication use, and nighttime awakening. The three measures completed in the evening are: ADSD, daytime rescue medication use, and impact on daytime activities. Rescue medication will also need to be reported through the duration of the study. The question on use of daily medication will need to be answered daily only in the 2 weeks before the baseline/*enrollment* visit.

[r] Patients should wear the physical activity and sleep monitor continuously (day and night) on their non-dominant wrist continuously from the time it is distributed until it is returned to the study site, as per instructions provided. Physical activity and sleep data will be collected continuously throughout the trial.

[s] If the Total IgE level is outside the dosing range per USPI dosing table, retesting is allowed once at the physician's discretion.

[t] All women of childbearing potential must have a negative serum pregnancy test during the screening period, prior to initiation of study drug.

[u] Pregnancy test is performed at the site for all female patients of childbearing potential. If the urine pregnancy test result is positive, dosing should be held and a serum pregnancy test should be performed. Once the pregnancy is confirmed, the patient must be discontinued from study drug.

[v] 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. Adverse events include exacerbations.

Appendix 2
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.
7. Collect serum samples for immunogenicity testing if clinically indicated.
8. Ask the patient to return for immunogenicity sample collection at the time of washout (approximately 16 weeks after last dose), if appropriate.

Appendix 3
Sampson's Criteria for Diagnosing Potential Cases of Anaphylaxis

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

   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, 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):

   - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms (e.g., hypotonia, syncope, incontinence)
   - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):

   - Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure
   - Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline

Source: Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–11.

Appendix 4
Morning Asthma Diary

Asthma Nighttime Symptom Diary (ANSD)

[INSTRUCTION 1] *We would like you to complete this diary every morning when you get up.*
[INSTRUCTION 2] *For each question, please choose the number that best describes your experience.*
[INSTRUCTION 3] *Please answer each question by thinking about your asthma symptoms last night from when you went to bed until now.*

[ITEM 1] Please rate your difficulty breathing at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as you can imagine**

[ITEM 2] Please rate your wheezing at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as you can imagine**

[ITEM 3] Please rate your shortness of breath at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as you can imagine**

Appendix 4: Morning Asthma Diary

[ITEM 4] Please rate your chest tightness at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 5] Please rate your chest pain at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

[ITEM 6] Please rate your cough at its worst since you went to bed last night.

0	1	2	3	4	5	6	7	8	9	10
None										As bad as you can imagine

Nighttime Awakening Due To Asthma

[INSTRUCTION] We would like you to complete this diary every morning when you get up during the two weeks prior to visit 3 (week 0/baseline/randomization), visit 6 (week 12) and visit 9 (week 24).

Did any of your asthma symptoms wake you up since you went to bed last night?

☐ Yes

☐ No

Rescue Medication Use

[INSTRUCTION] We would like you to complete this diary every morning when you get up for the entire duration of the study.

After going to sleep last night, did you take any rescue medication for your asthma symptoms (shortness of breath, cough, wheeze, or chest tightness)?

☐ No, I did not take any rescue medication

☐ Yes, I used a rescue inhaler

How many puffs of a rescue inhaler did you take? _____ puffs

☐ Yes, I used a nebulizer (breathing machine)

How many times did you use a nebulizer (breathing machine)? _____ times

Appendix 5
Evening Asthma Diary

Asthma Daytime Symptom Diary (ADSD)

[INSTRUCTION 1] *We would like you to complete this diary every night before you go to bed.*
[INSTRUCTION 2] *For each question, please choose the number that best describes your experience.*
[INSTRUCTION 3] *Please answer each question by thinking about your asthma symptoms today, from when you got up this morning until now.*

[ITEM 1] Please rate your difficulty breathing at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as you can imagine**

[ITEM 2] Please rate your Wheezing at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as you can imagine**

[ITEM 3] Please rate your shortness of breath at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as you can imagine**

[ITEM 4] Please rate your chest tightness at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as you can imagine**

[ITEM 5] Please rate your chest pain at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as you can imagine**

[ITEM 6] Please rate your cough at its worst since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as you can imagine**

Impact on Daily Activities

[INSTRUCTION] We would like you to complete this diary every night before you go to bed during the two weeks prior to visit 3 (week 0/baseline/randomization), visit 6 (week 12) and visit 9 (week 24).

Please rate how much your asthma symptoms limited you in your usual activities since you got up this morning.

0	1	2	3	4	5	6	7	8	9	10
Not at all										**As much as you can imagine**

Rescue Medication Use

[INSTRUCTION] We would like you to complete this diary every evening before you go to bed for the entire duration of the study.

Since you got up this morning, did you take any rescue medication for your asthma symptoms (shortness of breath, cough, wheeze, or chest tightness)?

- ☐ No, I did not take any rescue medication
- ☐ Yes, I used a rescue inhaler
  - How many puffs of a rescue inhaler did you take? _____ puffs
- ☐ Yes, I used a nebulizer (breathing machine)
  - How many times did you use a nebulizer (breathing machine)? _____ times

Compliance with Asthma Controller Medication

[INSTRUCTION] We would like you to complete this diary every night before you go to bed up during the two weeks prior to visit 3 (week 0/baseline/randomization)

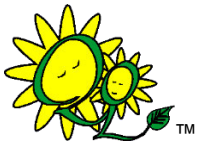
Did you take your preventive inhaler (medications) today?

