

Clinical Study Protocol with Amendment 02

A Phase 3, 24-Week Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study of Reslizumab Subcutaneous Dosing (110 mg Every 4 Weeks) in Patients With Oral Corticosteroid Dependent Asthma and Elevated Blood Eosinophils

Study Number C38072-AS-30027

NCT02501629

Protocol with Amendment 02 Approval Date: 18 July 2016

Clinical Study Protocol

Study Number C38072-AS-30027

A Phase 3, 24-Week Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study of Reslizumab Subcutaneous Dosing (110 mg Every 4 Weeks) in Patients With Oral Corticosteroid Dependent Asthma and Elevated Blood Eosinophils

Phase 3

IND number: 101,399 EudraCT number: 2015-001580-39

Protocol Approval Date: 18 July 2016

Sponsor (and Monitor)

Teva Branded Pharmaceutical
Products R&D, Inc.
41 Moores Road
Frazer, Pennsylvania 19355
United States

Authorized Representative

[Redacted]

Teva Branded Pharmaceutical Products R&D, Inc.

Sponsor’s Medical Expert

[Redacted]

Teva Global R&D

[Redacted]

Sponsor’s Safety Representative

[Redacted]

Teva Branded Pharmaceutical Products
R&D, Inc

[Redacted]

Confidentiality Statement

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Conference on Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR) and European Union (EU) Directives (as applicable in the region of the study); local country regulations; and the Sponsor’s Standard Operating Procedures (SOPs).

This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Pharmaceuticals. The recipient agrees that no information contained herein may be published or disclosed without written approval from the sponsor.

© 2015 Teva Branded Pharmaceutical Products R&D, Inc. All rights reserved.

AMENDMENT HISTORY

The protocol for Study C38072-AS-30027 (original protocol dated 15 April 2015) has been amended and reissued as follows:

Amendment 02	18 July 2016 44 patients enrolled to date
Amendment 01	27 January 2016 2 patients enrolled to date

INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 02

Original Protocol Dated 15 April 2015

IND Number: 101,399; EudraCT Number: 2015-001580-39

A Phase 3, 24-Week Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study of Reslizumab Subcutaneous Dosing (110 mg Every 4 Weeks) in Patients With Oral Corticosteroid Dependent Asthma and Elevated Blood Eosinophils

Phase 3

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

Tel: _____

I have read the protocol C38072-AS-30027 with Amendment 02 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes approval of this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the drug that were furnished to me by the sponsor to all physicians and other study personnel responsible to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the drug and the conduct of the study. I agree to keep records on all patient information, study drug shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations.

Principal Investigator	Signature	Date

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
██████████	████████████████████	<i>18 July 2016</i>

CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS

Central Institutional Review Board

[REDACTED]

Central Clinical Laboratory

[REDACTED]

[REDACTED]

[REDACTED]

Electronic Data Capture

[REDACTED]

[REDACTED]

Web Integrated Interactive Response Technology

[REDACTED]

Bioanalytical Pharmacokinetics Evaluation

Teva Pharmaceuticals
Global Bioassay and Technology
West Chester, PA 19380

Clinical Study Protocol with Amendment 02

Bioanalytical Immunogenicity Evaluation

Teva Pharmaceuticals
Global Bioassays and Technology
West Chester, PA 19380



Teva Pharmaceuticals
Global Bioassays and Technology
West Chester, PA 19380

Central Spirometry, eDiary, PEF meters, and ECG



CLINICAL STUDY PERSONNEL CONTACT INFORMATION

For medical issues, contact the physician listed below:

Oversight Lead Medical Monitor:

[REDACTED]

For centers in North America

[REDACTED]

[REDACTED]

For Centers in Latin America

[REDACTED]

For centers in Europe and countries outside the Americas

[REDACTED]

For operational issues, contact the operational lead listed below:

[REDACTED]

For serious adverse events:

Send by e-mail to the local safety officer/contract research organization (LSO/CRO). The email address will be provided in the serious adverse event (SAE) report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.

CLINICAL STUDY PROTOCOL SYNOPSIS

Study C38072-AS-30027

Title of Study: A Phase 3, 24-Week Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study of Reslizumab Subcutaneous Dosing (110 mg Every 4 Weeks) in Patients With Oral Corticosteroid Dependent Asthma and Elevated Blood Eosinophils

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc

IND Number: 101,399 **EudraCT Number:** 2015-001580-39

Name of Active Ingredient: Reslizumab

Name of Investigational Product: Reslizumab for subcutaneous injection, 110 mg/mL

Phase of Clinical Development: 3

Number of Investigational Centers Planned: ~155

Countries Planned: ~19

Planned Study Period: Q3 2015 to Q3 2017

Number of Patients Planned: Approximately 76 patients per treatment group for a total of 152 patients

Study Population: This study will enroll male and female patients, 12 years of age and older, with oral corticosteroid (OCS)-dependent asthma and elevated eosinophils. Patients 12 to <18 years of age are excluded from participating in South Korea, the Netherlands, Bulgaria, and Argentina, and patients 66 years of age and older are excluded from participating in South Korea.

Primary Objective: The primary objective of this study is to determine the ability of reslizumab (110 mg) administered subcutaneously (sc) once every 4 weeks to produce a corticosteroid-sparing effect (as demonstrated by percent reduction in daily OCS use) in patients with OCS-dependent asthma and elevated blood eosinophils, without loss of asthma control.

Secondary Objective: To evaluate the clinical benefits of reslizumab in the context of OCS reduction

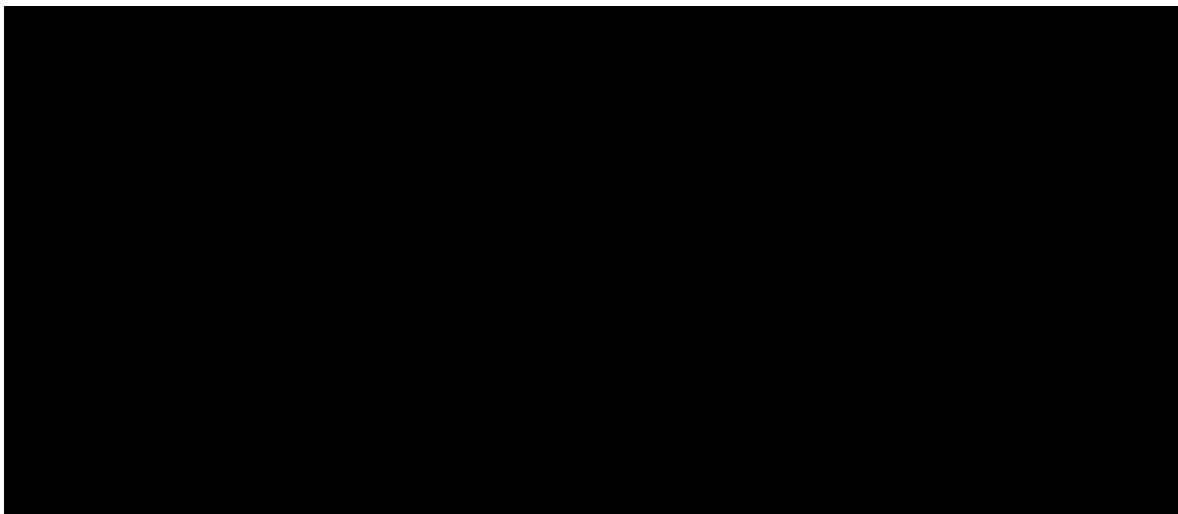
Other Objective: To evaluate the effect of reslizumab on standard asthma control measures during tapering of OCS in patients with OCS-dependent asthma.

Target Biomarker Objective: The target biomarker objective is to evaluate the effect of sc dosing of reslizumab on blood eosinophil counts.

Immunogenicity Objective: The immunogenicity objective is to evaluate the potential of sc dosing of reslizumab to raise anti-drug antibodies (ADAs).

Pharmacokinetic Objective: The pharmacokinetic (PK) objective is to characterize the PK of sc reslizumab in the study population.

Exploratory Objectives:



Safety Objective

- To evaluate the safety of chronic sc dosing of reslizumab and tapering of OCS

Study Endpoints:

Primary Efficacy Endpoint:

The primary efficacy variable and endpoint for this study is the categorized percent reduction in the daily OCS dose during weeks 20 to 24 as compared with the dose at the end of the optimization phase. Percent reduction will be categorized as follows:

- 90% to 100%
- 75% to <90%
- 50% to <75%
- >0% to <50%
- No decrease in OCS, or loss of baseline asthma control during weeks 20 through 24, or discontinuation from study drug

Loss of baseline asthma control will be defined as a forced expiratory volume in 1 second (FEV₁) value of less than 80% of baseline at the week 24 visit, or clinically significant worsening in Asthma Control Questionnaire (ACQ)-6 score (change in score of 0.5) at the week 24 visit compared with baseline, and/or clinical asthma exacerbation (CAE) 1 (as defined in the protocol) during weeks 20 through 24.

Secondary Efficacy Endpoints:

The secondary efficacy variables and endpoints for this study are as follows:

- Proportion of patients achieving $\geq 50\%$ reduction in OCS dose at weeks 20 to 24 relative to the OCS dose at date of randomization (DoR)/baseline, while maintaining asthma control

- Proportion of patients achieving dose reduction to ≤ 5 mg daily dose at weeks 20 to 24, while maintaining asthma control
- Percent change from DoR/baseline in OCS dose at weeks 20 to 24
- Proportion of patients achieving less than 5 mg decrement in OCS dose (ie, the minimal and non-responders) at weeks 20 to 24 compared with the OCS dose at DoR/baseline, while maintaining asthma control
- Clinical asthma exacerbation related:
 - Annualized rate of CAEs requiring a burst of systemic corticosteroid (injection, or if oral at least a doubling from the current OCS dose for at least 3 days); an asthma-specific hospital admission; or an asthma-specific emergency department visit during the treatment period (weeks 0 to 24)
- Proportion of patients discontinuing OCS at weeks 20 to 24, while maintaining asthma control

Other Prespecified Efficacy Endpoints:

The other efficacy endpoints are as follows:

- Time to first CAE
- Other clinic lung functions including the following:
 - Pre-bronchodilator FEV₁: change from DoR/baseline to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
 - Post-bronchodilator FEV₁: change from DoR/baseline to weeks 4, 12, 20, and 24 or early withdrawal
- Ambulatory lung function: change in morning (AM) and evening (PM) peak expiratory flow (PEF) from run-in baseline at each week through week 24 or early withdrawal
- Asthma Quality of Life (AQLQ) + 12 score: change from DoR/baseline to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- ACQ-6 score: change from DoR/baseline to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- Change in total inhalations of reliever bronchodilator (eg, short-acting beta-agonist, SABA) (number of inhalations per 24 hours: day+night) from run-in baseline at each week through week 24 or early withdrawal
- Number of nighttime awakenings due to asthma over the 24-week treatment period
- Change in total asthma symptom score from run-in baseline at each week through week 24 or early withdrawal
- European Quality of Life 5-dimension health state utility index (EQ-5D) score: change from DoR/baseline to week 24 or early withdrawal

- St. George’s Respiratory Questionnaire (SGRQ) score: change from DoR/baseline to weeks 12 and 24 or early withdrawal

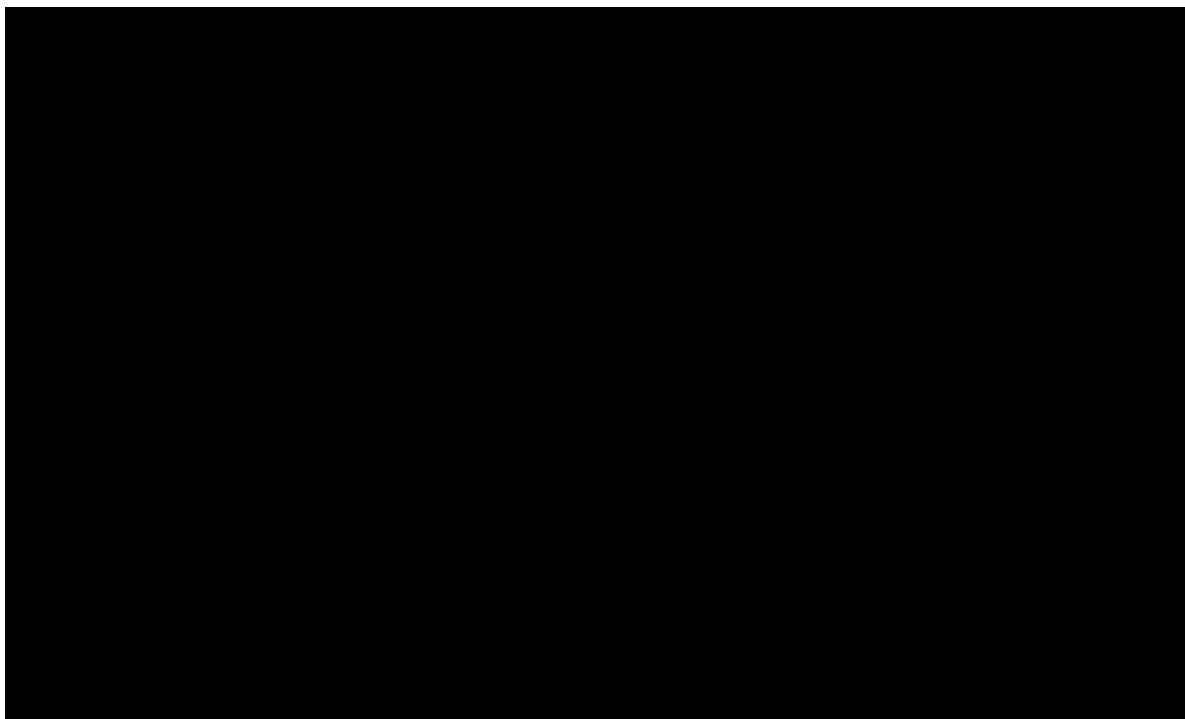
Target Biomarker Endpoints: The target biomarker endpoints are the blood eosinophil counts at DoR/baseline; weeks 4, 8, 12, 16, 20, and 24 or early withdrawal; and at the follow-up visit (approximately week 32).

Immunogenicity Endpoints: The immunogenicity endpoints are the immunogenicity incidence and the impact of ADA on clinical outcomes. The drug-emergent ADA response will be identified by analyzing ADA test results for serum samples obtained before the administration of study drug at DoR/baseline; weeks 4, 8 12, and 24 or early withdrawal; and at the follow-up visit (approximately week 32). An additional sample will be obtained at the late follow-up visit (approximately week 48).

Pharmacokinetic Endpoints: There are no specific endpoints related to PK. Measured concentrations will be used to characterize the PK of sc reslizumab in the studied population and to explore exposure-response relationships. Serum reslizumab concentrations will be determined from blood samples collected from each patient at DoR/baseline; and prior to study drug administration at weeks 4, 8 12, and 24 or early withdrawal; and at the follow-up visit (approximately week 32). An additional PK sample will be obtained at the late follow-up visit (approximately week 48).

Exploratory Endpoints:

The exploratory endpoints are as follows:



Safety Endpoints:

The safety endpoints for this study are as follows:

- Occurrence of adverse events throughout the study, including the week 32 follow-up visit
- Clinical laboratory evaluations of serum chemistry at screening, DoR, and periodically throughout the study
- Clinical laboratory evaluations of hematology throughout the study
- Vital signs (pulse, body temperature, respiratory rate, and blood pressure) measurements throughout the study
- Electrocardiogram (ECG) evaluation at screening and week 24 or early withdrawal
- Physical examination findings, including body weight measurements, throughout the study
- Signs and/or symptoms of adrenal insufficiency (OCS withdrawal effects) throughout the study
- Concomitant medication usage throughout the study, including the week 32 follow-up visit

General Design and Methodology:

This is a Phase 3, 24-week, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of sc reslizumab treatment at a dosage of 110 mg every 4 weeks in patients 12 years of age and older with OCS-dependent asthma and elevated blood eosinophils. The study will consist of a screening period of up to 2 weeks, followed by an optimization period of up to 10 weeks, a run-in period of at least 2 weeks, a 24-week double-blind treatment period, an 8-week follow-up period, and an additional 16-week follow-up period to collect drug wash-out samples for immunogenicity assessments. The patient may delay the early and/or late follow-up visits if the patient enrolls in an open-label, long-term safety study after end of treatment, if available.

During the optimization period, the patient's minimal effective OCS requirement will be determined. The patient's previous OCS will be standardized to an equivalent dose and regimen of prednisone to the nearest 2.5 mg daily. The patient's previous non-OCS background asthma controller medications will be continued unchanged throughout the pre-randomization period and the entire study. At the beginning of the optimization period, an asthma symptom diary and electronic peak flow meter will be distributed where the patient will record asthma symptoms, number of reliever bronchodilator inhalations, nighttime awakenings due to asthma requiring rescue inhaler, and AM and PM PEF. For optimization, the OCS dose should be reduced at 1-week intervals, for up to 10 weeks or until there is a worsening of asthma signs and symptoms (minimum 1 day in optimization). When either a lung function or symptomatic deterioration occurs, the patient will be returned to the previously effective OCS level, which will then constitute the minimally effective dose for the purpose of run-in. If this previously effective dose is no longer effective, the investigator can determine the clinically appropriate, minimally effective dose for the purpose of run-in. Note: Patient may enter run-in (V12) on the same day as

optimization ended if the patient is on the minimally effective prednisone dose (did not require a prednisone burst at end-optimization).

Patients whose minimal effective OCS dose remains between ≥ 5 mg and ≤ 40 mg of prednisone daily at the end of optimization may advance to run-in. During run-in, patients will continue to keep their daily asthma control diary and a PEF meter to perform daily self-monitoring of asthma symptoms while maintaining their minimally effective OCS dose and previous background asthma medications unchanged. The last 7 days of run-in will constitute the baseline level of control for analysis and as the basis for OCS reduction algorithm to be used during the treatment period. The optimization period will be considered finished when patients experience a worsening of asthma signs and symptoms or if a patient optimizes to an OCS dose of < 5 mg without a worsening of asthma signs and symptoms.

The post-randomization period consists of the treatment period, follow-up visit and late follow-up visit. During the treatment period, the patient will continue his/her usual non-OCS background asthma medication without change; the OCS dose will be tapered per protocol. The treatment periods consist of an induction period and an OCS reduction period. During the induction period, the minimally effective dose of OCS will be maintained, unchanged, during the first 4 weeks of the treatment period. During the OCS reduction period, the minimally effective OCS dose will be reduced per protocol at scheduled clinic visits from the beginning of week 5 (ie, end of the induction period) through week 20. If the OCS dose could not be decreased, it should be held constant, or may be increased to a previous level, at the investigator's discretion, until the next study visit at which dose reduction criteria are met. This dose will be maintained for the final 4 weeks of the treatment period.

If a patient elects to withdraw (or is discontinued from treatment by the investigator), every attempt will be made to continue the assessments subsequent to his/her withdrawal from the study.

Method of Blinding and Randomization: Patients will receive sc placebo or reslizumab 110 mg on a 1:1 basis in a randomized, double-blind fashion. Randomization will be assigned using interactive response technology. After randomization, patients and investigators will remain blinded to randomized treatment assignment during the study. The sponsor's personnel involved in the study will be blinded to the study drug identity after the run-in period until the database is locked for analysis and the treatment assignment is revealed, with the exception of the bioanalytical group (Global Bioassays and Technology), who, in order to facilitate PK and ADA sample analysis, will not be blinded. Eosinophils and monocytes will be redacted from the from the post baseline differential cell count reports to avoid the possibility of removing the blind.

In order to achieve balance between treatment groups in regard to average daily OCS use/requirement, randomization will be stratified by optimized, average daily OCS dose of > 10 mg or ≤ 10 mg and age (12 to < 18 years of age or ≥ 18 years of age) at baseline.

Study Drug Dose, Mode of Administration, and Administration Rate: Reslizumab will be administered as a fixed dose of 110 mg, as a sc injection in the upper arm(s) once every 4 weeks.

Investigational Product: Reslizumab for sc injection will be provided as a sterile solution presented as 110 mg (1 mL) per prefilled syringe, formulated at 110 mg/mL in [REDACTED] sodium acetate, with [REDACTED] sucrose, [REDACTED] polysorbate 80, pH 5.5 buffer.

Reference Therapy:

Placebo: Diluent solution administered sc

Comparison Drug: None

Duration of Patient Participation: The duration of patient participation is up to 62 weeks, including up to 2 weeks to satisfy screening criteria, up to 10 weeks to optimize OCS dose, a minimum 2-week run-in period on the optimized OCS dose, a 24-week treatment period, and an 8-week follow-up visit. It is expected that the optimization period will be shorter than 10 weeks for those patients who are at or near their optimal corticosteroid dose at enrollment. An additional late follow-up visit for immunogenicity testing will be performed 28 weeks after the last dose of study drug.

Criteria for Inclusion: Patients may be included in the study only if they meet all of the following criteria:

- a. The patient is male or female, 12 years of age and older, with a previous diagnosis of asthma. Patients 12 to <18 years of age are excluded from participating in South Korea, the Netherlands, and Argentina, and patients 66 years of age and older are excluded from participating in South Korea.
- b. Written informed consent is obtained. A patient 12 through <18 years of age must provide assent and his/her parent(s) or legal guardian(s) must provide consent.
- c. The patient continues to require an average daily maintenance dose of OCS for asthma of between 5 and 40 mg of prednisone or equivalent during the 3 months before screening. Patients on an OCS dose of >40 mg at screening who the investigator believes may be able to decrease OCS dose to ≤40 mg during the optimization period may also be enrolled. Note: every-other-day dosing that is within this daily average (ie, 10 to 80 mg) is allowed.
- d. The patient has a documented blood eosinophil level of at least 300/μL during the previous 12 months while on at least medium total daily dose of inhaled corticosteroid (ICS) based on Global Initiative for Asthma 2016 clinical comparability table (Appendix A of the protocol), or ≥300/μL at screening while on chronic OCS or that becomes manifest during the OCS optimization period or at the week -2 visit (end of optimization period/beginning of run-in period).
- e. The patient has required at least 880 μg of inhaled fluticasone propionate or equivalent daily PLUS another controller(s) (eg, long-acting beta-agonist [LABA], long-acting anti-muscarinic antagonist, leukotriene inhibitor, or theophylline), or documented intolerance to another controller, for at least 6 months before the screening visit. For a fixed-dose ICS/LABA preparation, the highest labeled dose in that region will satisfy this criterion. For patients 12 through <18 years of age, the ICS dose must correspond to at least a medium total daily ICS dose. Note: the dose and regimen of asthma controllers and any allergen immunotherapy should have been stable during the 30 days before signing the Informed Assent Form/Informed Consent Form (ICF).

- f. The patient has FEV₁ reversibility of at least 12% after administration of inhaled reliever medication according to the standard American Thoracic Society (ATS) or European Respiratory Society (ERS) protocol. Given the refractory nature of the disease in this population and the influence of high background controller medications on reversibility testing, documented FEV₁ reversibility of 12% or a provocation concentration producing a 20% fall in FEV₁ for methacholine of ≤ 8 mg/mL within 24 months of the screening visit, and performed according to the standard ATS/ERS procedures, would fulfill this criterion. Patients may be screened again if they did not meet spirometry/reversibility criteria initially. The duration between the date of Screen Failure and the re-screening must be >30 days.
- g. Females of childbearing potential (not surgically sterile by hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or 2 years postmenopausal) must have exclusively same-sex partners or use medically acceptable methods of birth control and must agree to continue use of this method for the duration of the study and for 5 months after the last study drug dose. Acceptable methods of birth control include intrauterine device, systemic hormonal contraceptive (oral, implanted, transdermal, or injected), barrier method with spermicide, abstinence, bilateral fallopian tube occlusion, and partner vasectomy.
- h. The patient must be willing and able to comply with study restrictions, willing and able to perform requisite procedures and to remain at the clinic for the required duration during the study period, and willing to return to the clinic for the follow-up evaluation as specified in this protocol.
- i. Except for the OCS, which will be adjusted per protocol, the patient must maintain his/her usual asthma controller regimen without change throughout the screening, optimization, run-in, and treatment periods.

Criteria for Exclusion: Patients will be excluded from participating in this study if they meet any of the following criteria:

- a. The patient has any clinically significant, uncontrolled medical condition (treated or untreated) that would interfere with the study schedule or procedures and interpretation of efficacy results or would compromise the patient's safety.
- b. The patient has another confounding underlying lung disorder (eg, chronic obstructive pulmonary disease, interstitial lung disease, bronchiectasis eosinophilic granulomatosis with polyangiitis [also known as Churg-Strauss syndrome], or allergic bronchopulmonary aspergillosis).
- c. The patient has a known hypereosinophilic syndrome.
- d. The patient has a history of any malignancy within 5 years of the screening visit, except for treated and cured non-melanoma skin cancers.
- e. The patient is pregnant or intends to become pregnant during the study or within 5 months from last dose of study drug or is lactating. Any woman becoming pregnant will be withdrawn from the study.
- f. The patient required treatment for an asthma exacerbation within 4 weeks of screening.

- g. The patient is a current smoker (ie, has smoked within the last 6 months before screening) or has a smoking history ≥ 10 pack-years.
- h. The patient is currently using any systemic immunosuppressive or immunomodulatory biologic (eg, anti-immunoglobulin E monoclonal antibody [mAb] or other mAb [eg, mepolizumab] or soluble receptor) or non-biologic (eg, methotrexate, cyclosporine), except maintenance OCS for the treatment of asthma. Previous use of such agents that occurred >5 half-lives from the screening visit may be allowed, if approved by the medical monitor.
- i. The patient participated in a clinical study within 30 days or 5 half-lives of the investigational drug before screening, whichever is longer.
- j. The patient was previously exposed to benralizumab within 12 months of screening.
- k. The patient was previously exposed to reslizumab
- l. The patient has a history of immunodeficiency disorder including human immunodeficiency virus.
- m. The patient has current suspected drug and/or alcohol abuse.
- n. The patient has had an active helminthic parasitic infection or was treated for one within 6 months of screening.
- o. The patient has a history of allergic reactions or hypersensitivity to any component of the study drug.
- p. The patient has a history of latex allergy. (The current prefilled syringe device has a natural rubber component to the needle shield.)

Criteria for Randomization

After completion of the optimization/run-in period, patients may continue in the study if they meet all of the following criteria:

- a. The patient must be using an average daily dose of no less than 5 mg of prednisone after OCS optimization. A patient requiring less than 5 mg of prednisone to maintain control should not be randomized.
- b. The patient must be using an average daily dose of no more than 40 mg of prednisone after OCS optimization. A patient requiring more than 40 mg of prednisone to maintain control should not be randomized.
- c. The patient should not have had an asthma exacerbation during the run-in period, defined as requiring a burst of systemic corticosteroid for an asthma worsening (injection, or if oral, at least a doubling from the current OCS dose for at least 3 days); an asthma-specific hospital admission; or an asthma-specific emergency department visit.
- d. The patient must have completed at least 4 days of diary entries (or any combination of 4 morning and 4 evening recordings) during the last 7 days of the run-in period.

Measures and Time Points:**Primary Efficacy Measure and Time Points**

The primary efficacy measure and endpoint for this study is the percent reduction in the daily OCS during weeks 20 to 24 compared with the dose at the end of the optimization phase.

Secondary Efficacy Measures and Time Points

The secondary efficacy measures and time points for this study are as follows:

- $\geq 50\%$ reduction in OCS dose, while maintaining asthma control, at weeks 20 to 24 relative to OCS dose at DoR/baseline
- Reduction to ≤ 5 mg daily dose at weeks 20 to 24, while maintaining asthma control
- OCS dose at weeks 20 to 24 relative to DoR/baseline
- Less than 5 mg decrement in OCS dose (ie, the minimal and non-responders) at weeks 20 to 24, while maintaining asthma control
- Clinical asthma exacerbation related:
 - Annualized rate of CAEs requiring a burst of systemic corticosteroid (injection, or if oral, at least a doubling from the current OCS dose for at least 3 days); an asthma-specific hospital admission; or an asthma-specific emergency department visit during the treatment period (weeks 0 to 24)
- OCS discontinuations at weeks 20 to 24, while maintaining asthma control

Other Efficacy Measures and Time Points

The other efficacy measures and their time points for this study are as follows:

- Time to first CAE
- other clinic lung functions including the following:
 - Spirometry, including pre-bronchodilator FEV₁ (at baseline/DoR; weeks 4, 8, 12, 16, 20, and 24 or early withdrawal) and post-bronchodilator FEV₁ (at baseline/DoR; weeks 4, 12, 20, and 24 or early withdrawal)
- Ambulatory lung function including AM and PM PEF based on the PEF meter (run-in baseline and weekly averages)
- AQLQ + 12 at DoR/baseline and weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- ACQ-6 at DoR/baseline and weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- Total reliever bronchodilator use (number of inhalations per 24 hours: day and night) based on the daily asthma control diary (run-in baseline and weekly averages)
- Nighttime awakenings due to asthma based on the daily asthma control diary (run-in baseline and weekly averages)
- Asthma symptoms based on the daily asthma control diary (run-in baseline and weekly averages)

- EQ-5D: baseline/DoR and week 24 or early withdrawal
- SGRQ score at DoR/baseline; weeks 12 and 24 or early withdrawal

Target Biomarker, Immunogenicity, and Pharmacokinetics Measures and Time Points

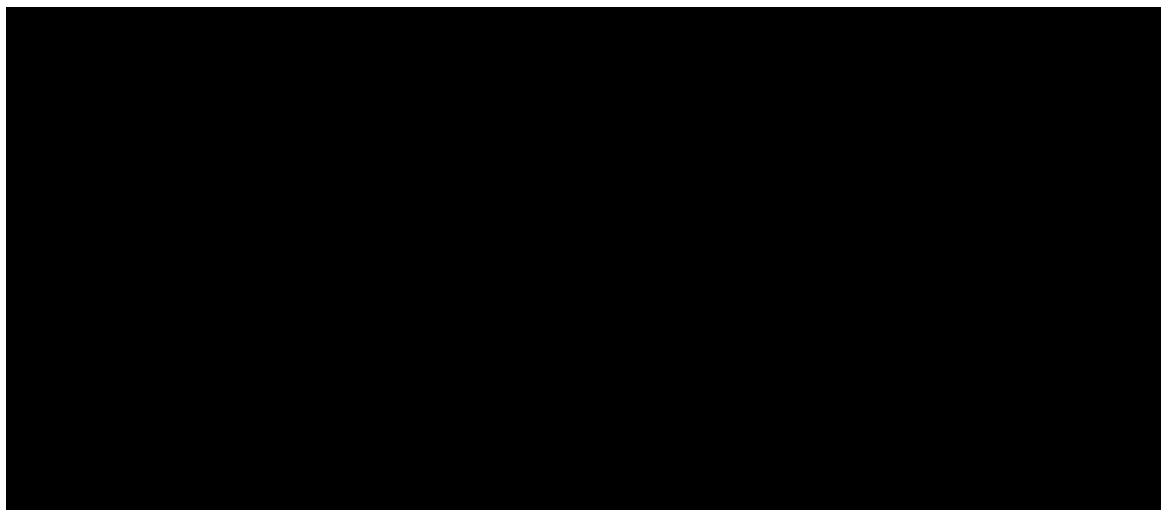
Target biomarkers: Blood eosinophils will be determined from blood samples collected from each patient at DoR/baseline; weeks 4, 8, 12, 16, 20, and 24 or early withdrawal. Blood eosinophils will also be determined from samples collected at the follow-up visit (approximately week 32).

Immunogenicity: Serum ADAs will be determined from blood samples collected from each patient at DoR/baseline; prior to study drug administration at weeks 4, 8, 12, and 24 or early withdrawal; and at the follow-up visit (approximately week 32). An additional sample will be obtained at the late follow-up visit (approximately week 48).

Pharmacokinetics: Serum reslizumab concentrations will be determined from blood samples collected from each patient at DoR/baseline, prior to study drug administration at weeks 4, 8, 12, 16, 20, and 24 or early withdrawal, and at the follow-up visit (approximately week 32). An additional PK sample will be obtained at the late follow-up visit (approximately week 48).

Exploratory Measures and Time Points

The following exploratory measures will be evaluated:



Safety Measures and Time Points

The following safety measures will be evaluated:

- Inquiries about adverse events throughout the study
- Clinical laboratory evaluations of serum chemistry at screening, DoR/baseline, and periodically throughout the study
- Clinical laboratory evaluations of hematology throughout the study
- Vital signs (pulse, body temperature, respiratory rate, and blood pressure) assessments throughout the study
- ECG at screening and week 24 or early withdrawal

- Physical examinations throughout the study
- Monitoring and evaluation of any signs and/or symptoms of adrenal insufficiency (OCS withdrawal effects) throughout the study
- Inquiries about concomitant medication usage throughout the study

Allowed and Disallowed Medications Before and During the Study:**Allowed:**

- Inhaled fluticasone propionate at 880 µg or equivalent daily PLUS another controller(s) (eg, LABA, LAMA, leukotriene inhibitor, or theophylline), for at least 6 months before the screening visit. For a fixed-dose ICS/LABA preparation, the highest labeled dose in that region will satisfy this criterion.
- For patients 12 through <18 years of age, the ICS dose must correspond to at least a medium total daily dose for the formulation.
- Allergen immunotherapy is allowed.
- Inhaled reliever medications are allowed as needed for the relief of intermittent asthma symptoms.
- Prior asthma medications such as ICS, leukotriene pathway modifiers, long-acting bronchodilators, and mast cell stabilizers may be taken concomitantly and should not be altered during this study unless patient safety is at risk.

Disallowed During the Study:

- Patients should refrain from using reliever inhalers for 6 hours before any study visit that includes spirometry or airway reversibility testing, including the screening visit.
- If a patient is taking LABAs, these should be withheld for 12 hours before any study visit that includes spirometry or airway reversibility testing, including the screening visit.
- Any immunosuppressive or immunomodulatory agents (biological and non-biological), including, but not limited to methotrexate, cyclosporine, and interferon (excluding systemic corticosteroids prescribed for asthma and maintenance allergen immunotherapy)
- All biologic therapies, including, but not limited to omalizumab (Xolair[®]), mepolizumab, benralizumab, lebrikizumab, and anti-tumor necrosis factor monoclonal antibodies
- All nonbiologic investigational drugs
- Inhaled nicotine (including electronic cigarettes)

Statistical Considerations:

Sample Size Rationale: The sample size was calculated based on the following assumptions:

- Categorical reduction in OCS dose after 24 weeks of treatment will have the following distribution for the placebo group:

Clinical Study Protocol with Amendment 02

- 10.9% of patients will have 90% to 100% reduction
 - 7.9% of patients will have 75% to <90% reduction
 - 14.8% of patients will have 50% to <75% reduction
 - 10.8% of patients will have 0% to <50% reduction
 - 55.6% of patients will have no reduction, loss of asthma control, or discontinuation from study drug
- The overall odds ratio between reslizumab and placebo based on proportional odds model will be 2.63.
 - Alpha level of 0.05

Based on the above assumptions, a sample size of 76 patients per group will provide 90% power to detect a significant effect of reslizumab over placebo on the probability for a higher categorical reduction of OCS dose.

Analysis of Primary Endpoint: For this study, the primary endpoint is the categorical reduction in OCS dose during weeks 20 to 24, compared with DoR/baseline dose, while maintaining asthma control. Five categories of reduction will be defined: 90% to 100% reduction, 75% to <90% reduction, 50% to <75% reduction, 0% to <50% reduction, and no decrease in OCS dose/loss of asthma control/discontinuation from study drug. This categorical endpoint will be analyzed using proportional odds model. The model will include the treatment group and randomization stratification factors as model factors and the OCS baseline dose and duration of historical OCS use (ie, before screening) as covariates. The overall odds ratio between reslizumab and placebo and its 95% confidence interval will be estimated.

For the primary analysis, patients who discontinue the study drug early will be considered as nonresponders and will be categorized in the lowest category of response.

Sensitivity analysis will use data collected after early discontinuation from the study drug. In this analysis, patients will be categorized according to the percent dose reduction at 24 weeks, regardless of whether they withdrew early from treatment or completed treatment.

If a patient elects to withdraw (or is discontinued from treatment by the investigator), every attempt will be made to continue the assessments subsequent to his/her withdrawal from the study.

Analysis of Secondary Endpoints: All efficacy variables will be summarized by treatment group. For continuous variables, the summary statistics will include number, mean, standard deviation, standard error, median, minimum, and maximum. For categorical variables, patient counts and percentages will be provided.

Proportion of patients achieving $\geq 50\%$ reduction in OCS dose at weeks 20 to 24 while maintaining asthma control, proportion of patients achieving dose reduction to ≤ 5 mg daily dose at weeks 20 to 24 while maintaining asthma control, proportion of patients achieving less than 5 mg decrement in OCS dose (ie, the minimal and non-responders) at weeks 20 to 24 while maintaining asthma control, and proportion of patients discontinuing OCS at weeks 20 to 24 while maintaining asthma control will be analyzed using a logistic regression model. The model

will include the treatment group and randomization stratification factors as model factors and the OCS baseline dose and duration of historical OCS use (ie, before screening) as covariates.

For the categorical secondary analysis, patients who discontinue the study drug early will be considered as nonresponders and will be categorized in the lowest category of response

Analysis of the mean percentage change from baseline in OCS dose at weeks 20 to 24 will use an analysis of covariance model with treatment group and stratification factors as model factors and the OCS baseline dose and duration of historical OCS use (ie, before screening) as covariates.

The frequency of CAEs will use the negative binomial (NB) regression model. The primary NB model will include the treatment group and randomization stratification factors as model factors and an offset variable. The offset variable will be calculated as the logarithm of follow-up duration minus the summed duration of exacerbations. The ratio of CAE rate between the treatment groups and its 95% confidence interval (CI) will be estimated from the NB model.

Additional covariates or factors may be added to the statistical models. These will be detailed in the statistical analysis plan.

Multiple Comparisons and Multiplicity: A fixed sequence multiple testing procedure will be implemented to test the primary and secondary variables while controlling the overall type I error rate at 0.05. If the resulting 2-sided p-value from the primary comparison is ≤ 0.05 , then the next comparison of interest (first secondary variable) will be interpreted inferentially at 0.05. This process will continue through the secondary variables either until all comparisons of interest are interpreted inferentially or until the point at which the resulting 2-sided p-value for a comparison of interest is >0.05 . At the point where $p > 0.05$, no further comparisons will be interpreted inferentially. The hierarchy of endpoints is as defined in Section 9.5.2 of the protocol.

No multiplicity adjustments will be made for other efficacy and exploratory efficacy analyses.

Analysis of Other/Exploratory Endpoints: Statistical modeling to be used for other and exploratory efficacy endpoints will be described and detailed in the statistical analysis plan.


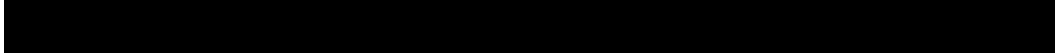

Safety and PK Analyses: Safety and PK data will be summarized using descriptive statistics by time point and/or treatment group, as appropriate.


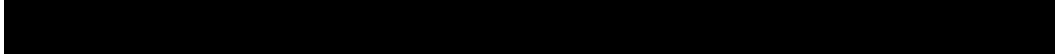
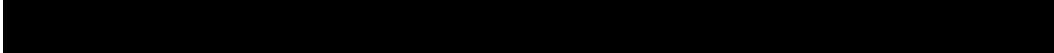
TABLE OF CONTENTS

TITLE PAGE	1
AMENDMENT HISTORY	2
INVESTIGATOR AGREEMENT.....	3
CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS	4
CLINICAL STUDY PERSONNEL CONTACT INFORMATION	6
CLINICAL STUDY PROTOCOL SYNOPSIS.....	7
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS.....	30
1. BACKGROUND INFORMATION	33
1.1. Introduction.....	33
1.2. Name and Description of Investigational Product.....	34
1.3. Findings From Nonclinical and Clinical Studies.....	34
1.3.1. Nonclinical Studies.....	34
1.3.2. Clinical Studies.....	35
1.3.2.1. Clinical Pharmacology Studies.....	35
1.3.2.2. Clinical Safety and Efficacy Studies	36
1.4. Known and Potential Risks and Benefits to Human Patients	38
1.4.1. Risks of Reslizumab	39
1.4.2. Benefits of Reslizumab.....	39
1.4.3. Overall Risk and Benefit Assessment for This Study	39
1.5. Selection of Drugs and Dosages	40
1.5.1. Justification for Dosage of Active Drug.....	40
1.5.2. Justification for Use of Placebo.....	41
1.6. Compliance Statement.....	41
1.7. Population To Be Studied and Justification.....	41
1.8. Location and Timing of Study.....	41
2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES	42
2.1. Purpose of the Study	42
2.2. Study Objectives.....	42
2.2.1. Primary Objective.....	42
2.2.2. Secondary Objective.....	42
2.2.3. Other Efficacy Objective.....	42

2.2.4.	Target Biomarker Objective	42
2.2.5.	Immunogenicity Objective	42
2.2.6.	Pharmacokinetic Objective	42
2.2.7.	Exploratory Objectives	42
2.2.8.	Safety Objective.....	43
2.3.	Study Endpoints.....	43
2.3.1.	Primary Efficacy Endpoint	43
2.3.2.	Secondary Efficacy Endpoints.....	43
2.3.3.	Other Prespecified Efficacy Endpoints.....	44
2.3.4.	Target Biomarker Endpoint	45
2.3.5.	Immunogenicity Endpoints.....	45
2.3.6.	Pharmacokinetic Endpoints	45
2.3.7.	Exploratory Endpoints	45
2.3.8.	Safety Endpoints	46
3.	STUDY DESIGN	47
3.1.	General Design and Study Schema.....	47
3.1.1.	Screening Period.....	47
3.1.2.	Optimization Period.....	47
3.1.3.	Run-In Period.....	49
3.1.4.	Treatment Period	49
3.1.4.1.	Handling of Asthma Exacerbations During the Treatment Period.....	51
3.2.	Justification for Study Design	53
3.3.	Primary and Secondary Measures and Time Points	53
3.3.1.	Primary Efficacy Measure and Time Points	53
3.3.2.	Secondary Efficacy Measures and Time Points	54
3.3.3.	Other Prespecified Efficacy Measures and Time Points	54
3.4.	Target Biomarker Measures and Time Points	55
3.5.	Immunogenicity Measures and Time Points	55
3.6.	Pharmacokinetic Measures and Time Points	55
3.7.	Exploratory Measures and Time Points.....	55
3.8.	Safety Measures and Time Points.....	55
3.9.	Randomization and Blinding	56
3.10.	Maintenance of Randomization and Blinding.....	56

3.10.1.	Randomization.....	56
3.10.2.	Blinding/Unblinding.....	56
3.11.	Drugs Used in the Study.....	57
3.11.1.	Investigational Product.....	57
3.11.2.	Placebo.....	58
3.12.	Drug Supply and Accountability.....	58
3.12.1.	Drug Storage and Security.....	58
3.12.2.	Drug Accountability.....	58
3.13.	Duration of Patient Participation and Justification.....	58
3.14.	Stopping Rules and Discontinuation Criteria.....	59
3.15.	Source Data Recorded on the Case Report Form.....	59
3.16.	Study Procedures.....	59
3.16.1.	Procedures for Screening and Enrollment (Visit 1).....	64
3.16.2.	Procedures Before Study Drug Treatment.....	65
3.16.2.1.	Procedures During the Optimization Period (Weeks –12 through –3 [Visits 2 through 11]).....	65
3.16.2.2.	Procedures During the Run-In Period (Week –2 [Visit 12]).....	66
3.16.2.3.	Procedures at Baseline/Day of Randomization (Week 0 [Visit 13]).....	66
3.16.3.	Procedures During Study Drug Treatment.....	68
3.16.3.1.	Double-Blind Treatment Period (Weeks 1 Through 24 [Visits 13 Through 19]).....	68
3.16.4.	Procedures After Study Drug Treatment.....	69
3.16.5.	Unscheduled Visits.....	70
4.	SELECTION AND WITHDRAWAL OF PATIENTS.....	72
4.1.	Patient Inclusion Criteria.....	72
4.2.	Patient Exclusion Criteria.....	73
4.3.	Justification for Key Inclusion and Exclusion Criteria.....	74
4.4.	Randomization criteria.....	74
4.5.	Criteria and Procedures for Discontinuation of Study Treatment and/or Study Withdrawal.....	75
4.5.1.	Discontinuation of Study Treatment.....	75
4.5.2.	Complete Withdrawal from Study.....	76
5.	TREATMENT OF PATIENTS.....	77

5.1.	Drugs Administered During the Study	77
5.2.	Restrictions	77
5.3.	Prior and Concomitant Therapy or Medication	77
5.4.	Procedures for Monitoring Patient Compliance	78
5.5.	Total Blood Volume	78
6.	ASSESSMENT OF EFFICACY AND IMMUNOGENICITY	79
6.1.	Primary Efficacy Measure and Justification	79
6.2.	Spirometry	79
6.3.	PEF monitoring	79
6.4.	Asthma Quality of Life Questionnaire for Patients 12 Years and Older	79
6.5.	Asthma Control Questionnaire	80
6.6.	Asthma Symptom Assessment	80
6.7.	Asthma Exacerbations	80
6.8.	European Quality of Life 5-Dimension Health State Utility Index	81
6.9.	Inhaled Reliever Medication Use	81
6.10.	Nighttime Awakenings Requiring Rescue Inhaler Use	81
6.11.		81
6.12.		81
6.13.		81
6.14.	St. George’s Respiratory Questionnaire	82
6.15.	Target Biomarker Measures	82
7.	ASSESSMENT OF SAFETY	83
7.1.	Adverse Events	83
7.1.1.	Definition of an Adverse Event	83
7.1.2.	Recording and Reporting Adverse Events	84
7.1.3.	Severity of an Adverse Event	85
7.1.4.	Relationship of an Adverse Event to the Study Drug	85
7.1.5.	Relationship of an Adverse Event to OCS Reduction	85
7.1.6.	Serious Adverse Events	86
7.1.6.1.	Definition of a Serious Adverse Event	86
7.1.6.2.	Expectedness	86
7.1.6.3.	Reporting a Serious Adverse Event	86
7.1.7.	Specific Protocol-Defined Adverse Events	88

7.1.7.1.	Adrenal Insufficiency	88
7.1.7.2.	Protocol-Defined Adverse Events for Expedited Reporting to Teva	89
7.1.7.3.	Specific Adverse Event Case Report Form Capturing	89
7.1.8.	Withdrawal Due to an Adverse Event	90
7.1.9.	Overdose of Study Drug	91
7.1.10.	Protocol Deviations Because of an Adverse Event	91
7.2.	Pregnancy	91
7.3.	Clinical Laboratory Tests	92
7.3.1.	Serum Chemistry	92
7.3.2.	Hematology.....	93
7.3.3.	Other Clinical Laboratory Tests	93
7.3.3.1.	Urinalysis.....	93
7.3.3.2.	Hepatitis B, Hepatitis C, and HIV	94
7.3.3.3.	Human Chorionic Gonadotrophin Tests.....	94
7.4.	Vital Signs	94
7.5.	Electrocardiography.....	94
7.6.	Physical Examinations.....	95
7.7.	Concomitant Therapy or Medication.....	95
7.8.	Methods and Timing of Assessing, Recording, and Analyzing Safety Data.....	95
8.	ASSESSMENT OF PHARMACOKINETICS/PHARMACODYNAMICS, AND IMMUNOGENICITY	96
8.1.	Pharmacokinetic Variables	96
8.1.1.	Specimen Sampling and Handling.....	96
8.1.2.	Shipment and Analysis of Samples	96
8.2.	Pharmacodynamic Variables	97
8.2.1.	Blood Eosinophil Counts.....	97
8.2.2.	Exploratory Biomarker Analysis	97
8.3.	Immunogenicity Testing.....	97
8.3.1.	Blood Sampling and Handling.....	97
8.3.2.	Shipment and Analysis of Samples	98
8.4.		98
8.4.1.		98
8.4.2.		99

8.5.		99
8.5.1.		99
8.5.2.		99
9.	STATISTICS	100
9.1.	Sample Size and Power Considerations	100
9.2.	Analysis Sets.....	100
9.2.1.	Intent-to-Treat Analysis Set.....	100
9.2.2.	Safety Analysis Set.....	101
9.2.3.	Additional Analysis Sets.....	101
9.2.3.1.	Per-Protocol Analysis Set.....	101
9.3.	Data Handling Conventions.....	101
9.4.	Study Population.....	101
9.4.1.	Patient Disposition.....	101
9.4.2.	Demographic and Baseline Characteristics	101
9.5.	Efficacy Analysis.....	102
9.5.1.	Primary Endpoint.....	102
9.5.2.	Secondary Endpoints	102
9.5.3.	Other Secondary Efficacy Endpoints:	103
9.5.4.	Exploratory Endpoints	103
9.5.5.	Target Biomarker Endpoint.....	104
9.5.6.	Planned Method of Analysis.....	104
9.5.6.1.	Primary Efficacy Analysis.....	104
9.5.6.2.	Sensitivity Analysis	104
9.5.6.3.	Secondary Efficacy Analysis.....	105
9.5.6.4.	Other Efficacy Analysis.....	105
9.5.6.5.	Exploratory Efficacy Analysis.....	105
9.6.	Multiple Comparisons and Multiplicity.....	105
9.7.	Safety Endpoints and Analysis	106
9.7.1.	Safety Endpoints	106
9.7.2.	Safety Analysis	106
9.8.	Pharmacokinetic Analysis	107
9.9.	Biomarker Analysis	107
9.10.	Pharmacodynamic Analysis.....	107

9.11.	Immunogenicity Analysis.....	107
9.12.	Planned Interim Analysis.....	107
9.13.	Reporting Deviations From the Statistical Plan.....	107
10.	DIRECT ACCESS TO SOURCE DATA/DOCUMENTS.....	108
11.	QUALITY CONTROL AND QUALITY ASSURANCE	109
11.1.	Protocol Amendments and Protocol Deviations and Violations	109
11.1.1.	Protocol Amendments	109
11.1.2.	Protocol Violations	109
11.2.	Information to Study Personnel.....	109
11.3.	Study Monitoring.....	110
11.4.	Clinical Product Complaints.....	110
11.4.1.	Product Complaint Information Needed From the Investigational Center.....	111
11.4.2.	Handling the Study Drug at the Investigational Center.....	111
11.4.3.	Adverse Events or Serious Adverse Events Associated with a Product Complaint	112
11.4.4.	Documenting a Product Complaint	112
11.5.	Audit and Inspection.....	112
12.	ETHICS	113
12.1.	Informed Consent/Assent	113
12.2.	Health Authorities and Independent Ethics Committees/Institutional Review Boards	113
12.3.	Confidentiality Regarding Study Patients	114
12.4.	Declaration of the End of the Clinical Study.....	114
12.5.	Registration of the Clinical Study.....	114
13.	DATA HANDLING, DATA QUALITY ASSURANCE, AND RECORD KEEPING	115
13.1.	Data Collection	115
13.2.	Data Quality Control.....	115
13.3.	Archiving of Case Report Forms and Source Documents.....	116
13.3.1.	Sponsor Responsibilities.....	116
13.3.2.	Investigator Responsibilities.....	116
14.	FINANCING AND INSURANCE.....	118
15.	REPORTING AND PUBLICATION OF RESULTS	119

16. REFERENCES120

17. SUMMARY OF CHANGES TO PROTOCOL122

17.1. Amendment 02 Dated 18 JULY 2016122

17.2. Amendment 01 Dated 27 January 2016.....135

APPENDIX A. GLOBAL INITIATIVE FOR ASTHMA ICS EQUIVALENCY
TABLE160

APPENDIX B. ASTHMA QUALITY OF LIFE QUESTIONNAIRE +12.....161

APPENDIX C. ASTHMA CONTROL QUESTIONNAIRE167

APPENDIX D. ASTHMA CONTROL DIARY169

APPENDIX E. EUROPEAN QUALITY OF LIFE 5-DIMENSION HEALTH STATE
UTILITY INDEX171

APPENDIX F. [REDACTED] ..174

APPENDIX G. ST. GEORGE’S RESPIRATORY QUESTIONNAIRE175

APPENDIX H. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS.....181

APPENDIX I. OPPORTUNISTIC INFECTIONS182

LIST OF TABLES

Table 1: Optimization Phase Prednisone Dose Reduction Algorithm.....49

Table 2: Eligibility Criteria for Scheduled Oral Corticosteroid Reductions During the Treatment Period (Must Meet All)50

Table 3: Oral Corticosteroid Decrements During the Treatment Period51

Table 4: Rationale for Protocol.....53

Table 5: Study Procedures and Assessments60

Table 6: Changes to the Protocol122

Table 7: Changes to the Protocol135

LIST OF FIGURES

Figure 1: Overall Study Schema52

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
βHCG	beta human chorionic gonadotropin
ACQ	Asthma Control Questionnaire
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AM	morning
anti-hIL-5	humanized anti-human interleukin-5
AQLQ	Asthma Quality of Life
ATS	American Thoracic Society
BUN	blood urea nitrogen
CAE	clinical asthma exacerbation
CBC	complete blood count
CDMS	clinical data management system
CFR	Code of Federal Regulations
CPK	creatinine phosphokinase
CPP	clinical project physician
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
DMC	Data Monitoring Committee
DoR	date of randomization
ECG	electrocardiography, electrocardiogram
eDiary	electronic diary
EOT	end of treatment
EQ-5D	European Quality of Life 5-dimension health state utility index
ERS	European Respiratory Society
EU	European Union
FEV ₁	forced expiratory volume in 1 second
FEF _{25%-75%}	forced expiratory flow at 25% and 75% of the forced vital capacity

Abbreviation	Term
FDA	Food and Drug Administration
FVC	forced vital capacity
GCP	Good Clinical Practice
HCV	hepatitis C
HEENT	Head, Eyes, Ears, Nose, and Throat
HIV	human immunodeficiency virus
IB	Investigator’s Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroids
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IL	interleukin
im	intramuscular
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
iv	intravenous
IWRS	Interactive Web Response System
LABA	long-acting beta-agonist
LSO	local safety officer
LSLV	Last Subject Last Visit
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NB	negative binomial
NOEL	no-observed-effect level
OCS	oral corticosteroid
PD	pharmacodynamics/s
PEF	peak expiratory flow
PGx	pharmacogenomic(s)
PK	pharmacokinetic/s

Abbreviation	Term
PM	evening
SABA	short-acting beta-agonist
sc	subcutaneous
SD	standard deviation
SDV	source document verification
SE	standard error
SGRQ	St. George's Respiratory Questionnaire
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US(A)	United States (of America)
WBC	white blood cell
WHO	World Health Organization
WHO Drug	World Health Organization (WHO) drug dictionary

1. BACKGROUND INFORMATION

1.1. Introduction

Asthma is a common chronic lung disorder characterized by inflammation and narrowing of the airways. Symptoms of asthma include cough, breathlessness, and wheezing. The most recent estimates suggest that as many as many as 334 million people in the world have asthma ([Global Asthma Network 2014](#)).

Inhaled corticosteroids (ICS) are the most effective treatment agents for the long-term control of asthma (see [EPR-3 2007](#) and [GINA 2014](#) for review). For patients whose asthma is not adequately controlled on daily ICS alone, the addition of long-acting beta-agonists (LABAs) or and/or other controller therapies often provides additional control. There are currently very few options for patients whose asthma is inadequately controlled on ICS/LABA. The most severely affected patients with asthma may require daily oral corticosteroid (OCS) doses to maintain asthma control ([GINA 2014](#)). Chronic use of daily OCS is associated with the severe adverse effects of an iatrogenic Cushing's syndrome, including increased risk of infections, impaired growth in children, hyperglycemia, low bone density, elevated blood pressure, cataracts, and adrenal insufficiency ([Walsh et al 2001](#), [Stanbury and Graham 1998](#)). Risk can be decreased by maintaining patients on the lowest possible dose of OCS and utilization of corticosteroid-sparing strategies.

Interleukin (IL)-5 is the prototypic maturation and survival factor for eosinophilic granulocytes, which has been strongly implicated in asthma pathogenesis ([Wardlaw et al 2000](#)). Eosinophils are major effector cells involved in the initiation and propagation of diverse inflammatory responses. A high blood eosinophil count is a risk factor for increased future asthma exacerbations and excessive short-acting beta-agonist (SABA) use after adjustment of potential confounders in adults with persistent asthma, which suggests a higher disease burden in patients with asthma and high blood eosinophil counts ([Tran et al 2014](#), [Zeiger et al 2014](#)).

Therapies directed against IL-5 or its receptor (mepolizumab, reslizumab, and benralizumab) work by reducing eosinophil counts in the circulation and in the airway and have recently met a clinical proof of concept (reduction in asthma exacerbations, improved Asthma Control Questionnaire [ACQ] scores, or improved lung function) in Phase 2 and Phase 3 studies in primarily adult populations with asthma and elevated sputum or blood eosinophils ([Castro et al 2011](#), [Haldar et al 2009](#), [Molfino et al 2012](#), [Nair et al 2009](#), [Ortega et al 2014](#), [Pavord et al 2012](#)).

Reslizumab is a humanized anti-human IL-5 monoclonal antibody (mAb) of the immunoglobulin G (IgG) 4/ κ isotype being developed for the treatment of uncontrolled asthma in patients with elevated blood eosinophils. Confirmatory Phase 3 safety and efficacy studies for administration of reslizumab by the intravenous (iv) route have concluded the clinical portion; results are notable for a significant reduction in clinical asthma exacerbations (CAEs) as well as improved lung function. The safety profile accumulated throughout the clinical development of reslizumab suggests that reslizumab may have a favorable benefit-risk profile in treating patients with asthma and elevated blood eosinophils. Therefore, this study was proposed to further

investigate the potential corticosteroid-reducing properties of reslizumab in patients with corticosteroid-dependent asthma and elevated eosinophils.

1.2. Name and Description of Investigational Product

Reslizumab (CEP38072) is a humanized anti-human interleukin-5 (anti-hIL-5) mAb of the immunoglobulin G4/κ isotype being developed for administration by the iv and subcutaneous (sc) routes.

A more detailed description of the product is given in Section 3.11.

1.3. Findings From Nonclinical and Clinical Studies

1.3.1. Nonclinical Studies

A correlation between IL-5–induced eosinophilia and pulmonary hyperreactivity was suggested by studies in the IL-5 gene knockout mouse (Foster et al 1996). When sensitized and challenged with antigen, mice lacking the IL-5 gene failed to develop airway eosinophilia, lung damage, or increased lung responsiveness. Otherwise, IL-5 gene knockout mice developed normally and had normal antibody and cytotoxic T-cell responses.

In vivo, reslizumab showed biological activity in several species, including mouse, guinea pig, rabbit, and monkey. Reslizumab inhibited eosinophilia in lungs or skin and reduced airway hyperresponsiveness after antigenic challenge in sensitized animals. Inhibition of pulmonary eosinophilia was observed for up to 8 weeks post-dose in mice and for up to 6 months in monkeys. The effects of reslizumab on eosinophilia in mice were additive with the effects of prednisolone.

In single-dose iv toxicity studies with reslizumab, no adverse effects were observed at the maximum doses administered (500 mg/kg in mice and rats; 100 mg/kg in monkeys). In repeat-dose studies, reslizumab was well tolerated by mice and monkeys given 2 iv doses of 1, 5, or 25 mg/kg reslizumab 14 days apart; the no-observed-effect level (NOEL) was 5 mg/kg in male mice and at least 25 mg/kg in female mice and monkeys. The 6-month studies in mice and monkeys with once-monthly dosing showed no toxicity and a NOEL of at least 25 mg/kg. The NOEL for evidence of reslizumab-related binding to nervous system tissues of monkeys was also at least 25 mg/kg. Reslizumab was not genotoxic and did not affect reproductive parameters. In safety pharmacology studies, reslizumab had no effect on parameters related to organ function. Available data indicate that reslizumab may bind to a human brain-specific brain link protein-1, which belongs to a superfamily of structural proteins that help bind cells to matrix by binding hyaluronic acid and negatively charged glycoproteins (Study D-38271).

Nonclinical studies in male cynomolgus monkeys, mice, and rats were performed to assess the absolute bioavailability of reslizumab following single and multiple sc doses. It was found that absolute bioavailability following sc administration of reslizumab was high (>75%) in all species. Subcutaneous administration of reslizumab in these studies was well tolerated. Mild, focal, intramuscular (im) macrophage infiltrates were found at the injection site in 1 monkey dosed with sc reslizumab. In addition, an acute sc irritation study in rats found that sc administration of reslizumab produced minimal to mild gross local tissue irritation. Following sc administration in nonclinical studies, approximately 20% to 50% of animals tested positive for

anti-reslizumab antibodies. The antibody response correlated with decreased serum concentrations in some, but not all, of these animals.

Further details may be found in the current Investigator’s Brochure (IB).

1.3.2. Clinical Studies

The pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and safety of iv reslizumab over the dose range of 0.03 mg/kg through 3 mg/kg have been characterized in 14 studies in patients and in healthy subjects.

1.3.2.1. Clinical Pharmacology Studies

The PK of reslizumab are similar following iv administration in patients and in healthy subjects. Following iv administration, maximum serum reslizumab concentrations (C_{max}) are typically attained at the end of the infusion and generally decline from peak in a biphasic manner. Mean terminal half-life ($t_{1/2}$) of reslizumab following multiple dose administration is approximately 24 days, resulting in an accumulation ratio of approximately 1.5- to 1.9-fold when administered every 4 weeks. Systemic exposure, as assessed by C_{max} and area under the concentration curve (AUC), increases in an apparently dose proportional manner over the dose range of 0.3 mg/kg through 3.0 mg/kg.

Following a single sc dose, bioavailability of reslizumab is approximately 67%. Peak serum reslizumab concentrations are typically observed approximately 7 days after sc administration. As expected, the remainder of the PK profile following sc administration is qualitatively similar to that observed following iv administration and exhibits a biphasic decline from peak with a long terminal $t_{1/2}$ (approximately 26 days).

Reslizumab has a small volume of distribution (V_d , approximately 5 L), suggesting minimal distribution to extravascular tissues. Based on the characteristics of reslizumab, renal or hepatic impairment and use of concomitant medications is unlikely to affect systemic exposure to reslizumab. The lack of effect of mild or moderate renal impairment or Grade 1/2 elevations in liver function tests on the PK of reslizumab was confirmed in population PK (PPK) analyses in asthma patients. In vitro data indicate that IL-5 and reslizumab are unlikely to affect cytochrome P450 (CYP) enzymes commonly implicated in drug-drug interactions and the results of the PPK analyses confirmed that concomitant use of leukotriene antagonists or systemic corticosteroid classes, as well as the individual drugs prednisone and montelukast, did not impact systemic exposure to reslizumab.

Other than a study performed to compare the PK, PD, and immunogenicity of reslizumab in Japanese and non-Japanese subjects, there were no dedicated studies for the assessment of the effect of demographic characteristics on the PK of reslizumab. Results of PPK analyses demonstrated that age, sex, and race (Caucasian, Black, Asian, ‘other’) have no notable impact on the PK of reslizumab; however, body weight was found to impact exposure. The PPK analyses also demonstrated no clear indication of reduced exposure to reslizumab in patients who developed antibodies to reslizumab (ie, were anti-drug antibody [ADA] positive).

Further details may be found in the current IB.

1.3.2.2. Clinical Safety and Efficacy Studies

The Phase 3 BREATH program in adults and adolescents with asthma evaluated the safety and efficacy of reslizumab administered iv every 4 weeks at 3 mg/kg (16-week Studies C38072/3081 and C38072/3084, 12-month Studies C38072/3082 and C38072/3083, and open-label safety extension Study C38072/3085) and 0.3 mg/kg (Study 3081 only). A significant reduction in the annual rate of asthma exacerbations and significant improvements in lung function, asthma-related quality of life, and patient-reported measures of asthma control (ACQ and Asthma Symptom Utility Index) were observed in patients with eosinophilic asthma defined by a screening blood eosinophil count of $\geq 400/\mu\text{L}$ (Studies 3081, 3082, and 3083).

In patients with asthma but without elevated blood eosinophils (Study 3084), reslizumab produced nonsignificant improvements in lung function and other measures of efficacy. In contrast, in patients with blood eosinophil levels $\geq 400/\mu\text{L}$, reslizumab produced significant improvements in lung function and other measures of efficacy.

A total of 2195 healthy volunteers and patients with moderate to severe asthma, eosinophilic esophagitis, eosinophilic gastritis, hypereosinophilic syndrome, or nasal polyposis had received at least 1 dose of reslizumab in 14 clinical studies.

The safety of reslizumab was evaluated in adults and in children in clinical studies summarized in the current IB. Single or multiple doses of iv reslizumab from 0.03 through 3.0 mg/kg were well tolerated, with a common adverse event profile similar to placebo. The majority of adverse events were generally mild to moderate in severity, and most adverse events were assessed as unrelated to study drug, as determined by the investigator. Overall, the nature and occurrence of the reported study drug-related adverse events did not raise any specific safety concerns.

The following summary relates to integrated adverse events data of the 5 asthma placebo-controlled completed studies (ie, Studies Res-5-0010, 3081, 3082, 3083, and 3084) that include the 3 mg/kg iv dose and every 4 weeks dosing regimen (up to 52 weeks). Serious adverse events and death cases from the open-label Study 3085 are also included in the relevant sections.

Common Adverse Events

The most common preferred terms (reported in $>5\%$ of patients in the reslizumab 3.0 mg/kg group) were asthma (232 [23%] and 289 [40%] patients in the reslizumab 3.0 mg/kg and placebo groups, respectively), nasopharyngitis (103 [10%] and 103 [14%] patients, respectively), upper respiratory tract infection (96 [9%] and 69 [10%] patients, respectively), headache (78 [8%] and 62 [9%] patients, respectively), and sinusitis (57 [6%] and 51 [7%] patients, respectively). There were no adverse events in the reslizumab-treated group that had an incidence higher than the placebo group by at least 1%.

Serious Adverse Events

The incidence of serious adverse events was similar in the reslizumab 3.0 mg/kg treatment group (6%) compared with the placebo treatment group (9%). The serious adverse event reported with the highest incidence was asthma (preferred terms of asthma, asthma crisis, and status asthmaticus), reported by 24 (3%) patients in the placebo group and 24 (2%) patients in the reslizumab 3.0 mg/kg group.