- ☐ Yes
- ☐ No

Appendix 6
Asthma Control Questionnaire 5 (ACQ5)

ASTHMA CONTROL QUESTIONNAIRE (ACQ)

(SYMPTOMS ONLY)



For further information:

Elizabeth Juniper, MCSP, MSc
Professor
20 Marcuse Fields
Bosham, West Sussex
PO18 8NA, England
Telephone: +44 1243 572124
Fax: +44 1243 573680
E-mail: juniper@qoltech.co.uk
Web: http://www.qoltech.co.uk

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ASTHMA CONTROL QUESTIONNAIRE©
(LANGUAGE VERSION FOR COUNTRY)

PATIENT ID: _____

DATE: _____

Please answer questions 1 - 5.

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you **woken by your asthma** during the night?
   - 0 Never
   - 1 Hardly ever
   - 2 A few times
   - 3 Several times
   - 4 Many times
   - 5 A great many times
   - 6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?
   - 0 No symptoms
   - 1 Very mild symptoms
   - 2 Mild symptoms
   - 3 Moderate symptoms
   - 4 Quite severe symptoms
   - 5 Severe symptoms
   - 6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities** because of your asthma?
   - 0 Not limited at all
   - 1 Very slightly limited
   - 2 Slightly limited
   - 3 Moderately limited
   - 4 Very limited
   - 5 Extremely limited
   - 6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?
   - 0 None
   - 1 A very little
   - 2 A little
   - 3 A moderate amount
   - 4 Quite a lot
   - 5 A great deal
   - 6 A very great deal

5. In general, during the past week, how much of the time did you **wheeze**?
   - 0 Not at all
   - 1 Hardly any of the time
   - 2 A little of the time
   - 3 A moderate amount of the time
   - 4 A lot of the time
   - 5 Most of the time
   - 6 All the time

Appendix 7
Clinician Global Impression of Change (CGIC)

How would you rate the change in the subject's asthma symptoms since starting taking the study drug?

- ☐ Very much improved
- ☐ Much improved
- ☐ Minimally improved
- ☐ No change
- ☐ Minimally worse
- ☐ Much worse
- ☐ Very much worse

Appendix 8
Dosing Table

Adult patients 18 years of age and older: Initiate dosing according to Table 1.

Table 1: Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Patients 18 Years of Age and Older with Asthma

Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight			
		30 – 60 kg	>60 – 70 kg	>70 – 90 kg	>90 – 150 kg
		Dose (mg)			
≥30 – 100	Every 4 weeks	150	150	150	300
>100 – 200		300	300	300	225
>200 – 300		300	225	225	300
>300 – 400	Every 2 weeks	225	225	300	
>400 – 500		300	300	375	
>500 – 600		300	375	Insufficient Data to Recommend a Dose	
>600 – 700		375			

*Dosing frequency:

- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

Number of Prefilled Syringes, Injections and Total Injection Volumes

XOLAIR Dose*	75 mg Syringes	150 mg Syringes	Total Volume Injected
150 mg	0	1	1 mL
225 mg	1	1	1.5 mL
300 mg	0	2	2 mL
375 mg	1	2	2.5 mL

* All doses in the table are approved for use in asthma patients. The 150 mg and 300 mg XOLAIR doses are also approved for use in CIU patients.

Appendix 9
Examples of Estimated Equipotent Daily Doses of Inhaled Corticosteroids in the United States

The following table lists inhaled corticosteroids commonly used in the United States at the time of protocol publication, to serve as examples of eligible corticosteroid doses.

Generic ICS/combination Name	Formulation	Brand Name	ICS Dose (μg)	Dose (μg) equivalent to 500 μg/d FP [a]	Dose (μg) equivalent to 1000 μg/d FP
Beclomethasone dipropionate	HFA-MDI	Qvar®	40,80	480[b]	960
Budesonide	DPI	Pulmicort Flexhaler®	90, 180	720	1440
Budesonide	DPI	Pulmicort Turbuhaler®	200	800	1600
Budesonide/formoterol	HFA-MDI	Symbicort®	80, 160	640	1280
Ciclesonide	HFA-MDI	Alvesco®	80, 160	320	640
Fluticasone propionate/ salmeterol	HFA-MDI	Advair® HFA	45, 115, 230	460	920
Fluticasone propionate	HFA-MDI	Flovent® HFA	44, 110, 220	440	880
Fluticasone propionate/ salmeterol	DPI	Advair Diskus®	100, 250, 500	500	1000
Fluticasone propionate	DPI	Flovent Diskus®	50, 100, 250	500	1000
Fluticasone furoate	DPI	Breo Ellipta®	100, 200	100	200[c]
Fluticasone furoate	DPI	Arnuity Ellipta®	100, 200	100	200[c]
Mometasone furoate/ formoterol	HFA-MDI	Dulera®	100, 200	400	800
Mometasone furoate	DPI	Asmanex Twisthaler®	110, 220	440	880

DPI = dry powder inhaler; FP = fluticasone propionate; HFA = hydrofluoroalkane; MDI = metered dose inhaler.

Note: Dose information is intended as a guide when determining eligibility for the studies and is not intended as a prescribing guide.

[a] GINA 2015.

[b] EPR3 2007.

[c] Busse et al. 2012.