Deaths

There were 4 deaths in the clinical development plan: 1 death occurred in a placebo-treated patient and 3 deaths occurred in the ongoing open-label study (Study C38072/3085). None of the deaths were considered related to reslizumab.

Laboratory Findings

No clinically meaningful changes in clinical laboratory values, vital signs measurements, electrocardiogram (ECG), or physical examination findings were noted in the completed studies with the exception of a decrease in eosinophil counts in the reslizumab groups, which was dose related and is expected in view of the mechanism of action of reslizumab. Small decreases in the mean values of total white blood cell counts were also observed in some studies and have been assessed as reflecting the decrease in the eosinophil component of the differential cell counts. The mean values of eosinophil and white blood cell counts returned to baseline values at the end of study follow-up visit (4 months after the last dose of reslizumab).

Adverse Drug Reactions

Anaphylaxis related to reslizumab infusion has been reported and is considered an adverse drug reaction (ADR). All cases of anaphylaxis early in the drug development occurred in the eosinophilic esophagitis studies and were deemed by the investigator as related to known food allergies and not to reslizumab. Three infusion-related reactions, reported as anaphylaxis, occurred during or shortly after reslizumab infusion in the BREATH studies and were characterized variously by skin or mucosal involvement, dyspnea, wheezing, gastrointestinal symptoms, and chills. The 3 events were treated at the study site, and patients were withdrawn from the study.

Myalgia (without evidence for muscle injury) was reported at a slightly higher rate in the reslizumab 3.0 mg/kg group (1%) than in the placebo group (0.5%) and is considered an ADR of reslizumab.

Additional Safety Considerations***Malignancy risk***

As of February 2015, there were 27 treatment-emergent adverse events reported by 24 patients related to malignancy for the entire clinical program, including placebo-treated patients. Malignancies in reslizumab-treated patients were of diverse tissues (colon, anal, melanoma, prostate, breast, lung, plasmacytoma, lymphoma, lung metastasis of a previous resected colon cancer, ovarian adenocarcinoma, borderline ovarian tumor, and nonmelanoma skin cancer cases).

In the asthma placebo-controlled studies utilizing the 3.0-mg/kg dose, incidence of overall malignancies was 6 patients (0.58%; 1 patient had both prostate cancer and skin squamous cell carcinoma) in the reslizumab 3.0-mg/kg treatment group and 2 patients (0.27%) in the placebo group. All malignancies in reslizumab-treated patients were diagnosed within less than 6 months from first reslizumab dosing, except for the skin squamous cell carcinoma.

In the combined placebo-controlled studies and long-term, open-label, safety extension Study C38072/3085, malignancies were reported in 21 patients. These included 5 cases of non-melanoma skin cancer. Most malignancies were diagnosed within less than 6 months after

starting reslizumab treatment, and in 5 cases, there was a previous medical history of malignancy.

A thorough analysis of malignancy cases did not suggest a causal relationship between reslizumab and cancer risk.

Infections

The immune response to parasitic infections may involve eosinophils; therefore, the clinical course of existing or new parasitic infections could potentially be complicated by a mechanism of action that lowers blood and tissue eosinophils. The iv reslizumab clinical protocols contained an exclusion criterion for patients with active or suspected helminth infestation/infection. The asthma Phase 3 studies were conducted in geographic regions in which helminth infections are prevalent, including South and Central America, Africa, and Asia. There were no helminth infections reported, and no difference was documented between the treatment groups in regards to adverse events that could be associated with gastrointestinal helminth infections.

The overall rate of infection adverse events was lower for reslizumab versus placebo-treated patients, with the types of infection events reported consistent with what would be expected in a primarily adult patient population with an underlying condition of asthma. No potential opportunistic infections were reported.

Pregnancy

The safety of reslizumab in pregnant women or developing fetus has not been studied, but nonclinical and clinical studies raised no specific concerns. As of December 2015, there have been 10 pregnancies during the entire clinical development of reslizumab, 2 of which occurred during the screening period of the study and 8 in patients receiving reslizumab. All patients were withdrawn from the study. Two pregnancies were terminated by an elective abortion with no complications, and 5 led to the birth of full-term infants with no malformations and no obstetric or perinatal complications. One male newborn had a neonatal jaundice that was reported as an unrelated adverse event and was assessed as physiological jaundice. One pregnancy case was lost to follow-up, and the outcome is unknown.

Immunogenicity

Anti-drug antibody responses were observed in 3.3% to 11.8% of patients in the completed Phase 3 studies in patients with asthma (iv administration every 4 weeks, >1000 patients evaluated for ADA). In general, the ADA responses were low in titer and often transient, and were not associated with an effect on reslizumab concentration, eosinophil count, or specific clinical manifestations (including hypersensitivity reactions).

Further details may be found in the current Investigator's Brochure.

1.4. Known and Potential Risks and Benefits to Human Patients

Information regarding risks and benefits of reslizumab to human patients may be found in the current IB.

1.4.1. Risks of Reslizumab

Most clinical safety data for reslizumab are based on the experience with iv administration of the drug. As described in Section 1.3.2, iv reslizumab has been generally well tolerated over the range of doses evaluated (ie, from 0.03 through 3 mg/kg). Systemic severe reactions (including anaphylaxis) and myalgia are considered ADRs of iv reslizumab.

There are limited safety data regarding sc administration of reslizumab. In Study C38072/1107 (Study 1107), 45 healthy volunteers received a single 220-mg sc injection of reslizumab. All adverse events were mild to moderate in severity. There were no deaths, serious adverse events, treatment-related adverse events, or withdrawals due to adverse events reported in this study.

1.4.2. Benefits of Reslizumab

As described in Section 1.3.2, results from clinical studies indicate improved asthma control and forced expiratory volume in 1 second (FEV₁) and a medically meaningful decreased rate of CAEs with reslizumab.

A reduction in OCS dose in OCS-dependent asthma with elevated eosinophils has been reported for the related anti-IL-5 investigational product, mepolizumab (Bel et al 2014), and is theorized to be a potential class effect. Additionally, the effect of reslizumab was pronounced in patients with severe asthma who were on OCS (Castro et al 2015).

In Studies Res-5-0010, 3081, 3082, 3083, and 3084, certain therapeutic classes of medications were used more frequently in the placebo group than in the reslizumab 3.0 mg/kg treatment group. These included antibacterials for systemic use (270 [26%] patients in the reslizumab 3.0 mg/kg treatment group and 290 [40%] patients in the placebo group), antihistamines for systemic use (375 [36%] patients in the reslizumab 3.0 mg/kg treatment group and 321 [44%] patients in the placebo group), corticosteroids for systemic use (246 [24%] patients in the reslizumab 3.0 mg/kg treatment group and 288 [39%] patients in the placebo group), and nasal preparations (325 [32%] patients in the reslizumab 3.0 mg/kg treatment group and 268 [37%] patients in the placebo group). These imbalances in concomitant medication use most likely reflect the substantial benefits that reslizumab treatment provided in improving respiratory symptoms, resulting in less need for additional treatment in the reslizumab group.

1.4.3. Overall Risk and Benefit Assessment for This Study

Improvement in lung function has been confirmed in 3 Phase 3 clinical studies with the iv dosage form. In addition to improved lung function, a significant reduction in CAEs over 52 weeks was observed in patients with moderate to severe asthma and elevated blood eosinophils in 2 Phase 3 clinical studies. Modeling and simulation data demonstrate that steady-state trough serum concentrations of reslizumab following administration of the proposed 110-mg sc dosing regimen are expected to fall within the range of exposures that produced meaningful effects on both blood eosinophils and FEV₁ in patients with eosinophilic asthma. Therefore, a fixed dose of 110 mg sc once every 4 weeks is anticipated to provide sufficient efficacy.

In completed studies, reslizumab was generally well tolerated over the dose range 0.03 through 3.0 mg/kg. The majority of adverse events in reslizumab-treated patients were mild to moderate in severity; considered to be unrelated to study drug treatment, as determined by the investigator; and, (as expected) associated with underlying asthma disease. There were no significant

differences in the adverse event profile between patients treated with reslizumab and patients treated with placebo, with the exception of the ADRs “systemic severe reactions (including anaphylaxis)” and “myalgia.” Three anaphylaxis reactions related to reslizumab infusions were reported during the BREATH asthma program; none of the patients were positive for ADA. All cases resolved with standard treatment, and treatment with reslizumab was permanently discontinued. Myalgia (without evidence for muscle injury) was reported at a slightly higher rate in the reslizumab 3.0-mg/kg group (1%) than in the placebo group (0.5%). The protocol includes measures to closely monitor and promptly address these ADRs to mitigate any potential harm to patients.

Consideration of the accumulated data on the clinical effects of reslizumab in patients with asthma suggests that patients with elevated blood eosinophils benefit the most from anti-human IL-5 therapy. The safety profile accumulated throughout the clinical development of reslizumab suggests that reslizumab would have a favorable benefit-risk profile in treating patients with asthma and elevated blood eosinophils whose symptoms remain inadequately controlled on standard-of-care asthma therapy.

1.5. Selection of Drugs and Dosages

1.5.1. Justification for Dosage of Active Drug

The platform of evidence that supports the range of the reslizumab dose response is based on the observed effects on lung function and other clinical endpoints in patients with eosinophilic asthma (Studies P00290 [0.3- and 1-mg/kg doses], Res-5-0010 [3-mg/kg dose], and 3081 [0.3- and 3-mg/kg doses]), on eosinophil depletion in the blood in healthy subjects (Study 1102 [0.3-, 1-, 2-, and 3-mg/kg doses]), and in the blood and affected tissue in patients with asthma (Studies I96-350, 3081, and P00290) and eosinophilic esophagitis (Study Res-5-0002 [1-, 2-, and 3-mg/kg doses]). Refer to the IB for summary and comprehensive presentation of these data. Briefly, treatment with iv reslizumab at a dose of 0.3 mg/kg produced substantially smaller and less durable reductions in the number of blood or tissue eosinophils (ie, sputum) than doses ≥ 1 mg/kg. In contrast, the magnitude of reductions in blood or tissue eosinophils at doses ≥ 1 mg/kg (ie, 1, 2, or 3 mg/kg) was similar. Improvements in patients in the reslizumab 0.3-mg/kg treatment group for FEV₁ were 0.129 L at week 16 ($p=0.0481$), but other efficacy endpoint results were more variable (eg, no treatment effect on forced vital capacity (FVC) and forced expiratory flow at 25% and 75% of the FVC (FEF_{25%-75%}) was observed for patients in the reslizumab 0.3-mg/kg treatment group). Therefore, iv doses of ≥ 1 mg/kg are anticipated to be clinically effective in most patients. Based on these clinical and eosinophil PD data, Teva has chosen reslizumab 110 mg administered once every 4 weeks as the fixed dose to study in the sc program. This approximates a 1-mg/kg iv dose for the average patient (ie, 70 kg) when adjusted to account for sc bioavailability (ie, 67%). Modeling and simulation demonstrate that steady-state trough serum concentrations of reslizumab following administration of the proposed 110 mg sc dosing regimen are expected to fall within the range of exposures that produced meaningful effects on both blood eosinophils and FEV₁ in patients with eosinophilic asthma. Therefore, a fixed dose of 110 mg sc once every 4 weeks is anticipated to provide sufficient efficacy.

1.5.2. Justification for Use of Placebo

A placebo control design is scientifically appropriate because placebo will be compared against reslizumab added on to an established treatment regimen. Patients will not be taken off their standard-of-care asthma therapy for this study.

1.6. Compliance Statement

This study will be conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [CFR] Parts 11, 50, 54, 56, 312, and 314, European Union [EU] Directive 20/EC and 28/EC). Any episode of noncompliance will be documented.

The investigator is responsible for performing the study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this study in accordance with the protocol will be documented in separate study agreements with the sponsor and other forms as required by national authorities.

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the study and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the applicable study staff must be familiar with the background to, and requirements of, the study and with the properties of the study drug(s) as described in the IB or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the study at that center and for contacts with study management, with the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and with local authorities.

1.7. Population To Be Studied and Justification

This study will enroll male and female patients, 12 years of age and older, with OCS-dependent asthma and elevated eosinophils. (Patients 12 to <18 years of age are excluded from participating in South Korea, the Netherlands, and Argentina, and patients 66 years of age and older are excluded from participating in South Korea.)

1.8. Location and Timing of Study

This study is planned to be conducted in 19 countries at 155 centers. It is expected to start in Q3 2015 and have a duration of approximately 2 years. Additional centers will be added, if needed. Expected duration of the study may also be extended dependent on enrollment rate and other factors.

2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1. Purpose of the Study

The purpose of this study is to establish the safety and efficacy of the sc formulation of reslizumab in patients with OCS-dependent asthma and elevated blood eosinophils.

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective of the study is to determine the ability of reslizumab (110 mg) administered sc once every 4 weeks to produce a corticosteroid-sparing effect (as demonstrated by percent reduction in daily OCS use) in patients with OCS-dependent asthma and elevated blood eosinophils, without loss of asthma control.

2.2.2. Secondary Objective

The secondary objective of this study is to evaluate the clinical benefits of reslizumab in the context of OCS reduction.

2.2.3. Other Efficacy Objective

Another efficacy objective of this study is to evaluate the effect of reslizumab on standard asthma control measures during tapering of OCS in patients with OCS-dependent asthma.

2.2.4. Target Biomarker Objective

The target biomarker objective is to evaluate the effect of sc dosing of reslizumab on blood eosinophil counts.

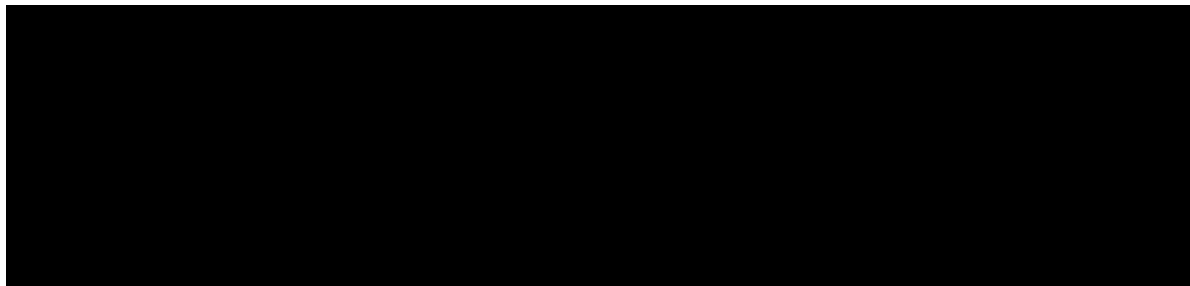
2.2.5. Immunogenicity Objective

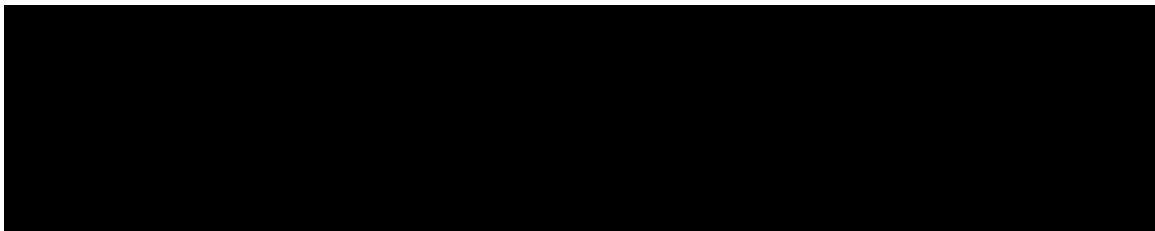
The immunogenicity objective is to evaluate the potential of sc dosing of reslizumab to raise ADAs.

2.2.6. Pharmacokinetic Objective

The PK objective is to characterize the PK of sc reslizumab in the study population.

2.2.7. Exploratory Objectives





2.2.8. Safety Objective

The safety objective is to evaluate the safety of chronic sc dosing of reslizumab and tapering of OCS as assessed by the following:

- occurrence of adverse events
- clinical laboratory evaluations of serum chemistry and hematology
- vital signs (pulse, respiratory rate, and blood pressure) measurements
- ECG findings
- physical examination findings, including body weight measurements
- signs and/or symptoms of adrenal insufficiency (OCS withdrawal effects)
- concomitant medication usage

2.3. Study Endpoints

2.3.1. Primary Efficacy Endpoint

The primary efficacy variable and endpoint for this study is the categorized percent reduction in the daily OCS dose during weeks 20 to 24 as compared with the dose at the end of the optimization phase. Percent reduction will be categorized as follows:

- 90% to 100%
- 75% to <90%
- 50% to <75%
- >0% to <50%
- No decrease in OCS, or loss of baseline asthma control during weeks 20 through 24, or discontinuation from study drug

Loss of baseline asthma control will be defined as FEV₁ value of less than 80% of baseline at the week 24 visit, or clinically significant worsening in ACQ-6 score (change in score of 0.5) at the week 24 visit compared with baseline, and/or CAEs during weeks 20 through 24 (as defined in Section 6.7).

2.3.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study are as follows:

- Proportion of patients achieving $\geq 50\%$ reduction in OCS dose at weeks 20 to 24 relative to the OCS dose at the date of randomization (DoR)/baseline, while maintaining asthma control
- Proportion of patients achieving dose reduction to ≤ 5 mg daily dose at weeks 20 to 24, while maintaining asthma control
- Percent change from DoR/baseline in OCS dose at weeks 20 to 24
- Proportion of patients achieving less than 5 mg decrement in OCS dose (ie, the minimal and non-responders) at weeks 20 to 24 compared with the OCS dose at DoR/baseline, while maintaining asthma control
- Clinical asthma exacerbation related:
 - Annualized rate of CAEs requiring a burst of systemic corticosteroid (injection, or if oral, at least a doubling from the current OCS dose for at least 3 days); an asthma-specific hospital admission; or an asthma-specific emergency department visit during the treatment period (weeks 0 to 24)
- Proportion of patients discontinuing OCS at weeks 20 to 24, while maintaining asthma control

2.3.3. Other Prespecified Efficacy Endpoints

The other efficacy endpoints are as follows:

- Time to first CAE
- Other clinic lung functions including the following:
 - Pre-bronchodilator FEV₁: change from DoR/baseline to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
 - Post-bronchodilator FEV₁: change from DoR/baseline to weeks 4, 12, 20, and 24 or early withdrawal
- Ambulatory lung function: change in morning (AM) and evening (PM) peak expiratory flow (PEF) from run-in baseline at each week through week 24 or early withdrawal
- Asthma Quality of Life (AQLQ) + 12 score: change from DoR/baseline to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- ACQ-6 score: change from DoR/baseline to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- Change in total inhalations of reliever bronchodilator medication (eg, SABA) (number of inhalations per 24 hours: day+night) from run-in baseline at each week through week 24 or early withdrawal
- Number of nighttime awakenings due to asthma over the 24-week treatment period
- Change in total asthma symptom score from run-in baseline at each week through week 24 or early withdrawal

- European Quality of Life 5-dimension health state utility index (EQ-5D) score: change from DoR/baseline to week 24 or early withdrawal
- St. George’s Respiratory Questionnaire (SGRQ) score: change from DoR/baseline to weeks 12 and 24 or early withdrawal

2.3.4. Target Biomarker Endpoint

The target biomarker endpoints are the blood eosinophil counts at DoR/baseline; weeks 4, 8, 12, 16, 20, and 24 or early withdrawal; and at the follow-up visit (approximately week 32).

2.3.5. Immunogenicity Endpoints

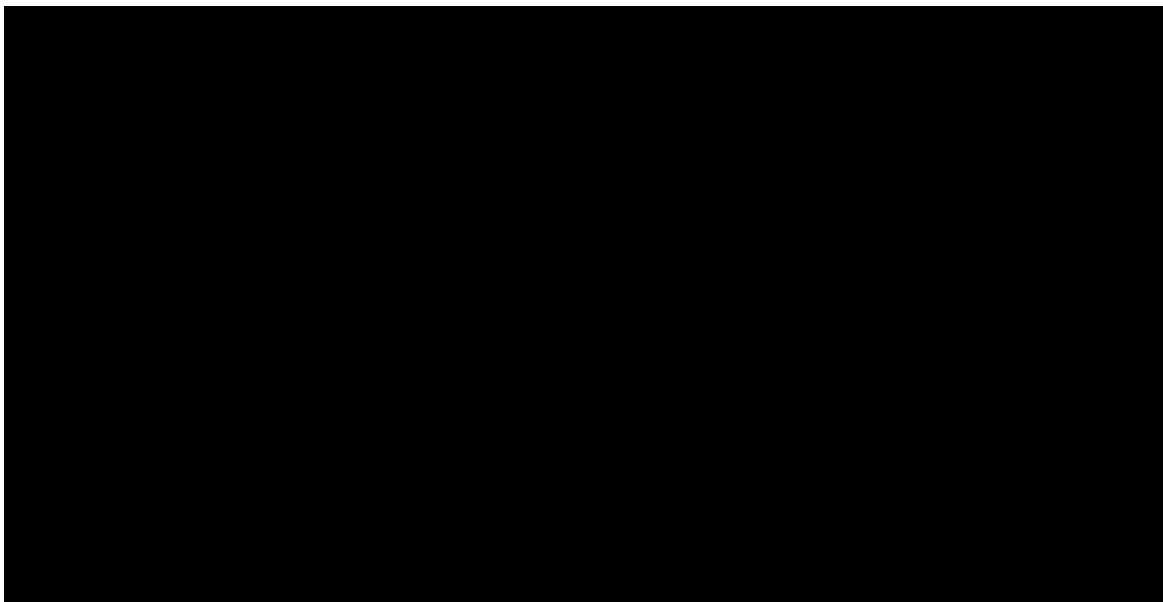
The immunogenicity endpoints are the immunogenicity incidence and the impact of ADA on clinical outcomes. The drug-emergent ADA response will be identified by analyzing ADA test results for serum samples obtained before the administration of study drug at DoR/baseline; prior to study drug administration at weeks 4, 8, 12, and 24 or early withdrawal; and at the follow-up visit (approximately week 32). An additional sample will be obtained at the late follow-up visit (approximately week 48).

2.3.6. Pharmacokinetic Endpoints

There are no specific endpoints related to PK. Measured concentrations will be used to characterize the PK of sc reslizumab in the studied population and to explore exposure-response relationships. Serum reslizumab concentrations will be determined from blood samples collected from each patient at DoR/baseline; and prior to study drug administration at weeks 4, 8, 12, and 24 or early withdrawal; and at the follow-up visit (approximately week 32). An additional PK sample will be obtained at the late follow-up visit (approximately week 48).

2.3.7. Exploratory Endpoints

The exploratory endpoints are as follows:





2.3.8. Safety Endpoints

Safety endpoints will include the following:

- occurrence of adverse events throughout the study, including the week 32 follow-up visit
- clinical laboratory evaluations of serum chemistry at screening, DoR, and periodically throughout the study
- clinical laboratory evaluations of hematology throughout the study
- vital signs (pulse, body temperature, respiratory rate, and blood pressure) measurements throughout the study
- ECG evaluation at screening and at week 24 or early withdrawal
- physical examination findings, including body weight measurements, throughout the study
- signs and/or symptoms of adrenal insufficiency (OCS withdrawal effects) throughout the study
- concomitant medication usage throughout the study, including the week 32 follow-up visit

3. STUDY DESIGN

3.1. General Design and Study Schema

This is a Phase 3, 24-week, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of sc reslizumab treatment at a dosage of 110 mg every 4 weeks in patients 12 years of age and older with OCS-dependent asthma and elevated blood eosinophils. The study will consist of a screening period of up to 2 weeks, followed by an optimization period of up to 10 weeks, a run-in period of at least 2 weeks, a 24-week double-blind treatment period, an 8-week follow-up period, and an additional 16-week follow-up period to collect drug wash-out samples for immunogenicity assessments. The patient may delay the early and/or late follow-up visits if the patient enrolls in an open-label, long-term safety study after end of treatment, if available.

3.1.1. Screening Period

Patients will begin screening up to 14 weeks before DoR. During the screening period, a signed and dated informed consent form (ICF) (and an assent form for children 12 through <18 years of age in accordance with local standards) will be obtained before a diagnosis of asthma is confirmed on the basis of patient history and by demonstration of airway reversibility. The patients will also be asked about their asthma medication compliance and to demonstrate their inhaler use technique. If the inhaler use technique is not optimal, patients will be taught the appropriate inhaler use technique during the screening period and should be reassessed before run-in. The patient will also have a complete blood count (CBC) determined. If the patient's eosinophil count is 300/ μ L or greater while on daily OCS and if the patient's medication compliance and inhaler use technique are optimal, the patient will be eligible to continue. Note: a patient will meet inclusion criteria if an eosinophil count of 300/ μ L or greater becomes manifest during the OCS optimization period or at the week -2 visit (end of optimization period/beginning of run-in period). Patient medical history; pre-bronchodilator spirometry; 12-lead ECG; physical examination; urinalysis; vital signs measurements; beta human chorionic gonadotropin (β HCG) serum pregnancy test (for all females of childbearing potential); testing for human immunodeficiency virus (HIV), hepatitis B, and hepatitis C(HCV); and concomitant medication history will also be assessed at screening.

To be eligible to enroll in the study, a patient will have an airway FEV₁ reversibility of at least 12% to beta-agonist administration, a blood eosinophil count of at least 300/ μ L while on daily OCS or during the OCS optimization period or at the week -2 visit or a documented blood eosinophil level of at least 300/ μ L during the previous 12 months while on at least medium dose ICS, a current fluticasone propionate dosage of at least 880 μ g daily or equivalent plus another controller, and will have met all the inclusion and none of the exclusion criteria.

3.1.2. Optimization Period

Patients who meet screening eligibility requirements will enter the optimization period for up to 10 weeks to determine the patient's minimal effective OCS requirement. The patient's previous OCS will be standardized to an equivalent dose and regimen of prednisone to facilitate optimization; the same formulation should be maintained through the end of treatment (EOT)

visit. It is expected that the optimization period will be shorter than 10 weeks for those patients who are at or near their optimal corticosteroid dose at enrollment. The patient's previous non-OCS background asthma controller medications will be continued unchanged throughout the pre-randomization period and the entire study. At the beginning of the optimization period, an asthma symptom diary and electronic peak flow meter will be distributed where the patient will record asthma symptoms, number of reliever bronchodilator inhalations, nighttime awakenings due to asthma requiring rescue inhaler, and AM and PM PEF.

For optimization, the prednisone dose should be reduced at 1-week intervals, according to the algorithm shown in Table 1, for up to 10 weeks, or until there is a worsening of asthma signs and symptoms. Worsening of asthma signs and symptoms should be based on the following:

- FEV1 <80% of the screening value AND/OR
- The physician's global assessment of asthma worsening based on trends in daily diary measures for the past 7 days compared with the week prior, as well as any physical examination signs

When either a lung function or a symptomatic deterioration occurs, the patient will be returned to the previously effective OCS level, which will then constitute the minimally effective dose for the purpose of run-in. If this previously effective dose is no longer effective, the investigator can determine the clinically appropriate minimally effective dose for the purpose of run-in.

Regarding the amount and rate of OCS reduction during dose optimization, in order to provoke a worsening of asthma signs and symptoms within the 10-week, monitored optimization period, OCS reduction should be attempted approximately every 1 week after evaluation in the clinic. The magnitude of OCS reduction will be based on the following Optimization Phase OCS Dose Reduction Algorithm ([Table 1](#)).

Table 1: Optimization Phase Prednisone Dose Reduction Algorithm

Time Course	Oral OCS Dose (mg/day)								
Visit 2 starting dose ^a	40+ ^b	35	30	25	20	15	10	7.5	5
1st reduction at Visit 2	35	30	25	20	15	10	7.5	5	2.5 ^c
+ 1 week	30	25	20	15	10	7.5	5	2.5 ^c	
+ 1 week	25	20	15	10	7.5	5	2.5 ^c		
+ 1 week	20	15	10	7.5	5	2.5 ^c			
+ 1 week	15	10	7.5	5	2.5 ^c				
+ 1 week	10	7.5	5	2.5 ^c					
+ 1 week	7.5	5	2.5 ^c						
+ 1 week	5	2.5 ^c							
+ 1 week	2.5 ^c								
+ 1 week									

^a Starting doses that fall between values shown in this table should utilize the algorithm for the higher of the 2 doses.

^b Patients who the investigator believes may be able to decrease OCS dose to 40 mg during the optimization period may be enrolled. OCS dose reduction during optimization for patients on >40 mg daily at that start of optimization should follow weekly reductions with magnitudes similar to those in the table (this may be discussed with medical monitor). Patients who require >40 mg OCS to maintain asthma control at the end of optimization will not be randomized.

^c Patients must be using an average daily dose of ≥ 5 mg OCS after optimization. Patients who require <5 mg OCS to maintain asthma control will not be randomized.

OCS=oral corticosteroid

Regarding eosinophil counts during the optimization period, blood eosinophils $\geq 300/\mu\text{L}$ that become manifest during OCS reductions during optimization, will count toward the eosinophil inclusion criterion for this study.

3.1.3. Run-In Period

Patients whose minimal effective OCS dose remains between ≥ 5 mg and ≤ 40 mg of prednisone daily at the end of optimization may advance to run-in (for at least 2 weeks). During run-in, patients will continue to keep their daily asthma control diary and a PEF meter to perform daily self-monitoring of asthma symptoms while maintaining their minimally effective OCS dose and previous background asthma medications unchanged. The frequency of symptoms, use of inhaled reliever bronchodilator, nighttime awakenings due to asthma requiring rescue inhaler, and ambulatory lung function during the last 7 days of run-in will constitute the baseline level of control for analysis and the basis for OCS reduction algorithm to be used during the treatment period.

3.1.4. Treatment Period

Patients continuing to meet eligibility criteria on the day of randomization (day 1, week 0) will be randomly assigned in a 1:1 ratio to receive placebo or reslizumab 110 mg once every 4 weeks

through week 20, followed by an EOT visit at week 24. Patients will begin treatment on day 1 after completing baseline assessments, and they will return to the research facility for outpatient visits every 4 weeks through week 24 (EOT visit) for safety, PK, PD, immunogenicity, and efficacy assessments as applicable.

During the treatment period, the patient will continue his/her usual non-OCS background asthma medication without change; the OCS dose will be tapered per protocol. The treatment periods consist of the following:

- **Induction:** The minimally effective dose of OCS will be maintained, unchanged, during the first 4 weeks of the treatment period to allow sufficient time for any potential treatment effect to become established.
- **OCS reduction:** The minimally effective OCS dose will be reduced per protocol at scheduled clinic visits from the beginning of week 5 (ie, end of the induction period) through week 20, as long as all 5 criteria in [Table 2](#) are met and there are no clinical manifestations of adrenal insufficiency. These 5 eligibility criteria assure that the patient's asthma control is not significantly worsened compared to baseline. The last possible dose reduction can occur at week 20. The algorithm for OCS reductions during the treatment period is given in [Table 3](#).

If the OCS dose could not be decreased, it should be held constant, or may be increased to a previous level, at the investigator's discretion, until dose reduction criteria are met.

- **Maintenance:** OCS will be held stable from week 20 through EOT at week 24.

Table 2: Eligibility Criteria for Scheduled Oral Corticosteroid Reductions During the Treatment Period (Must Meet All)

1	Forced expiratory volume in 1 second (FEV ₁) ≥80% of baseline ^a
2	AM PEF ≥80% of baseline mean AM PEF on at least 5 of the 7 days preceding the visit
3	Mean nighttime awakenings due to asthma requiring rescue inhaler over the preceding 7 days ≤ 150% increase over the baseline period
4	Reliever bronchodilator inhaler use does not exceed 150% of the baseline inhaler use per 24 hours on more than 2 of the preceding 7 days
5	No increase in OCS dose since the previous visit ^b

^a Baseline for clinic visit measures (FEV₁) is the DoR value. Baseline for diary measures is the average over the 7 days before DoR.

^b If a dose increase results in a return to the previous dose, then it is acceptable to attempt dose decrease again at the investigator's discretion.

AM=morning; DoR=date of randomization; FEV₁=forced expiratory volume in 1 second; PEF=peak expiratory flow; OCS=oral corticosteroid.

Table 3: Oral Corticosteroid Decrements During the Treatment Period

Time Course	Oral OCS Dose (mg/day)								
Optimized OCS dose	40	35	30	25	20	15	10	7.5	5
1st reduction	30	25	20	15	10	10	7.5	5	2.5
+ 4 weeks	20	15	10	10	7.5	7.5	5	2.5	0
+ 4 weeks	10	10	5	5	5	5	2.5	0	
+ 4 weeks	5	5	2.5	2.5	2.5	2.5	0		
+ 4 weeks	2.5	2.5	0	0	0	0			

3.1.4.1. Handling of Asthma Exacerbations During the Treatment Period

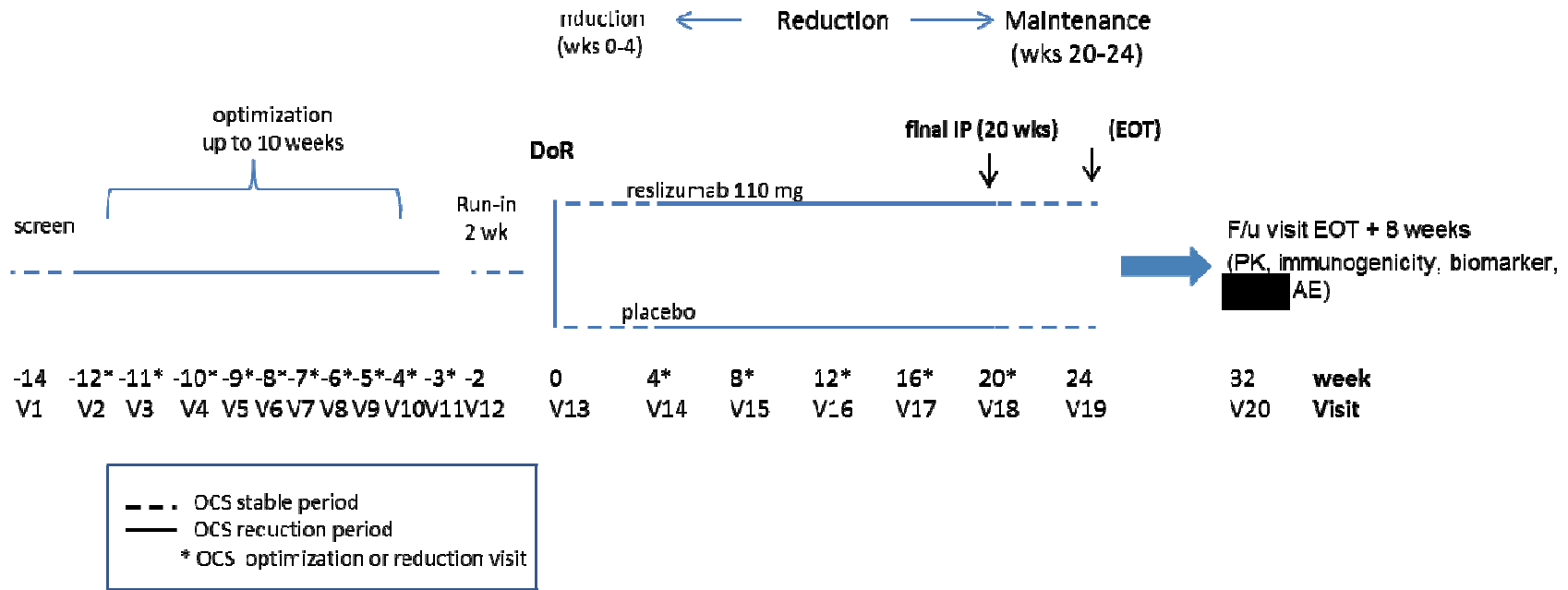
Patients should be treated with an OCS burst: 40 to 60 mg (or at least double the current dose) of OCS tapered over a 7- to 10-day period to a new maintenance dose of 2.5 mg above the pre-burst dose. It is understood that im or iv corticosteroid may also be administered as part of the treatment of the asthma exacerbation. If a second OCS burst (doubling of current dose) is required, the patient should be maintained on a fixed OCS dose without any tapering attempts for the remainder of the double-blind treatment phase and the follow-up period.

Patients who complete all scheduled visits will have final procedures and assessments performed at the EOT visit (visit 19). Patients who withdraw from the study before completing the 24-week treatment period will have visit 19 (week 24 \pm 7 days or early termination) procedures and assessments performed at their final visit. Patients will return for a follow-up evaluation 8 weeks (\pm 7 days) after the EOT visit in this study for assessment of pre-bronchodilator spirometry, ACQ-6 score, PK samples, adverse events, blood eosinophils, CAEs and related health care utilizations, and blood for ADA.

The assessments and procedures performed during each study visit are detailed in [Table 5](#) and [Section 3.16](#). If a patient elects to withdraw (or is discontinued from treatment by the investigator), every attempt will be made to continue the assessments subsequent to his/her withdrawal from the study (see [Section 4.5](#)).

The study schema is presented in [Figure 1](#).

Figure 1: Overall Study Schema




Note: An additional, late follow-up for immunogenicity and PK testing will be performed 28 weeks (±2 weeks) after the last dose of study drug (ie, approximately week 48).

AE=adverse event; DoR=day of randomization; EOT=end of treatment; [redacted] F/u=follow up; IP=investigational product; OCS=oral corticosteroid; PK=pharmacokinetic; V=visit; wk=week.

3.2. Justification for Study Design

The rationale for the design of the study is summarized in [Table 4](#).

Table 4: Rationale for Protocol

Area	Rationale
Study population	Representative of the OCS dependent asthma population with elevated blood eosinophils
Investigational product dosage regimen and duration of treatment	Sc dose and regimen based on BREATH iv program Study 3081
Choice of comparison drug(s) (placebo, active)	Placebo control is essential to establish efficacy and safety
Number of subjects (including number per treatment group)	Based on historical OCS reduction studies
Treatment blinding (ie, rationale for blinded or open-label design)	Double-blinding and randomized treatment allocation to prevent bias efficacy study
Primary analysis (measure, variable, time point, statistical test)	Reduction OCS dose is the primary objective
Inclusion of ancillary studies: PK, PD, PGx, immunogenicity	PK and target blood eosinophil PD are important to interpretation of efficacy results  Immunogenicity assessments are essential to evaluate the safety and efficacy of reslizumab
Key safety measures	Standard measures consistent with iv reslizumab studies in eosinophilic esophagitis and eosinophilic asthma

iv=intravenous; OCS=oral corticosteroid; PD=pharmacodynamic; PGx=pharmacogenomic; PK=pharmacokinetic; sc=subcutaneous.

3.3. Primary and Secondary Measures and Time Points

A more detailed description of the efficacy measures is provided in Section 6.

3.3.1. Primary Efficacy Measure and Time Points

The primary efficacy variable and endpoint for this study is the categorized percent reduction in the daily OCS during weeks 20 to 24 compared with the dose at the end of the optimization phase. Refer to Section 6.1 for additional details regarding the categorization of the reduction in OCS dose.

3.3.2. Secondary Efficacy Measures and Time Points

The secondary efficacy measures and time points include the following:

- $\geq 50\%$ reduction in OCS dose, while maintaining asthma control, at weeks 20 to 24 relative to OCS dose at DoR/baseline
- Reduction to ≤ 5 mg daily dose at weeks 20 to 24, while maintaining asthma control
- OCS dose at weeks 20 to 24 relative to DoR/baseline
- Less than 5 mg decrement in OCS dose (ie, the minimal and non-responders) at weeks 20 to 24, while maintaining asthma control
- Clinical asthma exacerbation related:
 - Annualized rate of CAEs requiring a burst of systemic corticosteroid (injection, or if oral, at least a doubling from the current OCS dose for at least 3 days); an asthma-specific hospital admission; or an asthma-specific emergency department visit during the treatment period (weeks 0 to 24)
- OCS discontinuations at weeks 20 to 24, while maintaining asthma control

These measures will be evaluated at the time points in [Table 5](#).

3.3.3. Other Prespecified Efficacy Measures and Time Points

The other efficacy measures and time points include the following:

- Time to first CAE
- Other clinic lung functions, including the following:
 - Spirometry, including pre- and post-bronchodilator FEV₁
- Ambulatory lung function including AM and PM PEF based on the PEF meter
- AQLQ + 12
- ACQ-6
- Total reliever bronchodilator inhalation use (number of inhalations per 24 hours: day and night) based on the daily asthma control diary
- Nighttime awakenings due to asthma requiring rescue inhaler based on the daily asthma control diary
- Asthma symptoms based on the daily asthma control diary
- EQ-5D
- SGRQ

These measures will be evaluated at the time points in [Table 5](#).

3.4. Target Biomarker Measures and Time Points

Blood eosinophils will be determined from blood samples collected at the time points indicated in [Table 5](#).

3.5. Immunogenicity Measures and Time Points

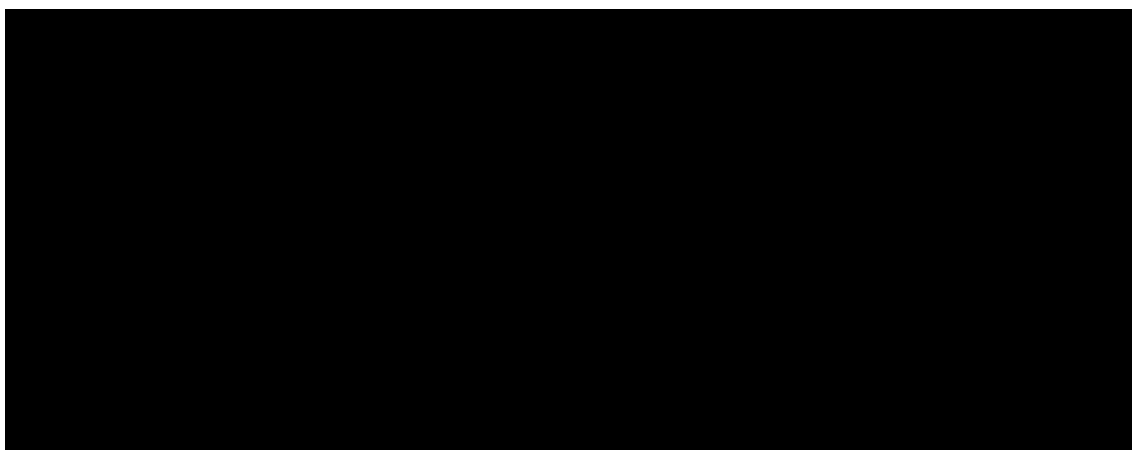
Serum ADAs will be determined from blood samples collected from each patient at the time points indicated in [Table 5](#).

3.6. Pharmacokinetic Measures and Time Points

Serum reslizumab concentration will be determined from blood samples collected from each patient at the time points indicated in [Table 5](#). A description of the PK measures is provided in Section [8.1](#).

3.7. Exploratory Measures and Time Points

The exploratory measures for this study include the following and will be evaluated at the time points indicated in [Table 5](#).



3.8. Safety Measures and Time Points

The following safety measures will be implemented throughout the study and evaluated at the time points in [Table 5](#):

- Inquiries about adverse events
- Clinical laboratory evaluations of serum chemistry
- Clinical laboratory evaluations of hematology
- Vital signs (pulse, body temperature, respiratory rate, and blood pressure) assessments
- ECGs
- Physical examinations

- Monitoring and evaluation of any signs and/or symptoms of adrenal insufficiency (OCS withdrawal effects)
- Inquiries about concomitant medication usage

A description of the safety measures is provided in Section 6.15.

3.9. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. In order to achieve balance between treatment groups with regard to average daily OCS use/requirement and age, randomization will be stratified by optimized, average daily OCS dose of >10 mg or ≤10 mg and age (12 to <18 years of age or ≥18 years of age) at baseline. Within each stratum, patients will be randomly assigned to receive treatment with sc reslizumab at a dosage of 110 mg every 4 weeks or a matching placebo in a 1:1 ratio. This system is used to ensure a balance across treatment groups.

The randomization list and treatment will be assigned to the relevant treatment groups through a qualified contract research organization (CRO), eg, via Interactive Web Response System (IWRS). Generation of the medication list and management of the interactive response technology (IRT) system will be done by a qualified CRO under the oversight of Teva's Clinical Supply Chain.

The sponsor's personnel involved in the study will also be blinded to the study drug identity after the run-in period until the database is locked for analysis and the treatment assignment is revealed, with the exception of the bioanalytical group (Global Bioassays and Technology), who, in order to facilitate PK and ADA sample analysis, will not be blinded. Eosinophils and monocytes will be redacted from the post-baseline differential cell count reports to avoid the possibility of removing the blind.

3.10. Maintenance of Randomization and Blinding

3.10.1. Randomization

Patient randomization codes will be maintained in a restricted access area within Teva Global Biometrics or in a secure manner with the vendor contracted to create the randomization list. At the time of analysis, when treatment codes are needed, the Teva statistician assigned to the study will make a request to unblind and will receive the unblinded codes.

3.10.2. Blinding/Unblinding

In order to complete the data analysis for PK, it may be necessary to assay samples before database lock. If so, the individuals responsible for sample analysis will know which patients received study drug and which patients received placebo. The randomization codes will be provided to personnel responsible for bioanalysis according to a process that will be predefined in the unblinding plan form (GBP_RD_703_FRM_02) according to Teva Standard Operating Procedure (SOP) GBP_RD_703. The form will be signed at the study initiation stage by the responsible Teva statistician, CRO statistician, and randomization code generator. After authorization has been obtained to release the codes, the randomization code generator at the CRO will provide the codes directly to the bioanalysis team; the statisticians (at Teva and the

CRO) will not be unblinded. Personnel responsible for bioanalysis will not have access to clinical safety and efficacy data and will provide concentration data to any other personnel who may require it in a manner that will not identify individual patients (ie, a dummy patient identifier will be linked to an individual patient’s concentration data).

For information about personnel who may be aware of treatment assignments, see Section 3.9. These individuals will not be involved in conduct of any study procedures or assessment of any adverse events, safety, or efficacy data.

In case of a serious adverse event or pregnancy, in which knowledge of the study drug assignment is needed to make treatment decisions, the investigator may unblind the patient’s drug assignment as deemed necessary, mainly in emergency situations. Individual treatment codes, indicating the treatment randomization for each randomly-assigned patient, will be available to the investigator(s) and/or pharmacist(s) at the study center via the IRT, both via telephone and internet. If possible, the sponsor should be notified of the event before breaking of the code. If this is not possible, the sponsor should be notified immediately afterward, and the patient’s drug code assignment should not be revealed. Breaking of the treatment code can always be performed by the site without prior approval by the sponsor.

When a blind is broken, the patient will be withdrawn from the study, and the event will be recorded onto the case report form (CRF). The circumstances leading to the breaking of the code should be fully documented in the investigator’s study files and in the patient’s source documentation. Treatment assignment should not be recorded in any study documents or source document.

In blinded studies, for adverse events that are defined as suspected, unexpected, serious adverse reaction (SUSAR; ie, reasonable possibility; see Section 7.1.4), the Global Patient Safety and Pharmacovigilance department may independently request that the treatment code be revealed (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for other personnel (eg, the investigator, Teva medical monitor, and study personnel) and the patient will not be withdrawn from the study.

In order to maintain the blinding in this study, each patient will receive either one 1.0-mL sc injection containing 110 mg of reslizumab or one 1.0-mL injection containing sterile placebo solution on each dosing day. Both reslizumab and placebo will be provided as clear solutions.

3.11. Drugs Used in the Study

A description of administration procedures is given in Section 5.1.

Additional details may also be found in the current version of the IB for reslizumab.

3.11.1. Investigational Product

Reslizumab will be provided as a sterile solution containing 110 mg (1.0 mL) reslizumab per syringe, formulated at 110 mg/mL in [REDACTED] sodium acetate, with [REDACTED] sucrose, [REDACTED] polysorbate 80, pH 5.5 buffer. The needle shields of the prefilled syringes contain natural rubber latex. Both reslizumab and placebo will be provided as clear solutions.

Reslizumab will be administered sc in a dosage of 110 mg (1.0 mL) every 4 weeks, depending on treatment assignment. A more detailed description of administration procedures is given in Section 5.1.

3.11.2. Placebo

Placebo will be provided as a sterile solution containing [REDACTED] sodium acetate, with [REDACTED] sucrose, [REDACTED] polysorbate 80, pH 5.5 buffer, presented as 1.0-mL per syringe. The needle shields of the prefilled syringes contain natural rubber latex.

Placebo will be administered as a sc injection. Each patient will receive a placebo dose of 1.0 mL injected sc, depending on treatment assignment.

A more detailed description of administration procedures is given in Section 5.1.

3.12. Drug Supply and Accountability

3.12.1. Drug Storage and Security

Reslizumab and matching placebo must be stored in a refrigerator at controlled temperature (2°C to 8°C), should not be frozen, and should be protected from light. Reslizumab and placebo will be kept in a secure area (eg, locked refrigerator). The site should have a process for monitoring the storage temperature of unused study drug.

3.12.2. Drug Accountability

Each study drug shipment will include a packing slip, listing of the contents of the shipment, and drug return instructions and any applicable forms.

Each investigator is responsible for ensuring that deliveries of study drug and other study materials from the sponsor are correctly received and recorded, handled and stored safely and properly in accordance with the CFR or local regulations, and used in accordance with this protocol.

A record of study drug accountability (ie, study drug and other materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused study drug will be disposed of or returned to the sponsor's designee.

3.13. Duration of Patient Participation and Justification

The study is expected to last up to 62 weeks and will consist of a screening period of up to 2 weeks, an optimization period of up to 10 weeks, a run-in period of at least 2 weeks on the optimized OCS dose, followed by a 24-week double-blind treatment period, an 8-week follow-up period. It is expected that the optimization period will be shorter than 10 weeks for those patients who are at or near their optimal corticosteroid dose at enrollment.

An additional, late follow-up for immunogenicity testing will be performed 28 weeks after the last dose of study drug. See Section 12.4 for the definition of the end of the study. The patient may delay the early and/or late follow-up visits if the patient enrolls in an open-label long-term safety study after end of treatment, if available.

3.14. Stopping Rules and Discontinuation Criteria

Other than pregnancy, there are no formal rules for study drug discontinuation in this study. During the conduct of the study, serious adverse events and adverse events of special interest will be reviewed by the sponsor (see Section 7.1.6) as they are reported from the investigational center to identify safety concerns. The study may be terminated by the sponsor at any time for reasons including, but not limited to a safety concern.

A patient may discontinue participation in the study at any time for any reason (eg, lack of efficacy, consent withdrawn, adverse event).

The investigator and/or sponsor can withdraw a patient from the study for reasons including, but not limited to, a change in the medical condition or an adverse event that alters the patient's benefit/risk (eg, pregnancy, a related severe hypersensitivity reaction, or related severe myalgia/muscle event), a protocol violation or deviation as defined in Section 11.1.2, or noncompliance.

3.15. Source Data Recorded on the Case Report Form

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed onto the CRF.

Data may not be recorded directly onto the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly onto the CRF.

If data are processed from other institutions (eg, clinical laboratory, central image center, electronic diary [eDiary] data), the results will be sent to the investigational center, where they will be retained but not entered into the CRF unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management) for direct entry into the clinical database (see Section 13.1). All data from other institutions will be available to the investigator.

The CRFs are filed in the sponsor's central file.

3.16. Study Procedures

Study procedures and assessments with their timings are summarized in Table 5. Detailed by-visit information is provided in the sections following the table. Detailed descriptions of each assessment are provided in Section 6 (efficacy assessments), Section 6.15 (safety assessments), and Section 8 (PK and other assessments).

Table 5: Study Procedures and Assessments

Procedures and assessments	Pretreatment		V12 Start run-in	Double-blind treatment period (visit/week)							Follow-up	Late follow-up
	V1	V2-V11		V13 ^a	V14 ^a	V15 ^a	V16 ^a	V17 ^a	V18 ^a	V19 ^a	V20	V21
	Start of screening period	Standardize and optimize maintenance OCS ^{abc}										
	Week -14 ^d	Between weeks -12 and -3		W -2	DoR	W4±7d	W8±7d	W12±7d	W16±7d	W20±7d	W24±7d/ EOT/ early termination	W32/EOT + 8w ±7d
Informed assent/consent	X											
Medical history	X											
Medication history	X											
Inclusion and/or exclusion criteria	X	X ^e	X	X								
Randomization criteria				X								
Reversibility testing ^f	X											
Pregnancy testing ^g	X			X	X	X	X	X	X	X	X	
Blood for HIV, hepatitis B, and hepatitis C	X											
CBC with differential ^h	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry tests ⁱ	X			X	X ^j	X ^j	X	X ^j	X ^j	X		
Urinalysis	X											
Full physical examination ^k	X											
Brief physical examination ^k		X	X	X	X	X	X	X	X	X		
Vital signs measurement ^k	X	X	X	X	X	X	X	X	X	X		
Height ^l and weight	X			X						X		

Table 5: Study Procedures and Assessments

Procedures and assessments	Pretreatment		V12 Start run-in	Double-blind treatment period (visit/week)							Follow-up	Late follow-up
	V1	V2-V11		V13 ^a	V14 ^a	V15 ^a	V16 ^a	V17 ^a	V18 ^a	V19 ^a	V20	V21
	Start of screening period	Standardize and optimize maintenance OCS ^{abc}										
	Week -14 ^d	Between weeks -12 and -3		W -2	DoR	W4±7d	W8±7d	W12±7d	W16±7d	W20±7d	W24±7d/ EOT/ early termination	W32/EOT + 8w ±7d
ECG ^k	X									X		
Provide and collect PEF meter		X								X		
Provide/collect electronic asthma control diary; reinforce diary and PEF compliance		X	X	X	X	X	X	X	X	X		
OCS reduction attempts		X			X	X	X	X	X			
Pre-bronchodilator spirometry ^m	X	X ⁿ		X	X	X	X	X	X	X	X	
Post-bronchodilator spirometry ^o				X	X		X		X	X	X	
PK samples ^p				X	X	X	X	X	X	X	X	X
Blood for ADA ^q				X	X	X	X			X	X	X
IP administration				X	X	X	X	X	X			
Injection site evaluation				X	X	X	X	X	X			

Table 5: Study Procedures and Assessments

Procedures and assessments	Pretreatment		V12 Start run-in	Double-blind treatment period (visit/week)							Follow-up	Late follow-up
	V1	V2-V11		V13 ^a	V14 ^a	V15 ^a	V16 ^a	V17 ^a	V18 ^a	V19 ^a	V20	V21
	Start of screening period	Standardize and optimize maintenance OCS ^{abc}										
	Week -14 ^d	Between weeks -12 and -3		W -2	DoR	W4±7d	W8±7d	W12±7d	W16±7d	W20±7d	W24±7d/ EOT/ early termination	W32/EOT + 8w ±7d
AQLQ+12				X	X	X	X	X	X	X		
ACQ-6				X	X	X	X	X	X	X	X	
EQ-5D				X						X		
St. George’s Respiratory questionnaire				X			X			X		
Assess CAEs and related HCU ^r				X	X	X	X	X	X	X		
Phadiatop allergy test				X								
OCS withdrawal effects inquiry ^s			X	X	X	X	X	X	X	X		
Adverse event inquiry ^t		X	X	X	X	X	X	X	X	X	X	
Concomitant medication inquiry	X	X	X	X	X	X	X	X	X	X	X	

^a The site will contact IWRS at every optimization and treatment visit.

^b The patient’s previous OCS should be switched to an equivalent, standardized prednisone formulation. Optimization may occur once OCS standardization is complete.

^c Attempts at OCS reduction should be made at 1-week intervals, for up to 10 weeks or until there is a worsening of asthma signs and symptoms, to help determine the patient’s lowest effective OCS dose. This period may be shortened if the lowest effective dose is achieved sooner. Eosinophil counts during the optimization period or at the week -2 visit may be considered in order to meet the eosinophil inclusion criteria for this study. Patients requiring an average daily dose of between ≥5 mg and ≤40 mg may proceed to run-in and maintained without change during run-in.

^d The screening period (between V1 and V2) can be less than 2 weeks if all of the screening inclusion criteria are met sooner. It is understood that not all procedures can be completed on the same day. In particular, the patient may need to return to satisfy the medication hold for screening pre bronchodilator FEV1 and reversibility testing.

Clinical Study Protocol with Amendment 02

- ^e Verify that essential screening inclusion criteria for asthma are met before entering optimization.
- ^f Reversibility testing is most conveniently performed at the same visit as the screening, pre-bronchodilator spirometry. All patients must undergo reversibility testing, even if they are submitting historical reversibility or methacholine provocation results to support inclusion criterion e. Reversibility testing may be repeated once, within the 2-week screening period.
- ^g β HCG serum pregnancy tests will be performed at screening; urine pregnancy testing will be performed every 4 weeks thereafter until week 24 or early withdrawal (female patients who are not 2 years postmenopausal or surgically sterile) and at the early follow-up visit (V20).
- ^h The patient must have had a blood eosinophil count $\geq 300/\mu\text{L}$ in the 12 months before ICF or $\geq 300/\mu\text{L}$ during screening or during OCS optimization or at the week -2 visit. A CBC with differential need not be repeated at every visit during the optimization period and should be done at the investigator's discretion if the eosinophil criteria were not met at screening.
- ⁱ CPK is collected with serum chemistry tests at scheduled visits. If a potentially clinically significant CPK level ($\geq 3.1 \times \text{ULN}$) is reported, initiate the CPK/myalgia CRF and clinical monitoring as outlined in Protocol Section 7.1.7.3.2.
- ^j CPK measurement only. CPK will be collected with PK sample.
- ^k Physical examination, vital signs, and ECG should be obtained before spirometry procedures and IP administration.
- ^l For adults, height will be measured at screening only. For patients < 18 years of age, height will be measured at screening, DoR, and EOT. Use of a stadiometer is preferable, if available, or use a cloth tape securely attached to the wall that will allow reproducible results. Height should be measured in centimeters, without shoes.
- ^m Pre-bronchodilator spirometry assessments should only be performed after withholding short-acting bronchodilators (ie, inhaled short-acting beta-agonists and/or short acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled LABAs and long-acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule. Spirometry should be performed prior to IP administration, if applicable.
- ⁿ Optional at visits 2-11.
- ^o For post-bronchodilatory spirometry, short-acting beta-agonists, such as salbutamol or albuterol, administered via a metered dose inhaler should be used. Four separate doses (eg, albuterol 360 μg or salbutamol 100 μg ex-valve) should be given by a metered dose inhaler as tolerated. Post-bronchodilator spirometry should be completed a minimum of 15 minutes after dosing of short-acting beta-agonist.
- ^p Blood samples for PK and ADA analysis will be drawn before administration of study drug.
- ^q If possible, a blood sample for measurement of serum reslizumab concentrations will be obtained from patients experiencing an adverse event leading to withdrawal, a serious adverse event, an observation of any severe hypersensitivity reaction (eg, anaphylaxis), or an exacerbation of asthma symptoms.
- ^r If a patient experiences worsening of his or her asthma symptoms, the patient is to call the study center within 48 hours (if possible) to be evaluated for his or her asthma symptoms. Procedures and assessments to be performed if an unscheduled visit occurs are described in Protocol Section 3.16.5.
- ^s Based on investigator's assessment.
- ^t Adverse event inquiry will occur before and after study drug administration at V3 to V16. Follow-up any prior messages from the post-injection eDiary symptom inquiry, as necessary. For systemic or severe hypersensitivity reactions possibly related to the study drug, initiate the anaphylaxis CRF. When such reactions are observed after study drug administration in the clinic, vital signs must be monitored using the unscheduled vital signs CRF. At the time of myalgia/muscular adverse events, CPK should be collected (initiate myalgia CRF).

ACQ-6=6-item Asthma Control Questionnaire; ADA=anti-drug antibody; AQLQ=Asthma Quality of Life Questionnaire; β HCG=beta human chorionic gonadotropin; CAE=clinical asthma exacerbation; CBC=complete blood count; CPK=creatinine phosphokinase; CRF = case report form; DoR=date of randomization; ECG=electrocardiogram; eDiary = electronic diary; EOT=end of treatment; EQ-5D=European Quality of Life 5-dimension health state utility index; FEV₁=forced expiratory volume in 1 second; HCU=health care utilizations; HIV=human immunodeficiency virus; ICF=Informed Consent Form; IP=Investigational Product; LABA=long-acting beta-agonist; OCS=oral corticosteroid; PEF=peak expiratory flow; PK=pharmacokinetic; ULN = upper limit of normal V=visit; W=week.

3.16.1. Procedures for Screening and Enrollment (Visit 1)

A signed and dated ICF will be obtained from all patients 18 years of age or older before any study-specific screening procedures are performed (see Section 12.1). For patients 12 through <18 years of age, a signed and dated ICF will be obtained from a parent/legal guardian, and a signed and dated assent form will be obtained from each patient before screening procedures commence, according to local IEC/IRB requirements. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the study-specific evaluations. In addition, disease-specific assessments performed within a specified timeframe before informed consent may be used for the study. Parents/legal guardians will acknowledge and agree to the possible use of this information for the study by giving informed consent.

After informed consent is obtained, patients who are screened will be assigned an 8-digit permanent identification number such that all patients from each investigational center are given consecutive identification numbers in successive order of inclusion. The first 2 digits of the screening number will be the number assigned to the country where the investigational center is located, the next 3 digits will be the designated investigator center number, and the last 3 digits will be assigned at the investigator center (eg, if the number assigned to the country is 01, the third patient screened at center 5 would be given the number of 01005003).

A patient who is screened but not randomized, for example, because entry criteria were not met, may be considered for screening once more, for example, if there is a change in the patient's medical background or a modification of study entry criteria. Patients may be screened again if they did not meet spirometry/reversibility criteria initially. The duration between the date of Screen Failure and the re-screening must be >30 days.

The following procedures will be performed at the screening visit (visit 1):

- Obtain written informed consent before any other study-related procedures are performed
- Review medical history
- Review prior and concomitant medication
- Review inclusion/exclusion criteria
- Perform reversibility testing if long-acting and short-acting inhaled bronchodilators were held for the specified time; if not, the patient should be brought back on another day to complete. Reversibility testing may be repeated once within the 2-week screening period. Airway reversibility will be demonstrated by measuring the change in FEV₁ before and after inhalation of SABA; reversibility testing should only be attempted after withholding short-acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long-acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule. SABAs, such as salbutamol or albuterol, administered via a metered dose inhaler should be used for reversibility testing. Four separate doses (eg, albuterol 360 µg or salbutamol 100 µg ex-valve) should be given by a metered

dose inhaler, as tolerated. Post-bronchodilator spirometry should be completed a minimum of 15 minutes after dosing of SABA.

- Perform serum pregnancy testing (female patients who are not 2 years postmenopausal or surgically sterile only)
- Perform clinical laboratory tests (chemistry, hematology, and urinalysis); only patients with an eosinophil counts of 300 eosinophils/ μ L or greater at screening while on chronic OCS, or those with a documented level of at least 300 eosinophils/ μ L during the previous 12 months will be eligible to continue in the study
 - Note: a patient will meet inclusion criteria if an eosinophil count of 300/ μ L or greater becomes manifest during the OCS optimization period or at the week -2 visit (end of optimization period/beginning of run-in period).
- Perform full physical examination
- Perform vital signs assessments (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate)
- Measure height and weight
- Perform ECG
- Perform pre bronchodilator spirometry
- Collect blood for HIV, hepatitis B, and hepatitis C testing
- Inform patients of study restrictions and compliance requirements

3.16.2. Procedures Before Study Drug Treatment

3.16.2.1. Procedures During the Optimization Period (Weeks –12 through –3 [Visits 2 through 11])

- Verify that essential screening inclusion criteria for asthma are met before entering optimization
- Perform hematology tests (CBC with differential) if the inclusion criterion of an eosinophil count of 300/ μ L or greater was not met at screening
- Perform brief physical examination
- Perform vital signs assessments
- Provide and collect PEF meter
- Provide/collect electronic asthma control diary; reinforce diary and PEF compliance
- Attempt OCS reduction
- Concomitant medication inquiry
- Adverse event inquiry

3.16.2.2. Procedures During the Run-In Period (Week –2 [Visit 12])

- Review inclusion/exclusion criteria
- Perform hematology tests (CBC with differential) if the inclusion criterion of an eosinophil count of 300/ μ L or greater was not met at prior visits
- Perform brief physical examination
- Perform vital signs assessments
- Provide/collect electronic asthma control diary; reinforce diary and PEF compliance
- Assess any OCS withdrawal effects (based on investigator's assessment)
- Perform concomitant medication inquiry
- Perform adverse event inquiry

For a minimum of 2 weeks after visit 12, patients will continue on their usual asthma medications and their optimized OCS dose and complete daily self-monitoring of symptoms using an asthma control diary and PEF meter.

3.16.2.3. Procedures at Baseline/Day of Randomization (Week 0 [Visit 13])

Patients who complete the run-in period will continue to visit 13, when baseline evaluations will be conducted.

The baseline visit (visit 13) will not take place more than 14 weeks after the screening visit. The following procedures will be performed at visit 13 before reslizumab or placebo administration:

- Review inclusion/exclusion criteria
- Review randomization criteria
- Perform urine pregnancy testing (female patients who are not 2 years postmenopausal or surgically sterile only)
- Perform clinical laboratory tests (chemistry and hematology)
- Perform brief physical examination
- Perform vital signs assessments (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate)
- Measure height and weight
- Complete asthma-specific tests
 - Collect and review electronic asthma control diary and reinforce diary and PEF compliance.
 - Pre-bronchodilator spirometry, including FEV₁, % predicted FEV₁, FVC, and FEF_{25%-75%}
 - Post-bronchodilator spirometry, including FEV₁, % predicted FEV₁, FVC, and FEF_{25%-75%}

- Complete the AQLQ+12
- Complete ACQ-6
- Collect blood for asthma biomarker analysis
- Collect blood for serum reslizumab concentration determination (PK assessment)
- Collect blood sample for immunogenicity (ie, ADA) assessment
- [REDACTED]
- [REDACTED]
- Complete EQ-5D
- [REDACTED]
- Complete SGRQ
- Assess CAEs and related health care utilizations
- Collect blood for Phadiatop allergy test ([Vidal et al 2005](#))
- Assess any OCS withdrawal effects (based on investigator’s assessment)
- Record any concomitant medications

A patient who is not randomly assigned to treatment on the basis of the results of baseline/DoR assessments (eg, because entry criteria were not met or enrollment did not occur within the specified time) may be considered for rescreening if there is a change in the patient’s medical background, a modification of study entry criteria, or other relevant change. A patient may be rescreened for this reason 1 time only. The duration between the first visit during the screening period and the rescreening must be >30 days. Patients may be screened again if they did not meet spirometry/reversibility criteria initially.

Patients who continue to meet the inclusion/exclusion criteria will be assigned a permanent unique randomization number and a treatment number generated by IRT. These 2 newly assigned numbers will be entered into the CRF, and study drug will be dispensed. The following procedures/assessments will be performed during and after administration of study drug on day 1:

- Patients will be observed for 1 hour after study injection/baseline/DoR assessments
- Evaluation of injection site for reaction at approximately 1 hour after dosing using the injection site CRF. Clinically significant injection site reactions should be recorded as an adverse event.
- If, during post-study drug observation, the patient develops clinical symptoms, vital signs should be collected. The patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section [7.1.7](#).

Remind the patients that they will receive a post-injection symptom inquiry via the eDiary.

3.16.3. Procedures During Study Drug Treatment

3.16.3.1. Double-Blind Treatment Period (Weeks 1 Through 24 [Visits 13 Through 19])

Study drug will be administered at approximately the same time in the morning on the days indicated in [Table 5](#). (Note: Patients must be observed for a minimum of 1 hour after study drug administration.)

3.16.3.1.1. Weeks 4, 8, 12, 16, 20, and 24 (Visits 14 Through 19)

During the study drug treatment period, patients will return to the study center once every 4 weeks (± 7 days) thereafter (relative to DoR/baseline) for administration of study drug and assessments until the end of the treatment period (week 24 or early withdrawal).

The following procedures/assessments will be performed before administration of study drug unless otherwise indicated:

- Perform urine pregnancy testing at weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- Perform hematology tests (CBC with differential) at weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- Perform serum chemistry tests (weeks 12 and 24 or early withdrawal) (a sample for CPK measurement only will also be collected on weeks 4, 8, 16, and 20).
- Perform brief physical examination at weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate) at weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- Measure height and weight (week 24 or early withdrawal) for patients 12 to <18 years of age
- Measure weight (week 24 or early withdrawal) for adult patients
- Perform ECG (week 24 or early withdrawal)
- Perform adverse event inquiry
- Complete asthma-specific tests
 - Provide and collect PEF meter (week 24 or early withdrawal)
 - Provide/collect electronic asthma control diary; reinforce diary and PEF compliance (weeks 4, 8, 12, 16, 20, and 24 or early withdrawal)
 - OCS reduction attempts (weeks 4, 8, 12, 16, and 20)
 - Pre-bronchodilator spirometry (weeks 4, 8, 12, 16, 20, and 24 or early withdrawal)
 - Post-bronchodilator spirometry (weeks 4, 12, 20, and 24 or early withdrawal)

- AQLQ +12 (weeks 4, 8, 12, 16, 20, and 24 or early withdrawal) (may be completed after study drug administration during the 1-hour observation period)
- ACQ-6 (weeks 4, 8, 12, 16, 20, and 24 or early withdrawal) (may be completed after study drug administration during the 1-hour observation period)
- Collect blood for asthma biomarker analysis (week 24 or early withdrawal)
- Assess CAEs and related health care utilizations
- Collect blood for serum reslizumab concentration determination (PK assessment) (weeks 4, 8, 12, 16, 20, and 24 or early withdrawal)
- Collect blood sample for immunogenicity assessment (weeks 4, 8, 12, and 24 or early withdrawal)
- [REDACTED]
- [REDACTED]
- Complete EQ-5D (week 24 or early withdrawal) (may be completed after study drug administration during the 1-hour observation period)
- [REDACTED]
- Complete SGRQ (weeks 12 and 24 or early withdrawal) (may be completed after study drug administration during the 1-hour observation period)
- Record any concomitant medications
- Investigational product (IP) administration (weeks 4, 8, 12, 16, and 20)
- Assess any OCS withdrawal effects (based on investigator’s assessment)

Additionally, the following procedures/assessments will be performed during and after administration of study drug:

- Patients will be observed for 1 hour after study injection.
- Evaluation of injection site for reaction at approximately 1 hour after dosing using the injection site CRF. Clinically significant injection site reactions should be recorded as an adverse event.
- If, during post-study drug observation, the patient develops clinical symptoms, vital signs should be collected. The patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.7.

Remind the patients that they will receive a post-injection symptom inquiry via the eDiary.

3.16.4. Procedures After Study Drug Treatment

Patients who participate in the study in compliance with the protocol for at least 24 weeks of double-blind treatment will be considered to have completed the treatment period. Patients who complete the follow-up visit (approximately week 32) will be considered as having completed the study. See Section 12.4 for the definition of the end of the study.

Patients who discontinue the study drug prematurely must be encouraged to continue to attend the regular scheduled visits and complete the prescribed safety and efficacy evaluations through the EOT/early withdrawal visit and the follow-up visit, if at all possible (see Section 4.5).

Patients who both discontinue the study drug and also withdraw from the study should have final evaluations performed on the last day they receive the study drug or as soon as possible thereafter. Patients should also return for the follow-up visit and procedures if at all possible (see Section 4.5).

Procedures for patients who withdraw prematurely from the study are described in Section 4.5. Following termination of the study, patients should be treated according to the standard of care, and as guided by the principal investigator.

Patients with ongoing adverse events or clinically significant abnormal laboratory test results (as interpreted by the investigator) will be monitored as described in Section 7.1.2 and Section 7.3, respectively.

The following procedures/assessments will be performed at the follow-up visit (EOT + 8 weeks \pm 7 days [visit 20]):

- Hematology tests (CBC with differential)



- Collect blood for serum reslizumab concentration determination (PK assessment)
- Collect blood sample for immunogenicity assessment
- Concomitant medication inquiry
- Adverse event inquiry
- Perform urine pregnancy test

The following procedures/assessments will be performed at the late follow-up visit (EOT + 24 weeks \pm 14 days [visit 21]):

- Collect blood for serum reslizumab concentration determination (PK assessment)
- Collect blood sample for immunogenicity assessment

3.16.5. Unscheduled Visits

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the investigator. The date and reason for the unscheduled visit as well as any other data obtained (eg, adverse events, concomitant medications and treatments, and results from procedures or tests) will be recorded on the CRF and within the patient's source notes.

Procedures performed during unscheduled visits include the following:

- Perform concomitant medication inquiry
- Perform vital signs measurements
- Perform adverse event inquiry

Clinical Study Protocol with Amendment 02

- Perform evaluation of any signs and/or symptoms of adrenal insufficiency (OCS withdrawal effects)
- Perform study compliance review

Other procedures may be performed at the discretion of the investigator.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study eligibility criteria to allow patients to enter a study are not granted by Teva (see Section 11.1.2).

4.1. Patient Inclusion Criteria

Patients may be included in the study only if they meet all of the following criteria:

- a. The patient is male or female, 12 years of age and older, with a previous diagnosis of asthma. Patients 12 to <18 years of age are excluded from participating in South Korea, the Netherlands, and Argentina, and patients 66 years of age and older are excluded from participating in South Korea.
- b. Written informed consent is obtained. During the screening period, a signed and dated informed consent form (ICF) (and an assent form for children 12 through <18 years of age in accordance with local standards) will be obtained before a diagnosis of asthma is confirmed on the basis of patient history and by demonstration of airway reversibility.
- c. The patient continues to require an average daily maintenance dose of OCS for asthma of between 5 and 40 mg of prednisone or equivalent during the 3 months before screening. Patients on an OCS dose of >40 mg at screening who the investigator believes may be able to decrease OCS dose to ≤40 mg during the optimization period may also be enrolled. Note: every-other-day dosing that is within this daily average (ie, 10 to 80 mg) is allowed.
- d. The patient has a documented blood eosinophil level of at least 300/μL during the previous 12 months while on at least medium total daily dose of ICS based on Global Initiative for Asthma 2016 clinical comparability table ([Appendix A](#)), or ≥300/μL at screening while on chronic OCS or that becomes manifest during the OCS optimization period or at the week -2 visit (end of optimization period/beginning of run-in period).
- e. The patient has required at least 880 μg of inhaled fluticasone propionate or equivalent daily PLUS another controller(s) (eg, LABA, long-acting anti-muscarinic antagonist, leukotriene inhibitor, or theophylline) or documented intolerance to another controller for at least 6 months before the screening visit. For a fixed-dose ICS/LABA preparation, the highest labeled dose in that region will satisfy this criterion. For patients 12 through <18 years of age, the ICS dose must correspond to at least a medium total daily ICS dose. Note: the dose and regimen of asthma controllers and any allergen immunotherapy should have been stable during the 30 days before signing the Informed Assent Form/ICF.
- f. The patient has FEV₁ reversibility of at least 12% after administration of inhaled reliever medication according to the standard American Thoracic Society (ATS) or European Respiratory Society (ERS) protocol. Given the refractory nature of the disease in this population and the influence of high background controller medications on reversibility testing, documented FEV₁ reversibility of 12% or a

- provocation concentration producing a 20% fall in FEV₁ for methacholine of ≤ 8 mg/mL within 24 months of the screening visit, and performed according to the standard ATS/ERS procedures, would fulfill this criterion. Patients may be screened again if they did not meet spirometry/reversibility criteria initially. The duration between the date of Screen Failure and the re-screening must be >30 days.
- g. Females of childbearing potential (not surgically sterile by hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or 2 years postmenopausal) must have exclusively same-sex partners or use medically acceptable methods of birth control and must agree to continue use of this method for the duration of the study and for 5 months after the last study drug dose. Acceptable methods of birth control include intrauterine device, systemic hormonal contraceptive (oral, implanted, transdermal, or injected), barrier method with spermicide, abstinence, bilateral fallopian tube occlusion, and partner vasectomy.
 - h. The patient must be willing and able to comply with study restrictions, willing and able to perform requisite procedures and remain at the clinic for the required duration during the study period, and willing to return to the clinic for the follow-up evaluation as specified in this protocol.
 - i. Except for the OCS, which will be adjusted per protocol, the patient must maintain his/her usual asthma controller regimen without change throughout the screening, optimization, run-in, and treatment periods.

4.2. Patient Exclusion Criteria

Patients will be excluded from participating in this study if they meet any of the following criteria:

- a. The patient has any clinically significant, uncontrolled medical condition (treated or untreated) that would interfere with the study schedule or procedures and interpretation of efficacy results or would compromise the patient's safety.
- b. The patient has another confounding underlying lung disorder (eg, chronic obstructive pulmonary disease, interstitial lung disease, bronchiectasis eosinophilic granulomatosis with polyangiitis [also known as Churg-Strauss syndrome], or allergic bronchopulmonary aspergillosis).
- c. The patient has a known hypereosinophilic syndrome.
- d. The patient has a history of any malignancy within 5 years of the screening visit, except for treated and cured nonmelanoma skin cancers.
- e. The patient is pregnant or intends to become pregnant during the study or within 5 months from last dose of study drug or is lactating. Any woman becoming pregnant during the study will be withdrawn from the study.
- f. The patient required treatment for an asthma exacerbation within 4 weeks of screening.
- g. The patient is a current smoker (ie, has smoked within the last 6 months before screening) or has a smoking history ≥ 10 pack-years.

- h. The patient is currently using any systemic immunosuppressive or immunomodulatory biologic agents (eg, anti-immunoglobulin E mAb or other mAb [eg, mepolizumab] or soluble receptor) or nonbiologic (eg, methotrexate, cyclosporine), except maintenance OCS for the treatment of asthma. Previous use of such agents that occurred >5 half-lives from the screening visit may be allowed, if approved by the medical monitor.
- i. The patient participated in a clinical study within 30 days or 5 half-lives of the investigational drug before screening, whichever is longer.
- j. The patient was previously exposed to benralizumab within 12 months of screening.
- k. The patient was previously exposed to reslizumab.
- l. The patient has a history of immunodeficiency disorder including HIV.
- m. The patient has current suspected drug and/or alcohol abuse.
- n. The patient has had an active helminthic parasitic infection or was treated for one within 6 months of screening.
- o. The patient has a history of allergic reactions or hypersensitivity to any component of the study drug.
- p. The patient has a history of latex allergy. (The current prefilled syringe device has a natural rubber component to the needle shield.)

4.3. Justification for Key Inclusion and Exclusion Criteria

The inclusion and exclusion criteria select for an OCS-dependent asthma phenotype with elevated eosinophils and that is likely to benefit from a targeted therapy such as reslizumab, while ensuring that enrolled patients are of sufficient health quality to ensure that participation in this study will not put them at unnecessary risk.

4.4. Randomization criteria

After completion of the optimization/run-in period, patients may continue in the study if they meet all of the following criteria:

- a. The patient must be using an average daily dose of no less than 5 mg of prednisone after OCS optimization. A patient requiring less than 5 mg of prednisone to maintain control should not be randomized.
- b. The patient must be using an average daily dose of no more than 40 mg of prednisone after OCS optimization. A patient requiring more than 40 mg of prednisone to maintain control should not be randomized.
- c. The patient should not have had an asthma exacerbation during the run-in period, defined as requiring a burst of systemic corticosteroid for an asthma worsening (injection, or if oral, at least a doubling from the current OCS dose for at least 3 days); an asthma-specific hospital admission; or an asthma-specific emergency department visit.

- d. The patient must have completed at least 4 days of diary entries (or any combination of 4 morning and 4 evening recordings) during the last 7 days of the run-in period.

4.5. Criteria and Procedures for Discontinuation of Study Treatment and/or Study Withdrawal

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), patients may voluntarily discontinue study treatment (ie, refuse study treatment but continue with study participation) or completely withdraw from the study (ie, with no further study participation or contact) at any time. The investigator also has the right to discontinue a patient from study treatment and/or withdraw a patient from the study in the event of intercurrent illness, adverse events, pregnancy (see Section 7.2), or other reasons concerning the health or well-being of the patient, or in the event of lack of cooperation.

If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event or a potentially clinically significant abnormal laboratory test result, monitoring will be continued until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made. The specific event or test result must be recorded on the source documentation and transcribed onto the CRF. If possible, a blood sample for measurement of serum reslizumab concentrations will be obtained from patients experiencing an adverse event leading to withdrawal, a serious adverse event, an observation of any severe hypersensitivity reaction (eg, anaphylaxis), or an exacerbation of asthma symptoms.

4.5.1. Discontinuation of Study Treatment

If premature discontinuation of study treatment occurs for any reason, the patient should continue attending remaining study visits while off study treatment. The patient will continue to receive study provided OCS (prednisone) treatment for the remainder of their participation in the study. The patient should not be considered withdrawn from the study due to interruption or discontinuation of study treatment. For this study, it is very important to continue collecting data from all patients whether or not they complete treatment.

If premature discontinuation of study treatment occurs, the patient should return to the clinic as soon as possible for a study treatment discontinuation visit. All evaluations should be performed as specified in the protocol for the early withdrawal visit (see Table 5). The investigator must determine the reason for and the date of discontinuation of study treatment and record this information in both the source documentation and the Study Drug Treatment Completion CRF. The patient's continued participation in the study must be discussed by the investigator and site staff with the patient; the investigator and site staff must also request the patient to continue attending study visits according to the study visit schedule with all assessments completed up to week 24 (visit 19). The OCS dose and safety assessments at week 24 (visit 19) are the priority assessments for patients that prematurely discontinue study treatment. At a minimum, the investigator should make every effort to obtain information regarding serious adverse events, OCS dose, and survival status at week 24. A safety follow-up visit (visit 20) should be conducted 8 weeks after visit 19.

4.5.2. Complete Withdrawal from Study

If a patient decides to completely withdraw from the study (ie, refuses any further study participation or contact), all study participation for that patient will cease and all data to be collected at subsequent visits will be considered missing. If a patient decides to completely withdraw from the study, every effort should be made to complete and report the observations outlined in Section 4.5.1 (Discontinuation of Study Treatment) before withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made, including an explanation of why the patient is withdrawing from the study. The reason for and date of withdrawal from the study must be recorded in the source documentation and the Double-Blind Treatment Period Completion CRF.

For patients who are lost to follow-up (ie, patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should make appropriate efforts to re-establish contact with patient; attempts to contact the patient should be documented in the source documents. If contact has not been re-established, efforts should still be made to locate the patient and obtain information regarding serious adverse events, OCS dose, and survival status at the end of the 24-week treatment period. A patient should only be designated as lost to follow-up if the site is unable to establish contact with the patient after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

5. TREATMENT OF PATIENTS

5.1. Drugs Administered During the Study

After successfully meeting entry criteria, eligible patients will be randomly assigned to study drug (110 mg of reslizumab or placebo) with stratification based on maintenance OCS dose of >10 mg or ≤10 mg and age (12 to <18 years of age or 18 years of age or older) at baseline, using IRT, which uses computerized central randomization. Study drug will be administered by qualified study personnel as sc injections in the upper arm(s) once every 4 weeks for a total of 6 doses.

The pre-filled syringe has a staked 27G 0.5-inch needle. Subcutaneous injections can be given at a 90° angle or at a 45° angle. The injection can be given at a 90° angle if 2 inches of skin can be grasped between the thumb and first finger. If only 1 inch of skin can be grasped, the injection should be done at a 45° angle. The sites where injections are given should be at least 1 inch away from each other. Product should be removed from the refrigerator and allowed to equilibrate at room temperature for 15 to 30 minutes before administration.

Study drug will be administered by qualified study personnel who will ensure that the study drug is administered in accordance with the protocol. The needle shields of the prefilled syringes contain natural rubber latex, which may cause allergic reactions; see exclusion criterion (p). Additional information regarding study drug can be found in the Pharmacy Manual.

A more detailed description of the reslizumab drug product is provided in Section 3.11.1. Study drug exposure will be measured and compliance to study drug administration will be monitored.

5.2. Restrictions

Medications prohibited before and/or during the study are described in Section 5.3. Restrictions are provided in the inclusion and exclusion criteria.

5.3. Prior and Concomitant Therapy or Medication

Any prior or concomitant therapy, medication, or procedure a patient has had at screening up to the end of the study period, including follow-up, will be recorded on the CRF. Generic or trade name, indication, and dosage will be recorded. Systemic corticosteroids and other medications will each be recorded in separate CRFs. The sponsor will encode all therapy and medication according to the World Health Organization (WHO) drug dictionary (WHO Drug).

Excluding OCS, which will be adjusted per protocol, the patient's baseline asthma therapy regimen (including, but not limited to, ICS, leukotriene antagonists, 5-lipoxygenase inhibitors, cromolyn) must be stable for 30 days before screening and continue without dosage changes throughout the study. Of note, prior asthma medications such as ICS, leukotriene pathway modifiers, long-acting bronchodilators, and mast cell stabilizers may be taken concomitantly and should not be altered during this study unless the patient's safety is at risk. Changes in background maintenance therapy must be discussed with the medical monitor.

The following medications will not be allowed during this study:

- Patients should refrain from using reliever inhalers for 6 hours before any study visit that includes spirometry or airway reversibility testing, including the screening visit.
- If a patient is taking LABAs, these should be withheld for 12 hours before any study visit that includes spirometry or airway reversibility testing, including the screening visit.
- Any immunosuppressive or immunomodulatory agents (biological and non-biological), including, but not limited to methotrexate, cyclosporine, and interferon (excluding systemic corticosteroids prescribed for asthma and maintenance allergen immunotherapy)
- All biologic therapies, including, but not limited to omalizumab (Xolair[®]), mepolizumab, benralizumab, lebrikizumab, and anti-tumor necrosis factor monoclonal antibodies
- All nonbiologic investigational drugs
- Inhaled nicotine (including electronic cigarettes)

At each clinic visit after the screening visit, the investigator will ask patients whether they have taken any medications (other than study drug), including over-the-counter medications, vitamins, or herbal or nutritional supplements, since the previous visit. Indication, dosage, and start and end dates should be entered on the appropriate CRF.

5.4. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance. A check of study drug compliance will be performed during each visit after the initial dispensation of study drug, and study drug accountability records will be completed. Compliance for OCS will be checked using pill counting at each study visit. If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn. The IEC/IRB should be notified.

5.5. Total Blood Volume

Blood draws will be separated by at least 2 weeks. The estimated total blood volume withdrawn over the entire study (including screening) is approximately 125 mL. To further reduce the volume of blood withdrawn, pediatric tubes will be used when possible.

6. ASSESSMENT OF EFFICACY AND IMMUNOGENICITY

6.1. Primary Efficacy Measure and Justification

Percent reduction in the daily OCS dose will be categorized as follows:

- 90% to 100%
- 75% to <90%
- 50% to <75%
- >0% to <50%
- No decrease in OCS, loss of baseline asthma control during weeks 20 through 24, or discontinuation from study drug

Loss of baseline asthma control will be defined as FEV₁ less than 80% of baseline at the week 24 visit, clinically significant worsening in ACQ-6 score (change in score of 0.5) at the week 24 visit compared with baseline, and/or CAE (as defined in Section 6.7) during weeks 20 through 24.

6.2. Spirometry

Pre-bronchodilator FEV₁, FVC, FEF_{25%-75%}, and post-bronchodilator FEV₁ will be measured using spirometry. The FEV₁ is the volume of air that can be forcibly exhaled from the lungs in the first second, measured in liters. The FVC is the volume of air that can be forcibly blown out after full inspiration, measured in liters. The FEF_{25%-75%} is the forced expiratory flow at 25% to 75% forced vital capacity. For post-bronchodilatory spirometry, SABAs, such as salbutamol or albuterol, administered via a metered dose inhaler should be used. Four separate doses (eg, albuterol 360 µg or salbutamol 100 µg ex-valve) should be given by a metered dose inhaler, as tolerated. Post-bronchodilator spirometry should be completed a minimum of 15 minutes after dosing of SABA. Spirometry will be done according to ATS/ERS 2005 procedural guidelines. The National Health and Nutrition Survey III reference equations will be used.

6.3. PEF monitoring

AM and PM ambulatory PEF will be measured using a PEF meter. PEF is the maximum speed of exhalation. AM and PM ambulatory PEF will be measured by the patient and recorded in the asthma control diary.

6.4. Asthma Quality of Life Questionnaire for Patients 12 Years and Older

The AQLQ +12 is a modified version of the standardized AQLQ (AQLQ[S]), which was developed to measure functional impairments experienced by adults ≥17 years of age. The AQLQ +12 is valid for patients 12 to 70 years of age and includes 32 questions in 4 domains (symptoms, activity limitation, emotional function, and environmental stimuli) (Juniper et al 1992, Wyrwich et al 2011). Patients are asked to recall their experiences during the

previous 2 weeks and score each of the questions on a 7-point scale where 7=no impairment and 1=severe impairment ([Appendix B](#)).

6.5. Asthma Control Questionnaire

The ACQ-6 is a validated asthma assessment tool that has been widely used ([Juniper et al 1999](#)). There are 6 self-assessment questions. Each item on the ACQ-6 has a possible score ranging from 0 to 6, and the total score is the mean of all responses ([Appendix C](#)).

6.6. Asthma Symptom Assessment

The asthma symptom score will be determined from the information recorded in the asthma control diary. A Likert-style scale will be used to quantify symptomatology. This scale has been used previously to assess changes in asthma symptoms in response to novel asthma treatments ([Shapiro et al 2000](#)). Every morning and evening, patients will indicate how much they are bothered by their asthma symptoms, as shown in [Appendix D](#).

6.7. Asthma Exacerbations

The number of CAEs requiring a burst of systemic corticosteroid (oral, iv, or im) and the time-to-first CAE will be measured.

A CAE is defined as a clinically judged deterioration in asthma control, as determined by the investigator and as evidenced by new or worsening asthma signs or symptoms based on the patient history, asthma control diary, physical examination, and/or ambulatory or clinic visit assessment of lung function AND that results in a medical intervention, including at least 1 of the following:

- use of systemic corticosteroids (injection, or if oral, at least a doubling from the current OCS dose for at least 3 days)
- asthma-specific hospital admission
- asthma-specific emergency department visit

Additional medication and/or medical intervention that would satisfy the CAE definition occurring within 7 days of the last day of a prior CAE event will be considered as part of the same event for analysis purposes.

The CAE start and stop dates will be collected in order to determine the exacerbation duration. The start date of a CAE will be the start date of the initial medical intervention (eg, use of systemic corticosteroids [injection, or if oral at least a doubling from the current OCS dose for at least 3 days], asthma-specific hospital admission, or asthma-specific emergency department visit, whichever comes first). The stop date is the last day of systemic corticosteroids (injectable), or for those with a doubling of the OCS dose, the stop date is when the return to their baseline dose, or the last day of an asthma-specific hospitalization or emergency department visit, whichever is later. For patients receiving at least a doubling from their current dose of OCS for at least 3 days that did not return to baseline (dose before exacerbation), an asthma exacerbation stop date will be the day that they have been on a new stable dose for at least 10 days.

If a patient experiences an asthma exacerbation, they should be treated with an OCS burst: 40 to 60 mg (or at least double his/her current dose) tapered over a 7- to 10-day period to a new maintenance dose of 2.5 mg above the pre-burst dose. It is understood that im or iv corticosteroid may also be administered as part of the treatment of the asthma exacerbation. If a second OCS burst is required, the patient should be maintained on a fixed OCS dose for the remainder of the double-blind treatment phase.

If possible, a blood sample for measurement of serum reslizumab concentrations will be obtained from patients experiencing an exacerbation of asthma symptoms, a serious adverse event, an observation of any severe hypersensitivity reaction (eg, anaphylaxis), or an adverse event leading to withdrawal.

6.8. European Quality of Life 5-Dimension Health State Utility Index

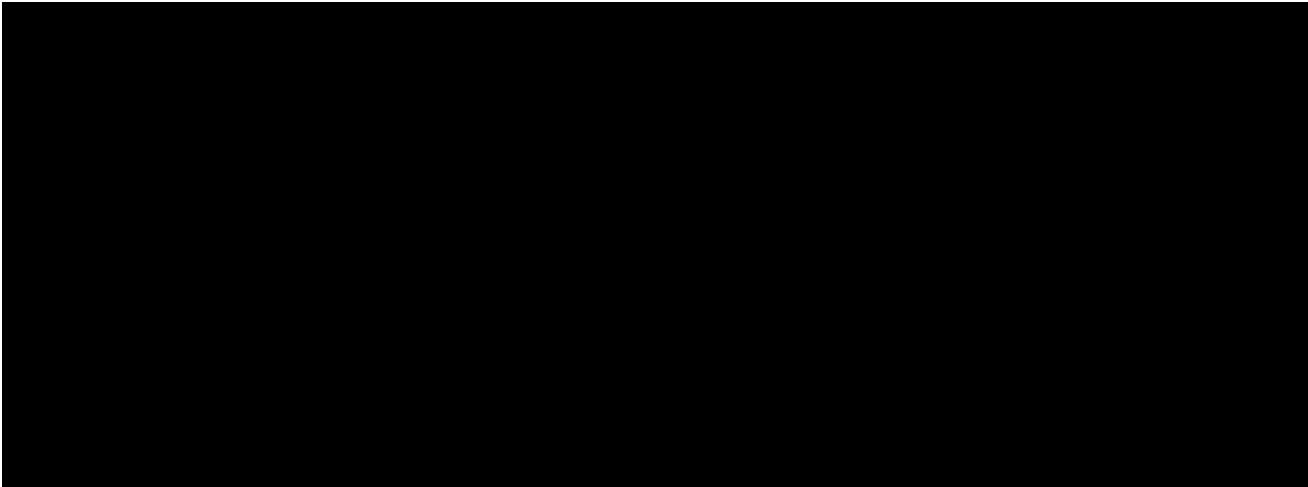
The EQ-5D is a standardized questionnaire that assesses overall state of health ([Appendix E](#)). The EQ-5D consists of 2 parts. In the first part, patients rate their health state in 5 health domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression using a scale of 1 to 3 where 1=no problem, 2=some problems, and 3=major problems. The second part consists of a 100 mm visual analog scale on which patients rate their perceived health state (0=worst imaginable health state, 100=best imaginable health state).

6.9. Inhaled Reliever Medication Use

The number of times asthma reliever therapy (number of inhalations) is used will be assessed by reviewing the electronic asthma control diary. Note: Inhaled reliever therapy used for exercise before treatment should not be recorded.

6.10. Nighttime Awakenings Requiring Rescue Inhaler Use

Patients will record nighttime awakenings and the amount of rescue medication taken in their electronic asthma control diary. The number of nighttime awakenings requiring rescue inhaler treatment will be determined based on the review of these recorded data.



6.14. St. George’s Respiratory Questionnaire

The St. George's Respiratory Questionnaire is a 50-item health status survey specific for chronic obstructive pulmonary disease and other respiratory diseases ([Appendix G; Barr et al 2000](#)).

6.15. Target Biomarker Measures

Biomarker measures will include blood eosinophils and [REDACTED]
[REDACTED]

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study staff by evaluating the following:

- Adverse events throughout the study
- Clinical laboratory test results (serum chemistry at screening, DoR/baseline, week 12, and week 24 or early withdrawal; hematology throughout the study; urinalysis at screening)
- Vital signs (pulse, respiratory rate, body temperature, and blood pressure) throughout the study
- ECG at screening and week 24 or early withdrawal
- Physical examination findings (including body weight and height measurements) throughout the study
- Signs and/or symptoms of adrenal insufficiency (OCS withdrawal effects) throughout the study
- Concomitant medication usage throughout the study

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment.

In this study, any adverse event occurring after the clinical study patient has signed the ICF should be recorded and reported as an adverse event.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study drug. Asthma exacerbation is an efficacy variable for this study and should be captured on the asthma exacerbation CRF; accordingly, asthma exacerbations should not be recorded as adverse events unless assessed as more severe than the patient's usual disease course. In this case, the investigator should determine if the adverse event is nonserious or serious based on seriousness criteria, as defined in Section 7.1.6. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication

- significant worsening (change in nature, severity, or frequency) of pre-existing conditions
- drug interactions
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant. (Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)
- events associated to study procedure (eg, clinically significant adrenal insufficiency)

7.1.2. Recording and Reporting Adverse Events

For adverse event recording, the study period is defined for each patient as that time period from signature of the ICF through the end of the follow-up period. For this study, the follow-up period is defined as 8 weeks after the EOT visit. Adverse events will be collected at each visit, including the follow-up visit, via adverse event inquiry.

All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed onto the CRF, regardless of the severity or seriousness of the event or judged relationship to the study drug. For serious adverse events, the Serious Adverse Event Form must also be completed and the serious adverse event must be reported immediately (see Section 7.1.6.3.1). The investigator does not need to actively monitor subjects for adverse events once the study has ended. Serious adverse events that occur to a patient after the end of the study should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.6.3.1.

At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open-ended question such as, “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe.” In addition, the eDiary will be programmed to query the patient about symptoms potentially consistent with hypersensitivity occurring during the 24 hour period following study drug injection. All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, also on the Serious Adverse Event Form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, returned to baseline, or until the patient is referred for continued care to another health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed onto the CRF. The approximate time of onset for each adverse event that starts within 24 hours of study drug administration will be also

recorded. The relationship of each adverse event to study drug treatment and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

7.1.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the choices on the following scale:

- Mild:** No limitation of usual activities
- Moderate:** Some limitation of usual activities
- Severe:** Inability to carry out usual activities

7.1.4. Relationship of an Adverse Event to the Study Drug

The relationship of an adverse event to the study drug is characterized as follows:

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events, which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	The relationship of an adverse event may be considered “no reasonable possibility” if it is clearly due to extraneous causes or if at least 2 of the following apply: <ul style="list-style-type: none"> • it does not follow a reasonable temporal sequence from the administration of the test drug. • it could readily have been produced by the patient’s clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • it does not follow a known pattern of response to the test drug. • it does not reappear or worsen when the drug is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty nor felt with a high degree of certainty to be related to the study drug.	The relationship of an adverse event may be considered “reasonable possibility” if at least 2 of the following apply: <ul style="list-style-type: none"> • it follows a reasonable temporal sequence from administration of the drug. • it cannot be reasonably explained by the known characteristics of the patient’s clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • it disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. • it follows a known pattern of response to the test drug.

7.1.5. Relationship of an Adverse Event to OCS Reduction

The relationship of an adverse event to OCS reduction (such as symptoms of adrenal insufficiency) will be indicated (yes/no) on the CRF.

7.1.6. Serious Adverse Events

7.1.6.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening adverse event (ie, the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event. Hospitalizations scheduled before study entry will not be considered serious adverse events, unless there was worsening of the preexisting condition during the patient's participation in this study. Note: Hospitalizations due to asthma exacerbation will be reported as serious adverse events if the presentation or outcome is more severe than the patient's known course of asthma
- persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

7.1.6.2. Expectedness

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The reference safety information for this study is the IB. The sponsor's Pharmacovigilance Department will determine the expectedness for all serious adverse events.

7.1.6.3. Reporting a Serious Adverse Event

7.1.6.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events (as described in Section 7.1.6.1) (including the protocol-defined follow-up period, described in Section 7.1.2), regardless of

judged relationship to treatment with the study drug, must be reported to the sponsor by the investigator within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor subjects for adverse events once the study has ended. Serious adverse events occurring to a patient after the study should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the local safety officer (LSO) or other designated personnel (a contract research organization [CRO] in a country without a sponsor LSO) (contact information is in the Clinical Study Personnel Contact Information section); the LSO will forward the report to the sponsor's Global Patient Safety & Pharmacovigilance Department.

The following information should be provided to record the event accurately and completely:

- study number
- investigator and investigational center identification
- patient number
- patient initials
- onset date and description of adverse event
- investigator's assessment of the relationship of the adverse event to the study drug (no reasonable possibility, reasonable possibility)

Additional information may include the following:

- age and sex of patient
- date of first dose of study drug
- date and amount of last administered dose of study drug
- action taken
- outcome, if known
- severity
- concomitant therapy (including doses, routes, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death:
 - cause of death (whether or not the death was related to study drug as determined by the investigator)
 - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease. The sponsor will also evaluate the expectedness of all serious adverse events.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigational center within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's Global Patient Safety & Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences form/XML file to the LSO/CRO for local submission to the regulatory authorities, IEC/IRBs, and investigators, according to regulations. The investigator is responsible for ensuring that the IRB/EC is also informed of the event, in accordance with local regulations.

Blinding will be maintained for the people who are involved directly in the study. Therefore, in case of a SUSAR, only the LSO/CRO will receive from pharmacovigilance the unblinded report for regulatory submission; the others will receive a blinded report.

Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event, but using the pregnancy form (see Section 7.2).

If possible, a blood sample for measurement of serum reslizumab concentrations will be obtained from patients experiencing a serious adverse event, an adverse event leading to withdrawal, an observation of any severe hypersensitivity reaction (eg, anaphylaxis), or an exacerbation of asthma symptoms.

7.1.6.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the study drug or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of reslizumab and the appropriate regulatory authorities (and IEC/IRB, if appropriate).

In addition to notifying the investigators and regulatory authorities (and IEC/IRB, if appropriate), other measures may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- altering the process of informed consent by modifying the existing consent form and informing current study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to reslizumab

7.1.7. Specific Protocol-Defined Adverse Events

7.1.7.1. Adrenal Insufficiency

Adrenal insufficiency will be treated as an adverse event.

Patients who experience the clinical symptoms of adrenal insufficiency (fatigue, weakness, anorexia, lightheadedness, abdominal pain, nausea/vomiting, myalgia) will be instructed to come to the study center for vital signs and evaluation by a physician if possible. Patients with severe symptoms will be instructed to proceed to the emergency department.

Blood samples will be taken for:

- cortisol level (before iv corticosteroids or oral corticosteroid dose increase if possible)
- calcium level
- sodium, potassium, chloride, glucose, creatinine, carbon dioxide, and blood urea nitrogen (BUN) levels
- CBC with differential

Patients determined to have mild symptoms of adrenal insufficiency may have their OCS dose increased back to the previously effective OCS level (at the investigator's discretion).

Patients determined to have clinically significant adrenal insufficiency will be instructed to (at minimum) double or triple their corticosteroid dose for ≥ 2 days.

Then, based on resolution of symptoms:

- If they recently (≤ 7 days) had a dose reduction, they will be instructed to return their corticosteroid dose to the previously effective OCS level.
- If they have not had a recent dose reduction and another factor precipitated the adrenal insufficiency (eg, infection), they should be treated for the inciting factor before OCS dose reduction.

7.1.7.2. Protocol-Defined Adverse Events for Expedited Reporting to Teva

For the purposes of this protocol, the following are considered protocol-defined adverse events for expedited reporting to Teva: anaphylaxis, newly diagnosed malignancy, opportunistic infection, and parasitic helminth infection. Protocol-defined adverse events for expedited reporting can be either serious or nonserious according to the criteria outlined in Section 7.1.6.1. The process for reporting a protocol-defined adverse event for expedited reporting is the same as that for reporting a serious adverse event (see Section 7.1.6.3). A list of potential opportunistic infections is found in [Appendix I](#).

7.1.7.3. Specific Adverse Event Case Report Form Capturing

7.1.7.3.1. Anaphylaxis/Hypersensitivity Reactions Case Report Form

Information about all suspected anaphylaxis events will be recorded on the Suspected Anaphylaxis/Hypersensitivity Reactions CRF, including the investigator's assessment if the event followed the definition of anaphylaxis based on the diagnostic criteria as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis ([Sampson et al, 2006](#)) ([Appendix H](#)). The Anaphylaxis/Hypersensitivity Reactions CRF should be initiated in real time (along with vital sign assessment) for events occurring after study drug administration in the clinic or as soon as possible for suspect events outside the clinic.

7.1.7.3.2. Creatine Phosphokinase/Muscular Adverse Events CRF

Potentially clinically significant creatine phosphokinase (CPK) elevations (with or without associated symptoms) or myalgia/muscle symptoms will be recorded as an adverse event and documented using the potentially clinically significant CPK/myalgia case report form. A potentially clinically significant CPK is defined as $\geq 3.1 \times$ the upper limit of normal (ULN) (Grade 3 based on the Food and Drug Administration [FDA] “Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials”).

If a potentially clinically significant CPK level ($\geq 3.1 \times$ ULN) occurs, the patient should attend an unscheduled visit for a physical examination and additional testing if indicated per investigator judgement. CPK levels will be re-tested at a minimum of every 7 to 10 days until the elevation is resolved, or if agreed with the medical monitor that no further testing is indicated. For $\geq 10 \times$ ULN elevations in CPK, repeat CPK level, urinalysis (including microscopy), serum electrolytes, BUN, and creatinine will be performed as soon as possible after receipt of the CPK result. Further testing of CPK levels should be undertaken as frequently as needed to manage patient care per investigator judgment, but should be at a minimum of every 7 to 10 days as above. Need for repeat urinalysis, serum electrolytes, BUN, and creatinine testing should be determined by the investigator. In addition, need for treatment (eg, administration of iv fluids and urine alkalinization) should be considered by the investigator.

In cases deemed by the investigator to be treatment-related elevations in CPK $\geq 10 \times$ ULN (eg, potentially rhabdomyolysis), study drug discontinuation should occur at least until CPK normalization or longer based on investigator clinical assessment.

7.1.8. Withdrawal Due to an Adverse Event

Any patient who experiences an adverse event may be withdrawn from the study or from study treatment at any time at the discretion of the investigator. If a patient is withdrawn wholly or in part because of an adverse event, both the adverse events page and termination page of the CRF will be completed at that time.

The patient will be monitored at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The investigator must inform the clinical project physician (CPP)/clinical leader as soon as possible of all patients who are being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient is withdrawn from the study or study drug for multiple reasons that include adverse events, the termination page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that, in the opinion of the investigator, is not severe enough to warrant discontinuation but requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be need to take a prohibited medication, not the adverse event.

If possible, a blood sample for measurement of serum reslizumab concentrations will be obtained from patients experiencing an adverse event leading to withdrawal, a serious adverse event, an

observation of any severe hypersensitivity reaction (eg, anaphylaxis), or an exacerbation of asthma symptoms.

Withdrawal from the study due to worsening of asthma or a CAE will be considered a withdrawal due to lack of effect, not a withdrawal due to an adverse event.

A patient should only be designated as lost to follow-up if the site is unable to establish contact with the subject after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

7.1.9. Overdose of Study Drug

Any dose of study drug (whether the investigational product, reference therapy, or a placebo), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor. When the identification of the study drug must be known, the investigator must follow the procedures outlined in Section 3.10.

Medication errors will be captured as protocol violations or deviations depending on the error.

7.1.10. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, departures from the protocol may be allowed on a case-by-case basis. After stabilization and/or treatment has been administered to ensure patient safety, the investigator or other physician in attendance must contact the medical monitor as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

7.2. Pregnancy

All pregnancies that occur during the study, or within 5 months after last IP injection, are to be reported immediately to the medical monitor, and the investigator must provide the Teva Global Pharmacovigilance Department with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event (see Section 7.1.6.3).

Any patient becoming pregnant during the study will be withdrawn. All patients who become pregnant will be monitored to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including spontaneous or voluntary termination, details of birth, and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after termination from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy does not continue to term, 1 of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.

- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.

7.3. Clinical Laboratory Tests

All clinical laboratory test results outside the reference range will be interpreted by the investigator as belonging to 1 of the following categories:

- abnormal but not a clinically significant worsening
- abnormal and a clinically significant worsening

A laboratory test result that has significantly worsened (according to medical judgment) from the baseline result will be recorded on the source documentation, transcribed onto the CRF as an adverse event, and monitored as described in Section 7.1.2. An adverse event includes a laboratory or diagnostic test abnormality (once confirmed by repeat testing) that results in the withdrawal of the patient from the study, the temporary or permanent cessation of treatment with study drug, or medical treatment or further diagnostic work-up.

In addition, potentially clinically significant values will be predefined by the sponsor for selected laboratory parameters (see Section 9.7.2) and will be detailed in the statistical analysis plan.

Clinical laboratory tests (serum chemistry and hematology) will be performed at the time points detailed in Table 5. Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are listed below.

7.3.1. Serum Chemistry

The following serum chemistry tests will be performed:

- sodium
- potassium
- chloride
- bicarbonate or carbon dioxide
- glucose
- BUN
- creatinine
- calcium
- CPK
- alanine aminotransferase
- aspartate aminotransferase
- alkaline phosphatase
- total protein
- albumin

- total bilirubin
- direct bilirubin
- [REDACTED]

7.3.2. Hematology

The following hematology tests will be performed:

- hemoglobin
- hematocrit
- platelet count
- absolute neutrophil count
- WBC count and differential count
 - polymorphonuclear leukocytes (neutrophils)
 - lymphocytes
 - eosinophils (blinded; absolute values)
 - monocytes (blinded)
 - basophils
- [REDACTED]

7.3.3. Other Clinical Laboratory Tests

Other clinical laboratory tests will be performed to ensure the safety of the patients but will not be used to assess the safety of the study drug.

7.3.3.1. Urinalysis

Urinalysis will be performed at screening and will include testing for the following:

- protein
- glucose
- ketones
- blood (hemoglobin)
- pH
- specific gravity
- microscopic
 - bacteria
 - red blood cells
 - WBCs

- casts
- crystals

7.3.3.2. Hepatitis B, Hepatitis C, and HIV

At screening, patients will have tests for hepatitis B, hepatitis C, and HIV.

7.3.3.3. Human Chorionic Gonadotrophin Tests

Women of childbearing potential will have a serum β HCG test at screening (visit 1). Human chorionic gonadotropin urine tests will be performed every 4 weeks thereafter until week 24 or early withdrawal, and at the early follow-up visit (visit 20). Any patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.

7.4. Vital Signs

Vital signs (pulse, blood pressure, body temperature, and respiratory rate) will be measured at time points specified in Table 5 and before other assessments (eg, blood draw and pulmonary function testing) and study drug administration. Vital signs include the following:

- pulse
- blood pressure
- body temperature
- respiratory rate

Before pulse and blood pressure are measured, the patient must be in a supine or semi-erect/seated position and resting for at least 5 minutes. The same position and arm should be used each time vital signs are measured for a given patient. For any abnormal vital sign finding, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as a clinically significant change (worsening) from a baseline value will be considered an adverse event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.

In addition, potentially clinically significant values will be predefined by the sponsor for selected vital parameters and will be detailed in the statistical analysis plan.

7.5. Electrocardiography

A 12-lead ECG will be conducted at screening and week 24. ECGs should be obtained before other assessments (eg, blood draw and pulmonary function testing) and study drug administration. Standard ECGs parameters will be recorded using a centralized process and the ECG will be interpreted locally by the principal investigator (or qualified physician) as normal or abnormal. If the ECG is read as abnormal, the principal investigator will indicate whether or not the abnormality is clinically significant (yes or no) and write in the detailed interpretation/diagnosis. Clinically significant abnormal ECG findings at screening should be recorded as part of the medical history. Any ECG finding that is judged by the investigator as a clinically significant change compared with a screening value will be considered an adverse

event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.

In addition, potentially clinically significant values will be predefined by the sponsor for selected ECG parameters and will be detailed in the statistical analysis plan.

7.6. Physical Examinations

Physical examinations, including height and weight will be performed at specified time points as outlined in Table 5. The “full” physical examination should include the following organ systems: General appearance; Head, Eyes, Ears, Nose, and Throat (HEENT); Chest and Lung; Heart; Abdomen; Musculoskeletal; Skin; Lymph Nodes; and Neurological. The “brief” physical examination should include at minimum the following organ systems: General appearance; HEENT; Chest and Lung; Heart; and Skin. Any physical examination finding that is judged by the investigator as a clinically significant change (worsening) compared with a baseline/DoR value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

7.7. Concomitant Therapy or Medication

Concomitant therapy or medication usage will be monitored throughout the study. Details of prohibited medications are found in Section 5.3.

7.8. Methods and Timing of Assessing, Recording, and Analyzing Safety Data

All adverse events will be reviewed on a periodic basis by the CPP/medical monitor according to the safety monitoring plan (eg, scheduled safety reviews for reslizumab) as interim/preliminary safety databases become available. Safety data will additionally be evaluated periodically and ad hoc (if necessary) in the Product Safety Group.

Methods and timing of assessing safety data are discussed in Section 3.16. Procedures for recording safety data are discussed in Section 13.1 and methods of analyses are discussed in Section 9.7.

8. ASSESSMENT OF PHARMACOKINETICS/PHARMACODYNAMICS, AND IMMUNOGENICITY

8.1. Pharmacokinetic Variables

Serum reslizumab concentration will be measured at time points indicated in [Table 5](#) using an appropriate validated method.

8.1.1. Specimen Sampling and Handling

Blood samples (3 mL) for the measurement of serum reslizumab concentration will be collected from all patients via venipuncture or indwelling catheter before each study drug administration at DoR/baseline and at weeks 4, 8, 12, 16, 20, and 24. Blood samples will also be collected at the week-32 follow-up visit and at the week-48 follow-up visit. If possible, a blood sample for measurement of serum reslizumab concentrations will also be obtained from patients experiencing a serious adverse event, adverse event leading to withdrawal, an observation of any severe hypersensitivity reaction (eg, anaphylaxis), or an exacerbation of asthma symptoms.

Samples will be collected into labeled serum separator tubes and inverted slowly at least 5 times to thoroughly mix the blood with the clotting activation agent. Labels for samples should include study number, randomization number, period, and nominal visit. Blood samples will be left standing upright at room temperature (20°C to 25°C) to clot for approximately 30 to 60 minutes. Samples should then be centrifuged at a minimum of 1500g for approximately 10 minutes at 4°C until clot and serum are well separated. If a 4°C centrifuge is not available, samples may be centrifuged at ambient temperature at 1500g for 10 minutes as long as measures are taken as appropriate to prevent samples from heating significantly during centrifugation. Separated serum will be transferred in approximately equal portions into 2 opaque, labeled, cryotubes (Aliquots A and B), immediately frozen in an upright position at a temperature within the range of –60°C to –90°C, and stored under these conditions until they are shipped to the bioanalytical facility. Storage at –15°C to –25°C is acceptable for a period of up to 60 days if a freezer with a temperature of –65°C or lower is not available. The listed temperatures must be maintained. Labels for samples should include study number, randomization number, period, nominal visit, set (A or B), and indication that they are PK samples.

The actual date and time of the start and end of each study drug administration and the date and time of collection of each PK sample will be recorded in the source and will be transcribed to the CRF.

8.1.2. Shipment and Analysis of Samples

Serum samples for all patients will be shipped from the investigational center to the central laboratory, where they will be stored until they are shipped to Teva or its designee for analysis. Samples will be stored in an upright position at a temperature within the range of –60°C to –80°C until assayed. The central laboratory will be notified before the shipment of the samples and will then be sent the shipping information when the samples are shipped. An electronic file containing sample demographics will be e-mailed to the bioanalytical laboratory and the Teva

Global Bioassays and Technology representative responsible for the bioanalysis for each shipment.

Set A samples will be transported, frozen with sufficient dry ice for 4 days, by next-day courier to the central laboratory.

Set B samples will be sent to the same laboratory as that for set A on a subsequent day by next-day courier (unless shipment to another facility is requested by the sponsor). Instructions as to the disposition of the B samples will be provided by the sponsor.

Sample shipments should be sent no later in the week than Wednesday morning for next-day delivery. Samples are not to arrive on the weekend.

Timing of the initiation of sample analysis will be determined by the Teva Global Bioassays and Technology representative responsible for the bioanalysis. The bioanalytical team will not be blinded for this analysis. Blood samples from placebo-treated patients will not be analyzed.

8.2. Pharmacodynamic Variables

Pharmacodynamic measures will include blood eosinophils and [REDACTED] measured at the time points indicated in [Table 5](#).

8.2.1. Blood Eosinophil Counts

Blood samples (2 mL) will be collected via venipuncture or an indwelling catheter at the time points detailed in [Table 5](#).

Details regarding the collection, handling, and shipment of samples for measurement are provided in the investigator laboratory manual and its associated specimen collection summary. The results of the differential will be blinded in the post-baseline differential cell count reports to avoid the possibility removing the blind.

8.2.2. Exploratory Biomarker Analysis

8.3. Immunogenicity Testing

8.3.1. Blood Sampling and Handling

Blood samples (5 mL) for the assessment of ADA response will be taken before dosing at the time points indicated in [Table 5](#). Unscheduled blood samples for ADA assessment will also be obtained from all patients (inside and outside of the United States) experiencing a serious adverse event, an adverse event leading to withdrawal, an observation of any severe hypersensitivity reaction (eg, anaphylaxis), or an exacerbation of asthma symptoms.

Samples will be collected into labeled serum separator tubes and inverted slowly at least 5 times to thoroughly mix the blood with the clotting activation agent. Labels for samples should include

study number, randomization number, period, and nominal visit. Blood samples will be left standing upright at room temperature (20°C to 25°C) to clot for approximately 30 to 60 minutes. Samples should then be centrifuged at a minimum of 1500g for approximately 10 minutes at 4°C until clot and serum are well separated. Samples may be centrifuged at ambient temperature at 1500g for 10 minutes as long as measures are taken as appropriate to maintain ambient temperature during centrifugation.

Separated serum will be transferred, in approximately equal portions, into 2 labeled cryovial tubes (primary Aliquot A and back-up Aliquot B) and stored in an ultralow freezer at –65°C or lower until they are shipped to a central or bioanalytical laboratory with temperature monitoring. Sample labels should include randomization number, period, study number, nominal visit, and indication that it is an ADA sample aliquot (A or B). Storage at –15°C to –20°C should not exceed 1 month if a freezer with a temperature of –65°C or lower is not available. The listed temperatures must be maintained. The actual times and dates of sampling will be recorded on the CRF.

8.3.2. Shipment and Analysis of Samples

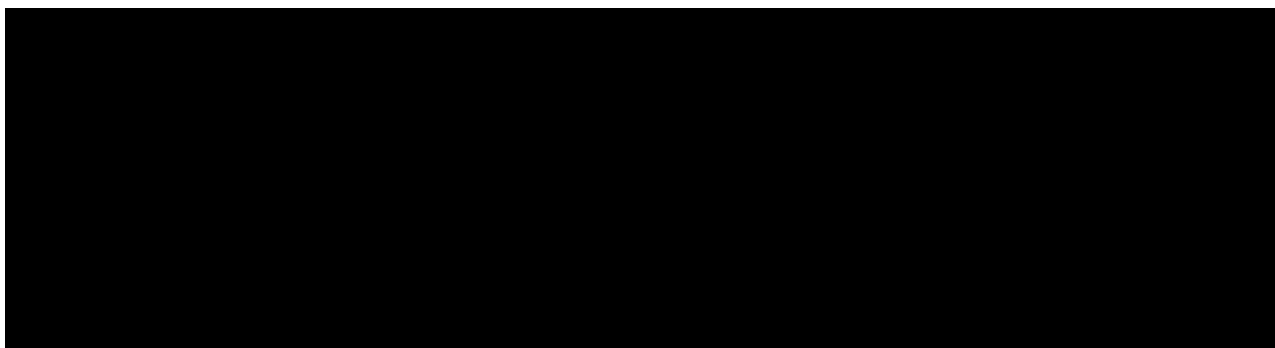
Serum samples for immunogenicity assessment for all patients will be shipped from the investigational center to the central laboratory, where they will be stored until they are shipped to the sponsor or its designee for analysis. Samples will be stored in an upright position at –65°C or lower until assayed. The central laboratory will be notified before the shipment of the samples and will be sent the shipping information when the samples are shipped. Set A samples will be transported with a temperature data logger and frozen with sufficient dry ice by next-day courier to the central laboratory.

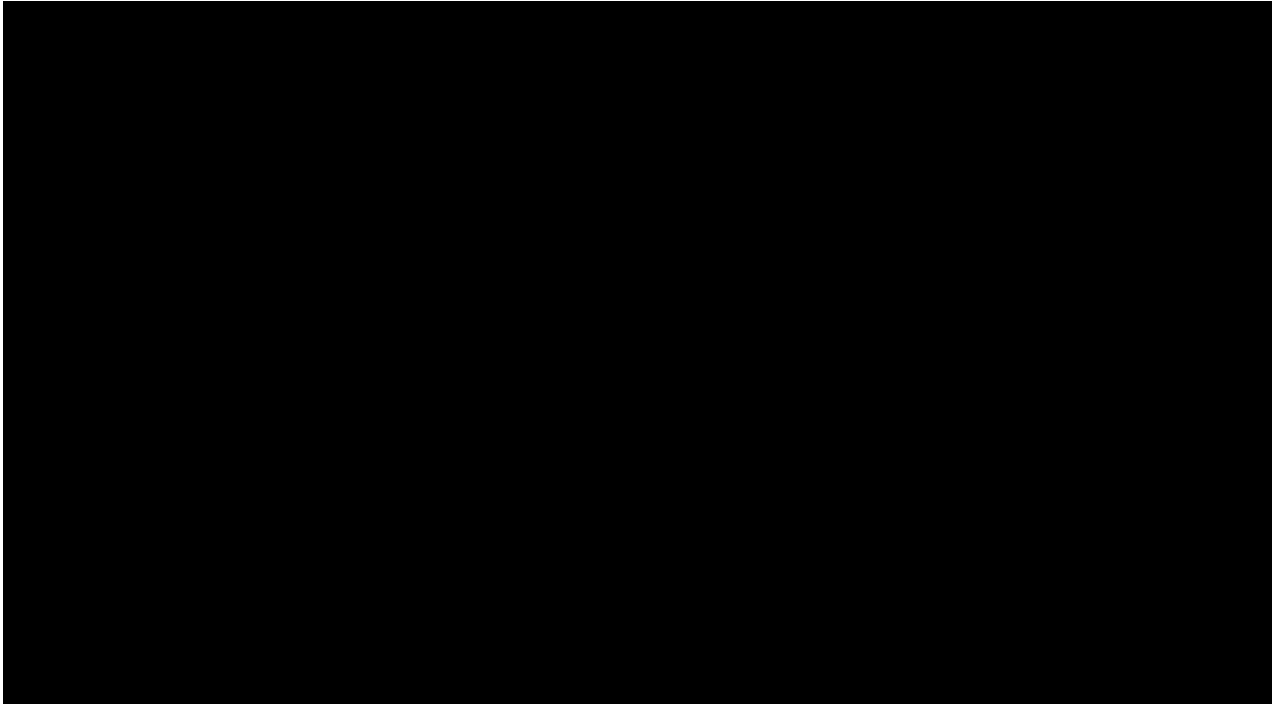
Set B samples will be sent to the same laboratory as that for set A on a later day by next-day courier (unless shipment to another facility is requested by the sponsor).

Sample shipments should be sent no later in the week than Wednesday morning for next-day delivery. Samples are not to arrive on the weekend.

Additional details regarding the collection, handling, and shipment of samples for measurement of ADAs are provided in the investigator laboratory manual and its associated specimen collection summary.

The serum samples from reslizumab-treated patients will be analyzed using a validated method for the detection of ADAs. The bioanalytical team will not be blinded for this analysis. Blood samples from placebo-treated patients will not be analyzed.





9. STATISTICS

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan. After finalization of the statistical analysis plan, any additional analyses or changes to analyses that may be required will be fully disclosed in the clinical study report.

9.1. Sample Size and Power Considerations

The primary efficacy variable and endpoint for this study is the percent reduction in the daily OCS dose during weeks 20 to 24 as compared with the dose at the end of the optimization phase. The study will be considered positive if the measure meets statistical significance at the respective predefined significance level. A statistically significant effect of reslizumab over placebo, as measured by the primary efficacy variable, is required to establish the efficacy of reslizumab treatment.

The sample size was calculated based on the following assumptions:

- Categorical reduction in OCS dose after 24 weeks of treatment will have the following distribution for the placebo group (based on [Bel et al 2014](#)):
 - 10.9% percent of subjects will have 90% to 100% reduction
 - 7.9% percent of subjects will have 75% to <90% reduction
 - 14.8% percent of subjects will have 50% to <75% reduction
 - 10.8% percent of subjects will have 0% to <50% reduction
 - 55.6% percent of subjects will have no reduction, loss of asthma control, or discontinuation from study drug
- The overall odds ratio between reslizumab and placebo based on proportional odds model will be 2.63
- Alpha level of 0.05

Based on the above assumptions, a sample size of 76 subjects per group will provide 90% power to detect a significant effect of reslizumab over placebo on the probability for a higher categorical reduction of OCS dose.

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomly assigned patients and will be used as the default population for primary efficacy analysis. In this population, treatment will be assigned based on the treatment to which patients were randomly assigned, regardless of which treatment they actually received.

9.2.2. Safety Analysis Set

The safety analysis set will include all patients who receive at least 1 dose of study drug. In this population, treatment will be assigned based upon the treatment patients actually receive, regardless of the treatment to which they were randomly assigned.

9.2.3. Additional Analysis Sets

9.2.3.1. Per-Protocol Analysis Set

The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients without major protocol violations.

Additional analysis sets may be detailed in the statistical analysis plan.

9.3. Data Handling Conventions

Sensitivity analyses for missing data will be detailed in the statistical analysis plan.

For most analyses, only the observed data from the patients will be used in the statistical analyses, ie, there is no plan to estimate missing data.

9.4. Study Population

The ITT analysis set (see Section 9.2.1) will be used for all study population summaries unless otherwise noted. Summaries will be presented by treatment group and for all patients.

9.4.1. Patient Disposition

Data from patients screened, patients screened but not randomly assigned, patients randomly assigned to treatment in the study, patients randomly assigned but not treated, patients in the safety analysis set, patients in the per-protocol analysis set, patients who complete the treatment period (week 24), patients who complete the study (see Section 3.16.4 for definition of study completion), and patients who did not complete treatment but were followed up until end of study will be summarized. Data from patients who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics, and the number of patients who discontinue the study drug but continue to attend study visits will be tabulated.

9.4.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, comorbidities, prior and concomitant medications, and ECG findings will be examined to assess the comparability of the treatment groups and will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation (SD), standard error (SE), median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

9.5. Efficacy Analysis

9.5.1. Primary Endpoint

The primary efficacy endpoint for this study is the categorical reduction in the daily OCS dose during weeks 20 to 24.

Percent reduction in the daily OCS dose will be categorized as follows:

- 90% to 100%
- 75% to <90%
- 50% to <75%
- >0% to <50%
- No decrease in OCS, loss of baseline asthma control during weeks 20 through 24, or discontinuation from study drug

Loss of baseline asthma control will be defined as FEV₁ less than 80% of baseline at the week 24 visit, clinically significant worsening in ACQ-6 score (change in score of 0.5) at the week 24 visit compared with baseline, and/or CAE during weeks 20 through 24.

9.5.2. Secondary Endpoints

The secondary efficacy endpoints for this study are the following:

- Proportion of patients achieving $\geq 50\%$ reduction in OCS dose at weeks 20 to 24 relative to the OCS dose at DoR/baseline, while maintaining asthma control
- Proportion of patients achieving dose reduction to ≤ 5 mg daily dose at weeks 20 to 24, while maintaining asthma control
- Percent change from DoR/baseline in OCS dose at weeks 20 to 24
- Proportion of patients achieving less than 5 mg decrement in OCS dose (ie, the minimal and non-responders) compared with the OCS dose at DoR/baseline at weeks 20 to 24, while maintaining asthma control
- Clinical asthma exacerbation-related:
 - Annualized rate of CAEs requiring a burst of systemic corticosteroid (injection, or if oral, at least a doubling from the current OCS dose for at least 3 days); an asthma-specific hospital admission; or an asthma-specific emergency department visit during the treatment period (weeks 0 to 24)
- Proportion of patients discontinuing OCS at weeks 20 to 24, while maintaining asthma control

The order of the secondary endpoints above is the order of hierarchy to be used for controlling type I error as described in Section [9.6](#).

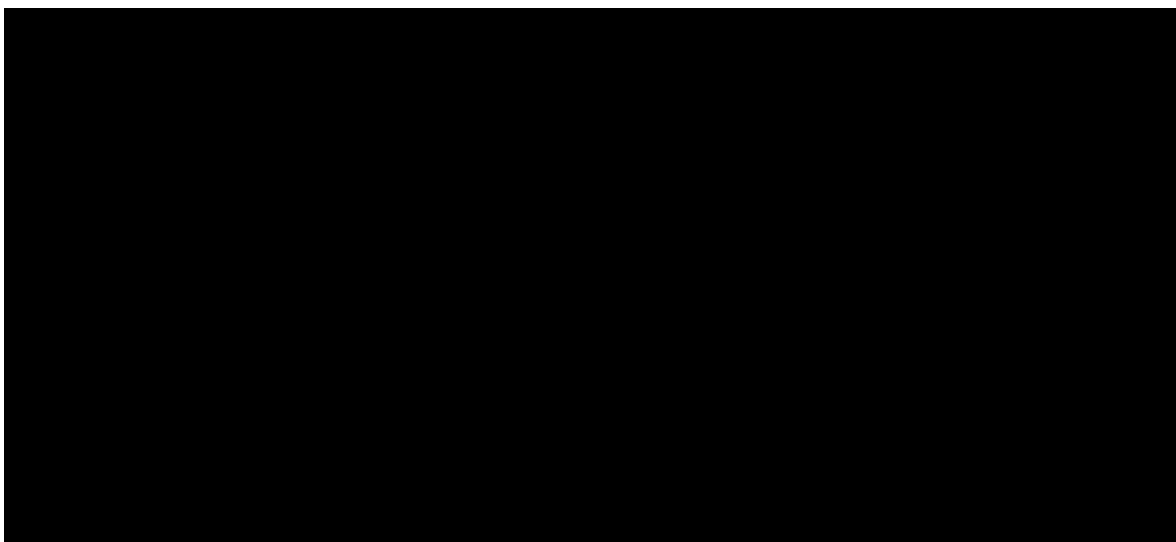
9.5.3. Other Secondary Efficacy Endpoints:

Other efficacy endpoints for this study are the following:

- Time to first CAE
- Other clinic lung functions including the following:
 - Pre-bronchodilator FEV₁: change from DoR/baseline to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
 - Post-bronchodilator FEV₁: change from DoR/baseline to weeks 4, 12, 20, and 24 or early withdrawal
- Ambulatory lung function: change in AM and PM PEF from run-in baseline at each week through week 24 or early withdrawal
- AQLQ + 12 score: change from DoR/baseline to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- ACQ-6: change from DoR/baseline to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- Change in total inhalations of reliever bronchodilator medication (eg, SABA) (number of inhalations per 24 hours: day+night) from run-in baseline at each week through week 24 or early withdrawal
- Number of nighttime awakenings due to asthma over the 24-week treatment period
- Change in total asthma symptom scores from run-in baseline at each week through week 24 or early withdrawal
- EQ-5D score: change from DoR/baseline to week 24 or early withdrawal
- SGRQ score: change from DoR/baseline to weeks 12 and 24 or early withdrawal

9.5.4. Exploratory Endpoints

Exploratory endpoints for this study are the following:



9.5.5. Target Biomarker Endpoint

The target biomarker endpoints are the blood eosinophil counts at DoR/baseline; weeks 4, 8, 12, 16, 20, 24 or early withdrawal; and at the follow-up visit (approximately week 32).

9.5.6. Planned Method of Analysis

The ITT analysis set (see Section 9.2.1) will be used for all efficacy analyses unless otherwise noted. Summaries will be presented by treatment group. The per-protocol analysis set will be used as sensitivity analysis for the primary analysis.

9.5.6.1. Primary Efficacy Analysis

The primary endpoint is the categorical reduction in OCS dose during weeks 20 to 24, compared with DoR/baseline dose, without loss of asthma control. Five categories of reduction will be defined: 90% to 100% reduction, 75% to <90% reduction, 50% to <75% reduction, >0% to <50% reduction, and no decrease in OCS dose/loss of asthma control/discontinuation from study drug. This categorical endpoint will be analyzed using proportional odds model. The model will include the treatment group and randomization stratification factors as model factors and the OCS baseline dose and duration of historical OCS use (ie, before screening) as covariates. The overall odds ratio between reslizumab and placebo and its 95% confidence interval will be estimated.

For the primary analysis, patients who discontinue the study drug early will be considered as nonresponders and will be categorized in the lowest category of response.

If a patient elects to withdraw (or is discontinued from treatment by the investigator), every attempt will be made to continue the assessments subsequent to his/her withdrawal from the study (see Section 4.5).

9.5.6.2. Sensitivity Analysis

Sensitivity analysis will include data collected after early discontinuation from study drug. In this analysis, patients will be categorized according to the percent dose reduction at 24 weeks regardless of whether they withdrew early from treatment or complete treatment. For patients who withdraw early, and for whom the sponsor fails to retrieve data after withdrawal despite all attempts to contact the patients, multiple imputation will be performed to determine the categorization according to the percent dose reduction at 24 weeks. Multiple imputations will use the post withdrawal data observed for patients who withdraw early and for which the sponsor succeeded to retrieve the data. The methodology and algorithm to be used for imputations will be detailed in the statistical analysis plan.

Other sensitivity analyses will include the following:

- Repeating the primary analysis on the PP analysis set
- “Tipping point” multiple imputation analysis to assess deviations from missing at random (MAR); details regarding this analysis will be provided in the SAP

Additional sensitivity analyses may be included and will be detailed in the statistical analysis plan.

9.5.6.3. Secondary Efficacy Analysis

All efficacy variables will be summarized by treatment group. For continuous variables, the summary statistics will include n, mean, SD, SE, median, minimum, and maximum. For categorical variables, patient counts and percentages will be provided.

The proportion of patients achieving $\geq 50\%$ reduction in OCS dose at weeks 20 to 24 while maintaining asthma control, proportion of patients achieving dose reduction to ≤ 5 mg daily dose at weeks 20 to 24 while maintaining asthma control, proportion of patients achieving less than 5 mg decrement in OCS dose (ie, the minimal and non-responders) at weeks 20 to 24 while maintaining asthma control, and proportion of patients discontinuing OCS at weeks 20 to 24 will be analyzed using a logistic regression model. The model will include the treatment group and randomization stratification factors as model factors and the OCS baseline dose and duration of historical OCS use (ie, before screening) as covariates.

For the secondary analysis, patients who discontinue the study drug early will be considered as nonresponders and will be categorized in the lowest category of response

Analysis of the mean percentage change from baseline in OCS dose at weeks 20 to 24 will use an analysis of covariance model with treatment group and stratification factors as model factors and the OCS baseline dose and duration of historical OCS use (ie, before screening) as covariates.

The frequency of CAEs will use the negative binomial (NB) regression model. The primary NB model will include the treatment group and randomization stratification factors as model factors and an offset variable. The offset variable will be calculated as the logarithm of follow-up duration minus the summed duration of exacerbations. The ratio of CAE rate between the treatment groups and its 95% confidence interval (CI) will be estimated from the NB model.

Additional covariates or factors may be added to the statistical models. These will be detailed in the statistical analysis plan.

9.5.6.4. Other Efficacy Analysis

Statistical modeling to be used for other efficacy endpoints will be described and detailed in the statistical analysis plan.

9.5.6.5. Exploratory Efficacy Analysis

Statistical modeling to be used for exploratory efficacy endpoints will be described and detailed in the statistical analysis plan.

9.6. Multiple Comparisons and Multiplicity

A fixed sequence multiple testing procedure will be implemented to test the primary and secondary variables while controlling the overall type I error rate at 0.05. If the resulting 2-sided p-value from the primary comparison is ≤ 0.05 , then the next comparison of interest (first secondary variable) will be interpreted inferentially at 0.05. This process continues through the secondary variables either until all comparisons of interest are interpreted inferentially or until

the point at which the resulting 2-sided p-value for a comparison of interest is >0.05 . At the point where $p>0.05$, no further comparisons will be interpreted inferentially. The hierarchy of endpoints is as defined in Section 9.5.2.

No multiplicity adjustments will be made for other efficacy and exploratory efficacy analyses.

9.7. Safety Endpoints and Analysis

Safety analyses will be performed on the safety analysis set.

9.7.1. Safety Endpoints

Safety measures and time points are provided in Section 3.8 and Table 5. The overall safety of reslizumab treatment will be assessed throughout the study by evaluating adverse events and the following additional safety variables.

- Clinical laboratory evaluations of serum chemistry at screening, DoR, week 12, and week 24 or early withdrawal
- Clinical laboratory evaluations of hematology throughout the study
- Vital signs assessments (pulse, body temperature, respiratory rate, and blood pressure) throughout the study
- ECGs at screening and week 24 or early withdrawal
- Physical examinations (including body weight measurements) throughout the study
- Signs and/or symptoms of adrenal insufficiency (OCS withdrawal effects) throughout the study
- Inquiries about concomitant medication usage throughout the study

9.7.2. Safety Analysis

Safety data will be summarized using descriptive statistics by time point and/or treatment group, as appropriate.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all adverse events starting after first study drug administration (overall and by severity), adverse events determined by the investigator to be related to study treatment (ie, reasonable possibility; see Section 7.1.4, with missing relationship will be counted as related) (overall and by severity), serious adverse events, adverse events causing discontinuation from study treatment, adverse events with onset during the follow-up period (ie, after the cessation of study treatment), and adverse events that begin within 24 hours after injection. Summaries will be presented by treatment group and for all patients. Patient listings of adverse events, serious adverse events, and adverse events leading to discontinuation will be presented and will include all adverse events reported (including before first study drug administration).

Changes in laboratory, ECG, and vital signs measurement data will be summarized descriptively. All values will be compared with prespecified boundaries to identify potentially clinically significant changes or values, and such values will be listed.

The use of concomitant medications coded with WHO Drug will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with study drug.

For continuous variables, descriptive statistics (n, mean, SD, SE, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided.

If any patient dies during the study, a listing of deaths will be provided and all relevant information will be discussed in the patient narrative included in the clinical study report.

9.8. Pharmacokinetic Analysis

Reslizumab concentration data will be summarized by time point and/or treatment group, as appropriate. An attempt will be made to correlate serum concentrations of reslizumab with measures of safety and/or efficacy. The data will be pooled with data from other studies and analyzed using PPK and PK/PD analysis and reported in a separate report.

9.9. Biomarker Analysis

Biomarker results will be summarized using descriptive statistics. Analyses correlating efficacy variables and biomarkers will be explored as appropriate.

9.10. Pharmacodynamic Analysis

Blood eosinophil counts will be summarized by treatment group and time point.

9.11. Immunogenicity Analysis

Anti-reslizumab antibody information will be described for subjects who test positive. Samples from placebo-treated patients will not be analyzed unless the patient elects to enroll into an available open-label safety study where the patient will receive reslizumab treatment. In this case the pre-dose (baseline) sample from the rolled-over placebo patient will be analyzed and reported along with post-treatment samples collected in the open-label safety study. Summaries will be provided if appropriate.

9.12. Planned Interim Analysis

No interim analysis is planned for this study.

9.13. Reporting Deviations From the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the complete statistical plan, the clinical study report, or any combination of these, as appropriate, and in accordance with applicable local and regional requirements and regulations.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The medical experts, study monitors, auditors, IEC/IRB, and health authority inspectors (or their agents) will be given direct access to source data and documentation (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with local requirements.

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, study drug label records, diary data, protocol required worksheets, and CRFs that are used as the source (see Section 3.15).

The investigator will maintain a confidential patient identification list that allows the unambiguous identification of each patient. All study-related documents must be kept until notification by the sponsor.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Protocol Amendments and Protocol Deviations and Violations

11.1.1. Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB and local competent authorities as applicable, except when necessary to address immediate safety concerns to the patients or when the change involves only logistics or administration. Each investigator and the sponsor will sign the protocol amendment.

11.1.2. Protocol Violations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol.

Important protocol deviations, referred to as protocol violations, are a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. Protocol violations include enrolling patients in violation of key eligibility criteria designed to ensure a specific patient population; failing to collect data necessary to interpret primary endpoints; noncompliance to study drug administration; use of prohibited medications; or any other deviations that may have an impact on the processes put in place for the care and safety of the patients or compromise the scientific value of the study.

Protocol violations will be identified and recorded by investigational center personnel on the CRF. All protocol violations will be reported to the responsible IEC/IRB, as required.

When a protocol violation is reported, the sponsor will determine whether to withdraw the patient from the study or permit the patient to continue in the study, with a documented decision from the Sponsor's medical representative. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

Deviations from the inclusion/exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol eligibility criteria was entered into a study, they must immediately inform the sponsor. If such patient has already completed the study or has withdrawn early, no action will be taken, but the incident will be recorded. If such patient is still participating in the study, a determination will be made by the sponsor and the investigator as to whether it is in the best interest of the patient to continue in the study.

11.2. Information to Study Personnel

The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new staff become involved). The investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the

investigational center authorization form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the investigator, and for ensuring they comply with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

11.3. Study Monitoring

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that patients have signed the ICF and the study is conducted according to applicable SOPs, the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and the investigator. The main responsibilities of the study monitor are to visit the investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitor will contact each investigator and visit the investigational center at regular intervals throughout the study. The study monitor will be permitted to check and verify the various records (CRFs and other pertinent source data records, to include specific electronic source documentation [see Section 3.15) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded. If electronic CRFs are used for the study, the study monitor will indicate verification by electronically applying source document verification (SDV) flags to the CRF and will ensure that all required electronic signatures are being implemented accordingly.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. Each investigator and assisting staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits and/or provided in follow-up written communication.

11.4. Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical drug supplies and/or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to the following:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc.)
- defective components
- missing or extra units (eg, primary container is received at the site with more or less than the designated number of units inside)

- incorrect packaging or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor or both
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the Product Complaint Form provided by Teva and emailing it to [REDACTED] within 48 hours of becoming aware of the issue.

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving a drug product, all relevant samples (eg, the remainder of the patient's drug supply) should be sent back to the sponsor for investigative testing whenever possible.

11.4.1. Product Complaint Information Needed From the Investigational Center

In the event that the Product Complaint Form cannot be completed, the investigator will obtain the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return Yes/No
- product was taken or used according to protocol Yes/No
- description or nature of complaint
- associated serious adverse event Yes/No
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

Note: Reporting a complaint must not be delayed because not all the required information can be immediately obtained. Known information must be immediately reported. The sponsor will collaborate with the investigator to obtain any outstanding information.

11.4.2. Handling the Study Drug at the Investigational Center

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the study drug.

If it is determined that the investigational center must return all of the study drug, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient.

11.4.3. Adverse Events or Serious Adverse Events Associated with a Product Complaint

If there is an adverse event or serious adverse event, the protocol should be followed.

11.4.4. Documenting a Product Complaint

The investigator will record a description of the product complaint in the source documentation as well as any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

11.5. Audit and Inspection

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, SOPs, GCPs, and applicable regulatory requirements. The sponsor Global Clinical Quality Assurance department, independent of the Global Clinical Development department, is responsible for determining the need for (and timing of) an investigational center audit.

The investigator must accept that regulatory authorities and sponsor representatives may conduct inspections to verify compliance with GCP guidelines.

12. ETHICS

Details of compliance with regulatory guidances and applicable laws are provided in Section 1.6.

12.1. Informed Consent/Assent

For patients 18 years of age and older, the investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the IEC/IRB. All written and/or oral information about the study will be provided in a language as nontechnical as practical and understood by the patient. The patient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documentation.

Written informed consent will be obtained from each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained, according to the IEC/IRB requirements. The patient's willingness to participate in the study will be documented in a consent form, which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The investigator will keep the original consent forms, and copies will be given to the patients. It will also be explained to the patients that the patient is free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

For patients 12 through <18 years of age, the investigator, or a qualified person designated by the investigator, should fully inform the patient and parent or other legally acceptable representative of all pertinent aspects of the study, including the written information approved by the IEC/IRB. All written and/or oral information about the study will be provided in a language as nontechnical as practical and understood by the parent or legally acceptable representative, and the patient as far as is practical. The patient and parent/legal representative should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documentation.

A personally signed and dated ICF will be obtained from each parent/legal representative and a signed and dated assent form will be obtained from each patient (if the patient is able) before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained; according to local IEC/IRB requirements. The forms will also be signed and dated by the person who conducted the informed consent discussion. The investigator will keep the original consent and assent forms, and copies will be given to the patients. It will also be explained to the patients (and parent/legal representative) that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

12.2. Health Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to the national/local health authorities and to each IEC/IRB for review. As required, the study will not start at a given investigational center

before the IEC/IRB and health authority (where applicable) for the center give written approval or a favorable opinion.

12.3. Confidentiality Regarding Study Patients

The investigator must assure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification code (eg, initials and identification number).

Personal medical information may be reviewed for the purpose of patient safety and/or verifying data in the source and transcribed onto the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, the quality assurance unit, and/or regulatory authorities. Personal medical information will always be treated as confidential.

12.4. Declaration of the End of the Clinical Study

Last Subject Last Visit (LSLV) treatment period is defined as end of treatment (approximately week 24). LSLV late follow up, for immunogenicity testing only, will be performed after the treatment period (approximately week 48). This will be considered the end of the trial for the purposes of end of trial notification.

For clinical investigational centers located in the EU, a declaration of the end of the clinical study will be made according to the procedures outlined in Directive 2001/20/ED, Article 10(c); for other countries, local regulations will be followed.

12.5. Registration of the Clinical Study

In compliance with local regulations and in accordance with Teva standard procedures, this clinical study may be registered on clinical trials registry websites.

13. DATA HANDLING, DATA QUALITY ASSURANCE, AND RECORD KEEPING

13.1. Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21 CFR part 11. The CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data from this study. Before using the CDMS, all users will receive training on the system and any study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient who provided informed consent according to the data source. Patient identity should not be discernible from the data provided on the CRF. Data will be verified using the data source by the study monitor, and reviewed for consistency by Data Management using both automated logical checks and manual review. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

With regard to data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, eDiary data), the results will be sent to the investigational center, where they will be retained but not entered into the CRF unless otherwise specified in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management) for direct entry into the clinical database. Laboratory test results will not be entered into the CRF unless otherwise noted in the protocol. All data from other sources will be available to the investigators.

For patients who enter a study but do not meet screening criteria, at a minimum, data for screen failure reason, demography, and adverse events from the time of informed consent will be entered into the CRF.

13.2. Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality assurance, will comply with international regulatory guidelines, including ICH GCP guidelines. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality assurance, will be described in a data-management plan.

CRFs received will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this study. Logical checks will be implemented to ensure data quality and accuracy. Any necessary changes will be made in the clinical database, and data review and validation

procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS. Discrepancies found will be queried.

Data corrections in the CDMS will be made using the CDMS update function. The system requires a reason for each change and keeps a complete audit trail of the data values, dates and times of modifications, and authorized electronic approvals of the changes.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate.

13.3. Archiving of Case Report Forms and Source Documents

13.3.1. Sponsor Responsibilities

The sponsor will have final responsibility for the processing and quality control of the data. Data management oversight will be carried out as described in the sponsor's SOPs for clinical studies.

Day to day data management tasks for this study are delegated to a contract organization, and these functions may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities. The original CRFs will be archived by the sponsor. Center-specific CRFs will be provided to the respective investigational centers for archiving.

13.3.2. Investigator Responsibilities

The investigator must maintain all written and electronic records, accounts, notes, reports and data related to the study and any additional records required to be maintained under country, state/province, or other local laws, including, but not limited to, the following:

- full case histories
- signed informed consent forms
- patient identification lists
- CRFs for each patient on a per-visit basis
- data results from other sources (eg, central laboratory, bioanalytical laboratory, central image center, eDiary data)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the study drug
- copies of all correspondence with sponsor, the IRB/IEC, and any regulatory authority

The investigator will retain all records related to the study until the CRO or sponsor sends written notification that records may be destroyed. If, after 10 years from study completion, or earlier in the case of the investigative center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written

request to sponsor at least 60 days before any planned disposition of study records. Upon receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

14. FINANCING AND INSURANCE

A separate clinical study agreement, including a study budget, will be entered into between each principal investigator and the sponsor (or the CRO designated by the sponsor) before the study drug is delivered.

This clinical study is insured in accordance with the corresponding local legal provisions. The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions. Excluded from the insurance cover are, inter alia, damages to health and worsening of previous existing disease that would have occurred or continued if the patient had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the sponsor.

For covered clinical studies (see 21CFR54), the investigator will provide the sponsor with financial information required to complete Form FDA 3454. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

15. REPORTING AND PUBLICATION OF RESULTS

The sponsor is responsible for ensuring that the public has access to the appropriate information about the study by conforming to local and regional requirements and regulations for registration and posting of results.

The sponsor is responsible for the preparation of a clinical study report, in cooperation with the coordinating investigator. The final report is signed by the sponsor and, if applicable, by the coordinating investigator.

When the sponsor generates reports from the data collected in this study for presentation to regulatory authorities, drafts may be circulated to the coordinating investigator for comments and suggestions. An endorsement of the final report will be sought from the coordinating investigator.

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor. The primary publication from this study will report the results of the study in accordance with the current “Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals” (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations. Authorship will be based on meeting all of the following 4 criteria:

- substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

16. REFERENCES

- Barr JT, Schumacher GE, Freeman S, LeMoine M, Bakst AW, Jones PW. American translation, modification, and validation of the St. George's Respiratory Questionnaire. *Clin Ther* 2000;22(9):1121-45.
- Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al; SIRIUS Investigators. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014;371(13):1189-97.
- Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2011;184(10):1125-32.
- Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *The Lancet* 2015. Published online.
- Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma — Summary Report 2007. National Asthma Education and Prevention Program.
- Foster PS, Hogan SP, Ramsay AJ, Matthaei KI, Young IG. Interleukin 5 deficiency abolishes eosinophilia, airways hyperreactivity, and lung damage in a mouse asthma model. *J Exp Med* 1996;183(1):195-201.
- The Global Asthma Report 2014. Auckland, New Zealand: Global Asthma Network, 2014.
- Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2014. Available at: <http://www.ginasthma.org>. Accessed 11 March 2015.
- Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2016. Available at: <http://www.ginasthma.org>. Accessed 06 June 2016.
- Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360(10):973-84.
- [REDACTED]
- International Committee of Medical Journal Editors (ICMJE). Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Available at: <http://www.icmje.org/recommendations/>. Accessed 02 July 2014.
- Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992;47(2):76-83.
- Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14(4):902-7.
- Molfino NA, Nowak R, Silverman RA, Rowe BH, Smithline H, Khan F, et al. Reduction in the Number and Severity of Exacerbations Following Acute Severe Asthma: Results of a Placebo-

Controlled, Randomized Clinical Trial with Benralizumab. *Am J Respir Crit Care Med* 2012;185:A2753.

Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360(10):985-93.

Ortega HG1, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;371(13):1198-207.

Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380(9842):651-9.

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr, Bock SA, Branum A, 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 [reprint in *Ann Emerg Med* 2006;47(4):373-80; PMID: 16546624]. *J Allergy Clin Immunol* 2006;117(2):391-7.

Shapiro GS, Klinger NM, Ekholm BP, Colice GL. Comparable bronchodilation with hydrofluoroalkane-134a (HFA) albuterol and chlorofluorocarbons-11/12 (CFC) albuterol in children with asthma. *J Asthma* 2000;37(8):667-75.

Stanbury RM and Graham EM, Systemic corticosteroid therapy — side effects and their management. *Br J Ophthalmol* 1998; 82(704):704-8.

Tran TN, Khattry DB, Ke X, Ward CK, Gossage D. High blood eosinophil count is associated with more frequent asthma attacks in asthma patients. *Ann Allergy Asthma Immunol* 2014;113(1):19-24.

Vidal C, Gude F, Boguete O, Fernández-Merino MC, Meijide LM, Rey J, et al. Evaluation of the phadiatop test in the diagnosis of allergic sensitization in a general adult population. *J Investig Allergol Clin Immunol* 2005;15(2):124-30.

Walsh LJ, Wong CA, Osborne J, Cooper S, Lewis SA, Pringle M, et al. Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. *Thorax* 2001; 56:279-84.

Wardlaw AJ, Brightling C, Green R, Woltmann G, and Pavord I. Eosinophils in asthma and other allergic diseases. *Br Med Bull* 2000;56(4):985-1003.

Wyrwich KW, Ireland AM, Navaratnam P, Nolte H, Gates DF, Jr. Validation of the AQLQ12+ among adolescents and adults with persistent asthma. *Qual Life Res* 2011;20(6):903-12.

Zeiger RS, Schatz M, Li Q, Solari PG, Zazzali JL, Chen W. Real-time asthma outreach reduces excessive short-acting β_2 -agonist use: a randomized study. *J Allergy Clin Immunol Pract* 2014;2(4):445-56.

17. SUMMARY OF CHANGES TO PROTOCOL

17.1. Amendment 02 Dated 18 JULY 2016

The revisions listed below have been made to the protocol Study C38072-AS-30027 and are considered substantial by the Teva Authorized Representative.

Table 6: Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
Clinical Study Personnel Contact Information		
<p><i>For Centers in Latin America</i></p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	<p><i>For Centers in Latin America</i></p> <p>[REDACTED]</p> <p>[REDACTED]</p>	<p>The contact physician for Latin America was updated and the operation lead was updated.</p>
Clinical Study Protocol Synopsis		
<p>During the optimization period, the patient’s minimal effective OCS requirement will be determined. The patient’s previous OCS will be standardized to an equivalent dose and regimen of prednisone to the nearest 2.5 mg <u>daily</u> for once daily regimens or 5 mg for every other day regimens. The patient’s previous non-OCS background asthma controller medications will be continued unchanged throughout the pre-randomization period and the entire study. At the beginning of the optimization period, an asthma symptom diary and electronic peak flow meter will be distributed where the patient will record asthma symptoms, number of reliever bronchodilator inhalations, nighttime awakenings due to asthma <u>requiring rescue inhaler</u>, and AM and PM PEF. For</p>	<p>During the optimization period, the patient’s minimal effective OCS requirement will be determined. The patient’s previous OCS will be standardized to an equivalent dose and regimen of prednisone to the nearest 2.5 mg daily. The patient’s previous non-OCS background asthma controller medications will be continued unchanged throughout the pre-randomization period and the entire study. At the beginning of the optimization period, an asthma symptom diary and electronic peak flow meter will be distributed where the patient will record asthma symptoms, number of reliever bronchodilator inhalations, nighttime awakenings due to asthma</p>	<p>Minor wording adjustment and language was added for clarity.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>optimization, the OCS dose should be reduced at 1-week intervals, for up to 10 weeks or until there is a worsening of asthma signs and symptoms (<u>minimum 1 day in optimization</u>). When either a lung function or symptomatic deterioration occurs, the patient will be returned to the previously effective OCS level, which will then constitute the minimally effective dose for the purpose of run-in. If this previously effective dose is no longer effective, the investigator can determine the clinically appropriate, minimally effective dose for the purpose of run-in. <u>Note: Patient may enter run-in (V12) on the same day as optimization ended if the patient is on the minimally effective prednisone dose (did not require a prednisone burst at end-optimization).</u></p>	<p>requiring rescue inhaler, and AM and PM PEF. For optimization, the OCS dose should be reduced at 1-week intervals, for up to 10 weeks or until there is a worsening of asthma signs and symptoms (minimum 1 day in optimization). When either a lung function or symptomatic deterioration occurs, the patient will be returned to the previously effective OCS level, which will then constitute the minimally effective dose for the purpose of run-in. If this previously effective dose is no longer effective, the investigator can determine the clinically appropriate, minimally effective dose for the purpose of run-in. Note: Patient may enter run-in (V12) on the same day as optimization ended if the patient is on the minimally effective prednisone dose (did not require a prednisone burst at end-optimization).</p>	
<p>Section 1.3.2: Clinical Studies</p>		
<p><u>Additional Safety Issues Considerations</u></p>	<p><u>Additional Safety Considerations</u></p>	<p>Section renamed for clarity and inclusiveness.</p>
<p>Additional Safety Issues <u>Considerations</u> <u>Malignancy</u> As of February 2015, there were 27 treatment-emergent adverse events reported by 24 patients related to malignancy for the entire clinical program, <u>including placebo-treated patients.</u></p>	<p><u>Additional Safety Considerations</u> <u>Malignancy</u> As of February 2015, there were 27 treatment-emergent adverse events reported by 24 patients related to malignancy for the entire clinical program, including placebo-treated patients.</p>	<p>Language was added to clarify that the number of reported events includes patients who received placebo in the overall clinical program.</p>
<p>Additional Safety Issues <u>Considerations</u> <u>Malignancy risk</u> Most malignancies were diagnosed within less than 6 months after starting reslizumab treatment, and in 4 5 cases, there was a previous medical history of malignancy.</p>	<p><u>Additional Safety Considerations</u> <u>Malignancy risk</u> Most malignancies were diagnosed within less than 6 months after starting reslizumab treatment, and in 5 cases, there was a previous medical history of malignancy.</p>	<p>The number of cases with previous medical history of malignancy was corrected.</p>
<p><u>New Text</u></p>	<p><u>Infections</u> The immune response to parasitic infections may involve eosinophils; therefore, the clinical course of existing or new parasitic infections could potentially be complicated by a mechanism of action that lowers blood and tissue eosinophils. The iv reslizumab clinical protocols contained an exclusion criterion for patients with active or suspected helminth</p>	<p>Additional safety consideration for infections added for clarity.</p>

Original text with changes shown	New wording	Reason/Justification for change
	<p>infestation/infection. The asthma Phase 3 studies were conducted in geographic regions in which helminth infections are prevalent, including South and Central America, Africa, and Asia. There were no helminth infections reported, and no difference was documented between the treatment groups in regards to adverse events that could be associated with gastrointestinal helminth infections.</p> <p>The overall rate of infection adverse events was lower for reslizumab versus placebo-treated patients, with the types of infection events reported consistent with what would be expected in a primarily adult patient population with an underlying condition of asthma. No potential opportunistic infections were reported.</p>	
Section 3: Study Design		
Section 3.1: General Design and Study Schema (Other sections affected by this change: Section 3.13)		
<p><u>3.1 General Design and Study Schema</u></p> <p>This is a Phase 3, 24-week, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of sc reslizumab treatment at a dosage of 110 mg reslizumab treatment at a fixed dose of 110 mg, administered sc once every 4 weeks in patients 12 years of age and older with OCS-dependent asthma and elevated blood eosinophils. The study will consist of a screening period of up to 2 weeks, followed by an optimization period of up to 10 weeks, a run-in period of at least 2 weeks, a 24-week double-blind treatment period, an 8-week follow-up period, and an additional 16-week follow-up period to collect drug wash-out samples for immunogenicity assessments. <u>The patient may delay the early and/or late follow-up visits if the patient enrolls in an open-label, long-term safety study after end of treatment, if available.</u></p>	<p><u>3.1 General Design and Study Schema</u></p> <p>This is a Phase 3, 24-week, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of sc reslizumab treatment at a dosage of 110 mg every 4 weeks in patients 12 years of age and older with OCS-dependent asthma and elevated blood eosinophils. The study will consist of a screening period of up to 2 weeks, followed by an optimization period of up to 10 weeks, a run-in period of at least 2 weeks, a 24-week double-blind treatment period, an 8-week follow-up period, and an additional 16-week follow-up period to collect drug wash-out samples for immunogenicity assessments. The patient may delay the early and/or late follow-up visits if the patient enrolls in an open-label, long-term safety study after end of treatment, if available.</p>	<p>Minor wording adjustment and language was added to clarify the timing of the follow-up evaluation in the circumstance that an open-label, long-term safety study becomes available to the patients.</p>
Section 3.1.3: Run-in Period (Other sections affected by this change: synopsis)		
<p>Patients whose minimal effective OCS dose remains between ≥ 5 mg and ≤ 40 mg of prednisone daily at the end of optimization may advance to run-in (for at least 2 weeks).</p>	<p>Patients whose minimal effective OCS dose remains between ≥ 5 mg and ≤ 40 mg of prednisone daily at the end of optimization may advance to run-in (for at least 2 weeks).</p>	<p>Clarification of OCS medication in run-in period.</p>

Original text with changes shown	New wording	Reason/Justification for change
Section 3.1.4: Treatment Period (Other sections affected by this change: Section 6.7)		
<p><u>OCS Reduction:</u> The minimally effective OCS dose will be reduced per protocol at scheduled clinic visits from the beginning of week 5 (ie, end of the induction period) through week 20, as long as all 5 criteria in Table 2 are met and there are no clinical manifestations of adrenal insufficiency. <u>These 5 eligibility criteria assure that the patient's asthma control is not significantly worsened compared to baseline.</u> The last possible dose reduction can occur at week 20. The algorithm for OCS reductions during the treatment period is given in Table 3.</p>	<p><u>OCS Reduction:</u> The minimally effective OCS dose will be reduced per protocol at scheduled clinic visits from the beginning of week 5 (ie, end of the induction period) through week 20, as long as all 5 criteria in Table 2 are met and there are no clinical manifestations of adrenal insufficiency. These 5 eligibility criteria assure that the patient's asthma control is not significantly worsened compared to baseline. The last possible dose reduction can occur at week 20. The algorithm for OCS reductions during the treatment period is given in Table 3.</p>	<p>Clarification of eligibility criteria with respect to asthma control.</p>
<p><u>3.1.4.1. Handling of Asthma Exacerbations During the Treatment Period</u> Patients should be treated with an OCS burst: 40 to 60 mg (or at least double the current dose) of OCS tapered over a 7- to 10-day period to a new maintenance dose of 2.5 mg above the pre-burst dose for once daily regimens or 5 mg above the pre-burst dose for every other day regimens.</p>	<p><u>3.1.4.1. Handling of Asthma Exacerbations During the Treatment Period</u> Patients should be treated with an OCS burst: 40 to 60 mg (or at least double the current dose) of OCS tapered over a 7- to 10-day period to a new maintenance dose of 2.5 mg above the pre-burst dose.</p>	<p>Language simplification made for clarity.</p>
Section 3.11: Drugs Used in the Study (Other sections affected by this change: Section 5.1)		
<p><u>Section 3.11.1 Investigational Product</u> Reslizumab will be provided as a sterile solution containing 110 mg (1.0 mL) reslizumab per syringe, formulated at 110 mg/mL in [REDACTED] sodium acetate, with [REDACTED] sucrose, [REDACTED] polysorbate 80, pH 5.5 buffer. The needle shields of the prefilled syringes contain natural rubber latex. Both reslizumab and placebo will be provided as clear solutions</p>	<p><u>Section 3.11.1 Investigational Product</u> Reslizumab will be provided as a sterile solution containing 110 mg (1.0 mL) reslizumab per syringe, formulated at 110 mg/mL in [REDACTED] sodium acetate, with [REDACTED] sucrose, [REDACTED] polysorbate 80, pH 5.5 buffer. The needle shields of the prefilled syringes contain natural rubber latex. Both reslizumab and placebo will be provided as clear solutions</p>	<p>Information regarding the natural rubber component of the prefilled syringe was added for transparency.</p>
<p><u>Section 3.11.2 Placebo</u> Placebo will be provided as a sterile solution containing [REDACTED] sodium acetate, with [REDACTED] sucrose, [REDACTED] polysorbate 80, pH 5.5 buffer, presented as 1.0-mL per syringe. <u>The needle shields of the prefilled syringes contain natural rubber latex.</u></p>	<p><u>Section 3.11.2 Placebo</u> Placebo will be provided as a sterile solution containing [REDACTED] sodium acetate, with [REDACTED] sucrose, [REDACTED] polysorbate 80, pH 5.5 buffer, presented as 1.0-mL per syringe. The needle shields of the prefilled syringes contain natural rubber latex.</p>	<p>Information regarding the natural rubber component of the prefilled syringe was added for transparency.</p>

Original text with changes shown	New wording	Reason/Justification for change
Section 3.13: Duration of Patient Participation and Justification		
<p>An additional, late follow-up for immunogenicity testing will be performed 28 weeks after the last dose of study drug. See Section 12.4 for the definition of the end of the study. <u>The patient may delay the early and/or late follow-up visits if the patient enrolls in an open-label, long-term safety study after end of treatment, if available.</u></p>	<p>An additional, late follow-up for immunogenicity testing will be performed 28 weeks after the last dose of study drug. See Section 12.4 for the definition of the end of the study. The patient may delay the early and/or late follow-up visits if the patient enrolls in an open-label, long-term safety study after end of treatment, if available.</p>	<p>Clarification of study duration and milestones.</p>
Section 3.14: Stopping Rules and Discontinuation Criteria		
<p>Other than pregnancy, there are no formal rules for early withdrawal from this study <u>for study drug discontinuation in this study.</u></p> <p>...</p> <p>The investigator and/or sponsor can withdraw a patient from the study for reasons including, but not limited to, a change in the medical condition or an adverse event that alters the patient’s benefit/risk (eg, pregnancy, a related severe hypersensitivity reaction, <u>or related severe myalgia/muscle event</u>), a protocol violation or deviation as defined in Section 11.1.2, or noncompliance.</p>	<p>Other than pregnancy, there are no formal rules for study drug discontinuation in this study.</p> <p>...</p> <p>The investigator and/or sponsor can withdraw a patient from the study for reasons including, but not limited to, a change in the medical condition or an adverse event that alters the patient’s benefit/risk (eg, pregnancy, a related severe hypersensitivity reaction, or related severe myalgia/muscle event), a protocol violation or deviation as defined in Section 11.1.2, or noncompliance.</p>	<p>Wording adjusted to clarify that with regard to pregnancy, the administration of study drug should be discontinued, but the patient does not need to be withdrawn from the study for being pregnant.</p> <p>Additional language was added to describe reasons for patient withdrawal.</p>
Section 3.16: Study Procedures; Table 5: Study Procedures and Assessments (Other sections affected by this change: Section 3.16.3.1.1)		
<p>V2-V11: Standardize and optimize maintenance OCS: Between weeks -12 and -4<u>-3</u></p>	<p>V2-V11: Standardize and optimize maintenance OCS: Between weeks -12 and -3</p>	<p>Correction to upper time limit for this time period.</p>
<p><u>Addition of CPK assessments at Week 4, 8, 16, and 20</u></p>	<p>Addition of CPK assessments at Week 4, 8, 16, and 20.</p>	<p>Clarification added based on request by Health Authorities.</p>
<p><u>Addition of Injection site evaluation at Visit 13-18</u></p>	<p>Injection site evaluation addition at Visit 13-18 (Day of Randomization to Week 20).</p>	<p>Row added aligning with IP visits for clarification of evaluation.</p>
<p>=</p>	<p>--</p>	<p>Minor adjustments to order of evaluations to align sequentially with timing</p>
<p>i. CPK is collected with serum chemistry tests at scheduled visits. If potentially clinically significant CPK (<u>≥3.1x ULN</u>) is reported,</p>	<p>i. CPK is collected with serum chemistry tests at scheduled visits. If a potentially clinically significant CPK level (<u>≥3.1x</u></p>	<p>Footnote modified for clarity.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>initiate the CPK/myalgia CRF. Urinalysis and selected chemistries, should be performed for 10x elevations as per CRF instructions, and CPK levels should be re tested every 7 to 10 days until the elevation is resolved or if agreed with the medical monitor that no further testing is indicated. and clinical monitoring as outlined in Protocol Section 7.1.7.3.2.</p>	<p>ULN) is reported, initiate the CPK/myalgia CRF and clinical monitoring as outlined in Protocol Section 7.1.7.3.2.</p>	
<p>--</p>	<p>j. CPK measurement only. CPK will be collected with PK sample.</p>	<p>New footnote added to support the additional CPK collection.</p>
<p>3.16.2.3 Procedures at Baseline/Day of Randomization (Week 0 [Visit 13])</p>		
<p>Patients who continue to meet the inclusion/exclusion criteria will be assigned a permanent unique randomization number and a treatment number generated by IRT. These 2 newly assigned numbers will be entered into the CRF, and study drug will be dispensed. <u>The following procedures/assessments will be performed during and after administration of study drug on day 1:</u></p> <ul style="list-style-type: none"> ● <u>Patients will be observed for 1 hour after study injection/baseline/DoR assessments</u> ● <u>Evaluation of injection site for reaction at approximately 1 hour after dosing using the injection site CRF. Clinically significant injection site reactions should be recorded as an adverse event.</u> ● <u>If, during post-study drug observation, the patient develops clinical symptoms, vital signs should be collected. The patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.7.</u> <p><u>Remind the patients that they will receive a post-injection symptom inquiry via the eDiary.</u></p>	<p>Patients who continue to meet the inclusion/exclusion criteria will be assigned a permanent unique randomization number and a treatment number generated by IRT. These 2 newly assigned numbers will be entered into the CRF, and study drug will be dispensed. The following procedures/assessments will be performed during and after administration of study drug on day 1:</p> <ul style="list-style-type: none"> ● Patients will be observed for 1 hour after study injection/baseline/DoR assessments ● Evaluation of injection site for reaction at approximately 1 hour after dosing using the injection site CRF. Clinically significant injection site reactions should be recorded as an adverse event. ● If, during post-study drug observation, the patient develops clinical symptoms, vital signs should be collected. The patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.7. <p>Remind the patients that they will receive a post-injection symptom inquiry via the eDiary.</p>	<p>Clarification of study procedures to reflect the schedule of assessments.</p>

Original text with changes shown	New wording	Reason/Justification for change
3.16.3.1.1 Weeks 4, 8, 12, 16, 20, and 24 (Visits 14 Through 19)		
Perform serum chemistry tests (weeks 12 and 24 or early withdrawal) <u>(a sample for CPK measurement only will also be collected on weeks 4, 8, 16, and 20).</u>	Perform serum chemistry tests (weeks 12 and 24 or early withdrawal) (a sample for CPK measurement only will also be collected on weeks 4, 8, 16, and 20).	Edited to align with modification to schedule of assessments.
<p><u>Additionally</u>, the following procedures/assessments will be performed during and after administration of study drug:</p> <ul style="list-style-type: none"> • Patients will be observed for 1 hour after study injection • <u>Evaluation of injection site for reaction at approximately 1 hour after dosing using the injection site CRF. Clinically significant injection site reactions should be recorded as an adverse event.</u> • If, during post-study drug observation, the patient develops clinical symptoms, vital signs should be collected. The patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.7. <p>Remind the patients that they will receive a post-injection symptom inquiry via the eDiary.</p>	<p>Additionally, the following procedures/assessments will be performed during and after administration of study drug:</p> <ul style="list-style-type: none"> • Patients will be observed for 1 hour after study injection • Evaluation of injection site for reaction at approximately 1 hour after dosing using the injection site CRF. Clinically significant injection site reactions should be recorded as an adverse event. • If, during post-study drug observation, the patient develops clinical symptoms, vital signs should be collected. The patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.7. <p>Remind the patients that they will receive a post-injection symptom inquiry via the eDiary.</p>	Added to align with modification to schedule of assessments and to fully outline the assessments required
Section 4.1: Selection and Withdrawal of Patients (Other sections affected by these changes: Study Synopsis)		
<p><u>4.1 Patient Inclusion Criteria</u></p> <p>c. The patient continues to require an average daily maintenance dose of OCS or equivalent for asthma of between 5 and 40 mg <u>of prednisone or equivalent</u> during the 3 months before screening. Patients on an OCS dose of >40 mg at screening who the investigator believes may be able to decrease OCS dose to ≤40 mg during the optimization period may also be enrolled. Note: every-other-day dosing that is within this daily average (ie, 10 to 80 mg) is allowed.</p>	<p><u>4.1 Patient Inclusion Criteria</u></p> <p>c. The patient continues to require an average daily maintenance dose of OCS for asthma of between 5 and 40 mg of prednisone or equivalent during the 3 months before screening. Patients on an OCS dose of >40 mg at screening who the investigator believes may be able to decrease OCS dose to ≤40 mg during the optimization period may also be enrolled. Note: every-other-day dosing that is within this daily average (ie, 10 to 80 mg) is allowed.</p>	The inclusion criterion was revised for clarity at the request of the Health Authority.
<p>d. The patient has a documented blood eosinophil level of at least 300/μL during the previous 12 months while on at least</p>	<p>d. The patient has a documented blood eosinophil level of at least 300/μL during the previous 12 months while on</p>	GINA Guidance version updated.

Original text with changes shown	New wording	Reason/Justification for change
<p>medium total daily dose of ICS based on Global Initiative for Asthma 20152016 clinical comparability table (Appendix A), or $\geq 300/\mu\text{L}$ at screening while on chronic OCS or that becomes manifest during the OCS optimization period or at the week -2 visit (end of optimization period/beginning of run-in period)</p>	<p>at least medium total daily dose of ICS based on Global Initiative for Asthma 2016 clinical comparability table (Appendix A), or $\geq 300/\mu\text{L}$ at screening while on chronic OCS or that becomes manifest during the OCS optimization period or at the week -2 visit (end of optimization period/beginning of run-in period)</p>	
<p>f. The patient has FEV1 reversibility of at least 12% after administration of inhaled reliever medication according to the standard American Thoracic Society (ATS) or European Respiratory Society (ERS) protocol. Given the refractory nature of the disease in this population and the influence of high background controller medications on reversibility testing, documented FEV1 reversibility of 12% or a provocation concentration producing a 20% fall in FEV1 for methacholine of ≤ 8 mg/mL within 24 months of the screening visit, and performed according to the standard ATS/ERS procedures, would fulfill this criterion. <u>Patients may be screened again if they did not meet spirometry/reversibility criteria initially. The duration between the date of Screen Failure and the re-screening must be >30 days.</u></p>	<p>f. The patient has FEV1 reversibility of at least 12% after administration of inhaled reliever medication according to the standard American Thoracic Society (ATS) or European Respiratory Society (ERS) protocol. Given the refractory nature of the disease in this population and the influence of high background controller medications on reversibility testing, documented FEV1 reversibility of 12% or a provocation concentration producing a 20% fall in FEV1 for methacholine of ≤ 8 mg/mL within 24 months of the screening visit, and performed according to the standard ATS/ERS procedures, would fulfill this criterion. Patients may be screened again if they did not meet spirometry/reversibility criteria initially. The duration between the date of Screen Failure and the re-screening must be >30 days.</p>	<p>Criterion revised for clarity and alignment with case report form instructions.</p>
<p>g. Females of childbearing potential (not surgically sterile <u>by hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or</u> 2 years postmenopausal) must have an exclusively same-sex partner or use a medically acceptable method of contraception, and must agree to continue use of this method for the duration of the study and for 5 months after last study drug dose. Acceptable methods of contraception include intrauterine device (IUD), steroidal contraceptive (oral, implanted, transdermal, or injected), barrier method with spermicide, abstinence, <u>bilateral fallopian tube occlusion, and</u> partner vasectomy.</p>	<p>g. Females of childbearing potential (not surgically sterile by hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or 2 years postmenopausal) must have an exclusively same-sex partner or use a medically acceptable method of contraception, and must agree to continue use of this method for the duration of the study and for 5 months after last study drug dose. Acceptable methods of contraception include intrauterine device (IUD), steroidal contraceptive (oral, implanted, transdermal, or injected), barrier method with spermicide, abstinence, bilateral fallopian tube occlusion, and partner vasectomy.</p>	<p>Criterion revised for clarity and alignment with case report form.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>m. Pre-bronchodilator spirometry assessments should only be performed after withholding short-acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long-acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule. <u>Spirometry should be performed prior to IP administration, if applicable</u></p>	<p>m. Pre-bronchodilator spirometry assessments should only be performed after withholding short-acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long-acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule. Spirometry should be performed prior to IP administration, if applicable</p>	<p>Clarification of timing for spirometry.</p>
<p>4.5 Criteria and Procedures for Discontinuation of Study Treatment and/or Study Withdrawal</p>		
<p>If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event or a potentially clinically significant abnormal laboratory test result, monitoring will be continued until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made. The specific event or test result must be recorded on the source documentation and transcribed onto the CRF. <u>If possible, a blood sample for measurement of serum reslizumab concentrations will be obtained from patients experiencing an adverse event leading to withdrawal, a serious adverse event, an observation of any severe hypersensitivity reaction (eg, anaphylaxis), or an exacerbation of asthma symptoms.</u></p>	<p>If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event or a potentially clinically significant abnormal laboratory test result, monitoring will be continued until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made. The specific event or test result must be recorded on the source documentation and transcribed onto the CRF. If possible, a blood sample for measurement of serum reslizumab concentrations will be obtained from patients experiencing an adverse event leading to withdrawal, a serious adverse event, an observation of any severe hypersensitivity reaction (eg, anaphylaxis), or an exacerbation of asthma symptoms.</p>	<p>Statement added per request of Health Authority.</p>
<p>5.3: Prior and Concomitant Therapy or Medication</p>		
<p>Any prior or concomitant therapy, medication, or procedure a patient has had <u>at screening up to the end of the study period</u> 4 weeks before study drug administration and up to the end of the study period, including follow-up, will be recorded on the CRF.</p>	<p>Any prior or concomitant therapy, medication, or procedure a patient has had <u>at screening up to the end of the study period</u>, including follow-up, will be recorded on the CRF.</p>	<p>Clarification of text.</p>

Original text with changes shown	New wording	Reason/Justification for change
5.5: Total Blood Volume		
<p>Blood draws will be separated by at least 2 weeks. The estimated total blood volume withdrawn over the entire study (including screening) is approximately 120<u>125</u> mL.</p>	<p>Blood draws will be separated by at least 2 weeks. The estimated total blood volume withdrawn over the entire study (including screening) is approximately 125 mL.</p>	<p>Increased to account for additional CPK draws.</p>
Section 7.1: Adverse Events		
<p>7.1.1. Definition of an Adverse Event ...</p> <p>An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study drug. <u>Asthma exacerbation is an efficacy variable for this study and should be captured on the asthma exacerbation CRF; accordingly, asthma exacerbations should not be recorded as adverse events unless assessed as more severe than the patient's usual disease course. In this case, the investigator should determine if the adverse event is nonserious or serious based on seriousness criteria, as defined in Section 7.1.6.</u> A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events. Accordingly, an adverse event can include any of the following:</p> <ul style="list-style-type: none"> ● intercurrent illnesses ● physical injuries ● events possibly related to concomitant medication ● significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions (Note: A condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and that occurs during this study should be recorded as an adverse event.) ● drug interactions ● laboratory or diagnostic... <p>Worsening of the disease under study (ie,</p>	<p>7.1.1. Definition of an Adverse Event ...</p> <p>An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study drug. Asthma exacerbation is an efficacy variable for this study and should be captured on the asthma exacerbation CRF; accordingly, asthma exacerbations should not be recorded as adverse events unless assessed as more severe than the patient's usual disease course. In this case, the investigator should determine if the adverse event is nonserious or serious based on seriousness criteria, as defined in Section 7.1.6. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events. Accordingly, an adverse event can include any of the following:</p> <ul style="list-style-type: none"> ● intercurrent illnesses ● physical injuries ● events possibly related to concomitant medication ● significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions ● drug interactions ● laboratory or diagnostic... 	<p>Clarification of the reporting of the disease under study as an adverse event.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>asthma), including asthma exacerbations requiring additional controller medication, will be collected as an efficacy assessment in this study. The aforementioned worsening of asthma should be recorded as an adverse event only if the presentation or outcome is more severe than would typically be expected from the normal course of the disease in a particular patient.</p>		
<p><u>Section 7.1.6.1 Definition of a Serious Adverse Event</u></p> <ul style="list-style-type: none"> inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event or that they occurred as a consequence of the event. Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study will not be considered serious adverse events <u>Hospitalizations scheduled before study entry will not be considered serious adverse events, unless there was worsening of the preexisting condition during the patient’s participation in this study. Note:-Hospitalizations due to asthma exacerbation will be reported as serious adverse events if the presentation or outcome is more severe than the patient’s known course of asthma</u> 	<p><u>Section 7.1.6.1 Definition of a Serious Adverse Event</u></p> <ul style="list-style-type: none"> inpatient hospitalization or prolongation of existing hospitalization; which means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event. Hospitalizations scheduled before study entry will not be considered serious adverse events, unless there was worsening of the preexisting condition during the patient’s participation in this study. Note: Hospitalizations due to asthma exacerbation will be reported as serious adverse events if the presentation or outcome is more severe than the patient’s known course of asthma 	<p>Alignment between protocol language, adverse event reporting instructions, and processes.</p>
<p>Section 7.1.7: Specific Protocol-Defined Adverse Events (Other sections affected by this change: Appendix I)</p>		
<p><u>Section 7.1.7.2: Protocol-Defined Adverse Events for Expedited Reporting to Teva</u></p> <p>For the purposes of this protocol, the following are considered protocol-defined adverse events for expedited reporting to Teva: anaphylaxis, newly diagnosed malignancy, opportunistic infection, and parasitic helminth infection. Protocol defined adverse events for expedited reporting can be either serious or nonserious according to the criteria outlined in Section 7.1.6.1. The process for reporting a protocol-defined adverse event for expedited reporting is the same as that for reporting a serious adverse</p>	<p><u>Section 7.1.7.2: Protocol-Defined Adverse Events for Expedited Reporting to Teva</u></p> <p>For the purposes of this protocol, the following are considered protocol-defined adverse events for expedited reporting to Teva: anaphylaxis, newly diagnosed malignancy, opportunistic infection, and parasitic helminth infection. Protocol defined adverse events for expedited reporting can be either serious or nonserious according to the criteria outlined in Section 7.1.6.1. The process for reporting a protocol-defined adverse event</p>	<p>A list of opportunistic infections was provided to increase investigators’ awareness of the potential for opportunistic infection during reslizumab treatment.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>event (see Section 7.1.6.3). A list of potential opportunistic infections is found in Appendix I.</p>	<p>for expedited reporting is the same as that for reporting a serious adverse event (see Section 7.1.6.3). A list of potential opportunistic infections is found in Appendix I.</p>	
<p><u>7.1.7.3.1. Anaphylaxis/Hypersensitivity Reactions Case Report Form</u> Information about all suspected systemic reactions anaphylaxis events will be recorded on the Suspected Anaphylaxis/Hypersensitivity Reactions CRF, including the investigator's assessment if the event followed the definition of anaphylaxis based on the diagnostic criteria as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis (Sampson et al 2006) (Appendix G H). The Anaphylaxis/Hypersensitivity Reactions CRF should be initiated in real time (along with vital sign assessment) for events occurring after study drug administration in the clinic or as soon as possible for suspect events outside the clinic.</p>	<p><u>7.1.7.3.1. Anaphylaxis/Hypersensitivity Reactions Case Report Form</u> Information about all suspected anaphylaxis events will be recorded on the Suspected Anaphylaxis/Hypersensitivity Reactions CRF, including the investigator's assessment if the event followed the definition of anaphylaxis based on the diagnostic criteria as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis (Sampson et al 2006) (Appendix H). The Anaphylaxis/Hypersensitivity Reactions CRF should be initiated in real time (along with vital sign assessment) for events occurring after study drug administration in the clinic or as soon as possible for suspect events outside the clinic.</p>	<p>The appendix referencing the diagnosis of anaphylaxis reactions was corrected.</p>
<p>7.1.7.3.2. Creatine Phosphokinase/Muscular Adverse Events CRF</p>		
<p>Potentially clinically significant creatine phosphokinase (CPK) elevations (with or without associated symptoms) or myalgia/muscle symptoms will be recorded as an adverse event and documented using the potentially clinically significant CPK/myalgia case report form. A potentially clinically significant CPK is defined as $\geq 3.1 \times$ upper limit of normal (Grade 3 based on the Food and Drug Administration [FDA] “Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials”).</p> <p><u>If a potentially clinically significant CPK level ($\geq 3.1 \times$ ULN) occurs, the patient should attend an unscheduled visit for a physical examination and additional testing if indicated per investigator judgement. CPK levels will be re-tested at a minimum of every 7 to 10 days until the elevation is resolved, or if agreed with the medical monitor that no further testing is indicated. For $\geq 10 \times$ ULN elevations in CPK, repeat CPK level, urinalysis (including microscopy), serum electrolytes, BUN, and</u></p>	<p>Potentially clinically significant creatine phosphokinase (CPK) elevations (with or without associated symptoms) or myalgia/muscle symptoms will be recorded as an adverse event and documented using the potentially clinically significant CPK/myalgia case report form. A potentially clinically significant CPK is defined as $\geq 3.1 \times$ upper limit of normal (Grade 3 based on the Food and Drug Administration [FDA] “Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials”).</p> <p>If a potentially clinically significant CPK level ($\geq 3.1 \times$ ULN) occurs, the patient should attend an unscheduled visit for a physical examination and additional testing if indicated per investigator judgement. CPK levels will be re-tested at a minimum of every 7 to 10 days until the elevation is resolved, or if agreed with the medical monitor that no further testing is indicated. For $\geq 10 \times$ ULN elevations in</p>	<p>Requested edits from Health Authority and for overall clarity.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><u>creatinine will be performed as soon as possible after receipt of the CPK result. Further testing of CPK levels should be undertaken as frequently as needed to manage patient care per investigator judgment, but should be at a minimum of every 7 to 10 days as above. Need for repeat urinalysis, serum electrolytes, BUN, and creatinine testing should be determined by the investigator. In addition, need for treatment (eg, administration of iv fluids and urine alkalinization) should be considered by the investigator..</u></p> <p><u>In cases deemed by the investigator to be treatment-related elevations in CPK $\geq 10 \times$ ULN (eg, potentially rhabdomyolysis), study drug discontinuation should occur at least until CPK normalization or longer based on investigator clinical assessment.</u></p>	<p>CPK, repeat CPK level, urinalysis (including microscopy), serum electrolytes, BUN, and creatinine will be performed as soon as possible after receipt of the CPK result. Further testing of CPK levels should be undertaken as frequently as needed to manage patient care per investigator judgment, but should be at a minimum of every 7 to 10 days as above. Need for repeat urinalysis, serum electrolytes, BUN, and creatinine testing should be determined by the investigator. In addition, need for treatment (eg, administration of iv fluids and urine alkalinization) should be considered by the investigator.</p> <p>In cases deemed by the investigator to be treatment-related elevations in CPK $\geq 10 \times$ ULN (potentially rhabdomyolysis), study drug discontinuation should occur at least until CPK normalization or longer based on investigator clinical assessment.</p>	
<p>9.11 Immunogenicity Analysis</p>		
<p>Anti-reslizumab antibody information will be described for subjects who test positive. Samples from placebo-treated patients will not be analyzed <u>unless the patient elects to enroll into an available open-label safety study where the patient will receive reslizumab treatment. In this case the pre-dose (baseline) sample from the rolled-over placebo patient will be analyzed and reported along with post-treatment samples collected in the open label safety study.</u> Summaries will be provided if appropriate.</p>	<p>Anti-reslizumab antibody information will be described for subjects who test positive. Samples from placebo-treated patients will not be analyzed unless the patient elects to enroll into an available open-label safety study where the patient will receive reslizumab treatment. In this case the pre-dose (baseline) sample from the rolled-over placebo patient will be analyzed and reported along with post-treatment samples collected in the open label safety study. Summaries will be provided if appropriate.</p>	<p>Updated to accommodate baseline ADA testing in previous placebo patients.</p>
<p>Appendix A</p>		
<p>Global Initiative for Asthma ICS Equivalency Table and Row added for fluticasone fuorate total daily dose</p>	<p>Global Initiative for Asthma ICS Equivalency Table and Row added for fluticasone fuorate total daily dose</p>	<p>Title amended for clarity. Additional row added to account for fluticasone fuorate total daily dose as per GINA 2016 guidance.</p>

Original text with changes shown	New wording	Reason/Justification for change
Appendix I		
<u>Appendix I. Opportunistic Infections</u>	Appendix I. Opportunistic Infections	Appendix added per Health Authority request.

17.2. Amendment 01 Dated 27 January 2016

The revisions listed below have been made to the protocol Study C38072-AS-30027 and are considered substantial by the Teva Authorized Representative.

Table 7: Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
Title Page:		
<p>[REDACTED]</p> <p>Teva Branded Pharmaceutical Products R&D, Inc</p> <p>[REDACTED]</p>	<p>[REDACTED]</p> <p>Teva Branded Pharmaceutical Products R&D, Inc</p> <p>[REDACTED]</p>	Sponsor’s Safety Representative was changed.
Clinical Study Personnel Contact Information:		
[REDACTED]	[REDACTED]	The back-up Medical Monitor for North America was changed.
[REDACTED]	[REDACTED]	The name of the [REDACTED] was corrected.
[REDACTED]	[REDACTED]	The operational lead was changed for this study.

Original text with changes shown	New wording	Reason/Justification for change
Section 1.3.2.2: Clinical Safety and Efficacy Studies:		
<p>A total of 2195 healthy volunteers and patients with moderate to severe asthma, eosinophilic esophagitis, eosinophilic gastritis, hypereosinophilic syndrome, or nasal polyposis had received at least 1 iv-dose of reslizumab in 14 clinical studies.</p>	<p>A total of 2195 healthy volunteers and patients with moderate to severe asthma, eosinophilic esophagitis, eosinophilic gastritis, hypereosinophilic syndrome, or nasal polyposis had received at least 1 dose of reslizumab in 14 clinical studies.</p>	<p>The word “iv” was removed, as the 2195 subjects included 45 subjects who received sc reslizumab in Study 1107.</p>
<p>Serious adverse events and death cases from the ongoing open-label study (Study 3085) are also included in the relevant sections.</p>	<p>Serious adverse events and death cases from the open-label Study 3085 are also included in the relevant sections.</p>	<p>The language was updated, as Study 3085 has been completed since the last version of the protocol.</p>
<p><u>Serious Adverse Events</u></p> <p>The incidence of serious adverse events was similar in the reslizumab 3.0 mg/kg treatment group (6%) compared towith the placebo treatment group (9%). The serious adverse event reported with the highest incidence was asthma (preferred terms of asthma, asthma crisis, and status asthmaticus), reported by 24 (2%) patients in reslizumab 3.0 mg/kg group and 24 (3%) patients in the placebo group and 24 (2%) patients in the reslizumab 3.0 mg/kg group.</p> <p><u>Deaths</u></p> <p>...</p> <p><u>Laboratory Findings</u></p> <p>No clinically meaningful changes in clinical laboratory values, vital signs measurements, electrocardiogram (ECG), or physical examination findings were noted in the completed studies, with the exception of a decrease in eosinophil counts in the reslizumab groups, which was dose related and is expected in view of the mechanism of action or of reslizumab. MildSmall decreases in the mean values of total white blood cell (WBC) counts waswere also observed in some studies and has have been assessed as reflecting the decrease in the eosinophil count in hypereosinophilic patientscomponent of the differential cell counts. The mean values of eosinophil and WBCwhite blood cell counts returned to baseline values at the end of study follow-up visit (4 months after the last dose of reslizumab).</p>	<p><u>Serious Adverse Events</u></p> <p>The incidence of serious adverse events was similar in the reslizumab 3.0 mg/kg treatment group (6%) compared with the placebo treatment group (9%). The serious adverse event reported with the highest incidence was asthma (preferred terms of asthma, asthma crisis, and status asthmaticus), reported by 24 (3%) patients in the placebo group and 24 (2%) patients in the reslizumab 3.0 mg/kg group.</p> <p><u>Deaths</u></p> <p>...</p> <p><u>Laboratory Findings</u></p> <p>No clinically meaningful changes in clinical laboratory values, vital signs measurements, electrocardiogram (ECG), or physical examination findings were noted in the completed studies with the exception of a decrease in eosinophil counts in the reslizumab groups, which was dose related and is expected in view of the mechanism of action or reslizumab. Small decreases in the mean values of total white blood cell counts were also observed in some studies and have been assessed as reflecting the decrease in the eosinophil component of the differential cell counts. The mean values of eosinophil and white blood cell counts returned to baseline values at the end of study follow-up visit (4 months after the last dose of reslizumab).</p>	<p>Subheaders were added for easier identification of contents.</p> <p>The presentation of SAE data was made consistent with the presentation elsewhere in the document.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>As expected with administration of a mAb, hypersensitivity/anaphylactic reactions were <u>Adverse Drug Reactions</u></p> <p><u>Anaphylaxis related to reslizumab infusion has been</u> reported and are considered <u>an</u> adverse drug reactions (ADRs). All cases of anaphylaxis early in the drug development plan occurred in the eosinophilic esophagitis studies and were deemed by the investigator as related to known food allergies by the investigator and not to reslizumab. There were 3 <u>Three</u> infusion-related anaphylaxis reactions, <u>reported as anaphylaxis, occurred during or shortly after</u> related to reslizumab <u>infusion</u> in the BREATH studies <u>and</u> were characterized; all <u>variously by skin or mucosal involvement, dyspnea, wheezing, gastrointestinal symptoms, and chills. The 3 events</u> were treated at the study site, and the patients were withdrawn discontinued from the study.</p> <p>Myalgia (<u>without evidence for muscle injury</u>), which was <u>reported at a</u> slightly higher <u>incidence</u> in the reslizumab 3.0 mg/kg group (1%) than in the placebo group (0.5%) and anaphylaxis are considered an ADRs <u>of reslizumab</u>.</p>	<p><u>Adverse Drug Reactions</u></p> <p>Anaphylaxis related to reslizumab infusion has been reported and is considered an adverse drug reaction (ADR). All cases of anaphylaxis early in the drug development plan occurred in the eosinophilic esophagitis studies and were deemed related to known food allergies by the investigator and not to reslizumab.</p> <p>Three infusion-related reactions, reported as anaphylaxis, occurred during or shortly after reslizumab infusion in the BREATH studies and were characterized variously by skin or mucosal involvement, dyspnea, wheezing, gastrointestinal symptoms, and chills. The 3 events were treated at the study site, and patients were withdrawn from the study.</p> <p>Myalgia (without evidence for muscle injury) was reported at a slightly higher incidence in the reslizumab 3.0 mg/kg group (1%) than in the placebo group (0.5%) and is considered an ADR of reslizumab.</p>	<p>The text was updated based on the most recent data.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><u>Additional Safety Issues</u> <u>Malignancy risk</u> As of September 2014February 2015, there were 2427 treatment-emergent adverse events reported by 2124 patients related to malignancy for the entire clinical program. The malignancies in the reslizumab-treated patients were of diverse tissues origin (1-colon, 1-anal, 3-melanoma, 2-prostate, 3-breast, 2-lung, 1-plasmacytoma, 1-lymphoma, 1-lung metastasis of a previous resected colon cancer, <u>ovarian adenocarcinoma, borderline ovarian tumor,</u> and 5-nonmelanoma skin cancer cases reported as nonserious events).</p> <p>In the placebo-controlled <u>asthma</u> studies <u>utilizing the 3.0-mg/kg dose,</u> the incidence of the overall malignancies was 6 (0.58%) <u>patients (0.58%)</u> patients; 1 patient had <u>both</u> prostate cancer and skin squamous cell carcinoma) in the reslizumab 3.0-mg/kg treatment group and 2 <u>patients</u> (0.27%) patients in the placebo group; a. All malignancies in the reslizumab-treated patients were diagnosed within less than 6 months from first reslizumab dosing, with the exception of <u>for</u> the skin squamous cell carcinoma.</p> <p>In the <u>combined</u> placebo-controlled studies and the long-term, open-label, safety extension Study C38072/3085, there were a total of 19 patients with malignancies <u>were reported in 1921 patients,</u> including <u>These included,</u> including 5 <u>cases of</u> nonmelanoma skin cancer. Most malignancies were diagnosed within less than half a year <u>6 months</u> after starting reslizumab treatment, and in 54 of these cases, there was a previous medical history of malignancies <u>malignancy.</u> The <u>A thorough</u> analysis of malignancy cases (ie, comparison of the malignancy rate to the general population malignancy [using the National Cancer Institute Surveillance, Epidemiology, and End Results Program], time to diagnosis, and nature and types of malignancies) did not suggest association <u>a causal relationship</u> between reslizumab and malignancies <u>cancer risk.</u></p>	<p><u>Additional Safety Issues</u> <u>Malignancy risk</u> As of February 2015, there were 27 treatment-emergent adverse events reported by 24 patients related to malignancy for the entire clinical program. The malignancies in reslizumab-treated patients were of diverse tissues (colon, anal, melanoma, prostate, breast, lung, plasmacytoma, lymphoma, lung metastasis of a previous resected colon cancer, ovarian adenocarcinoma, borderline ovarian tumor, and nonmelanoma skin cancer cases).</p> <p>In the placebo-controlled asthma studies utilizing the 3.0-mg/kg dose, incidence of overall malignancies was 6 patients (0.58%; 1 patient had both prostate cancer and skin squamous cell carcinoma) in the reslizumab 3.0-mg/kg treatment group and 2 patients (0.27%) in the placebo group. All malignancies in reslizumab-treated patients were diagnosed within less than 6 months from first reslizumab dosing, except for the skin squamous cell carcinoma.</p> <p>In the combined placebo-controlled studies and long-term, open-label, safety extension Study C38072/3085, malignancies were reported in 21 patients. These included 5 cases of nonmelanoma skin cancer. Most malignancies were diagnosed within less than 6 months after starting reslizumab treatment, and in 5 cases, there was a previous medical history of malignancy. A thorough analysis of malignancy cases did not suggest a causal relationship between reslizumab and cancer risk.</p>	<p>The text was updated based on the most recent data.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><u>Pregnancy</u></p> <p>The safety of reslizumab in pregnant women or in the developing fetus has not been studied, but nonclinical and completed and ongoing clinical studies raised no specific concerns. There were <u>To date, there have been</u> 10 pregnancies during the entire clinical development of reslizumab, 2 of which occurred during the screening period of the study and 8 were in patients receiving reslizumab. All patients were withdrawn from the study. Two pregnancies ended in <u>were terminated by</u> an elective abortion with no complications, and 5 concluded with <u>led to the birth of</u> full-term live births of infants with no malformations and no obstetric or perinatal complications. One male baby <u>newborn</u> had a neonatal jaundice that was reported as an unrelated adverse event and was assessed as a physiological jaundice. There was <u>One</u> pregnancy case that was lost to follow-up, and the outcome is unknown.</p> <p>No clinically meaningful changes in clinical laboratory values, vital signs measurements, electrocardiogram (ECG), or physical examination findings were noted in the completed studies, with the exception of a decrease in eosinophil counts in the reslizumab groups, which was dose related and is expected in view of the mechanism of action of reslizumab. Mild decrease in the mean value of total white blood cell (WBC) counts was also observed in some studies and has been assessed as reflecting the decrease in the eosinophil count in hypereosinophilic patients. The mean values of eosinophil and WBC counts returned to baseline values at the end of study follow up visit (4 months after the last dose of reslizumab).</p>	<p><u>Pregnancy</u></p> <p>The safety of reslizumab in pregnant women or in the developing fetus has not been studied, but nonclinical and clinical studies raised no specific concerns. To date, there have been 10 pregnancies during the entire clinical development of reslizumab, 2 of which occurred during the screening period of the study and 8 in patients receiving reslizumab. All patients were withdrawn from the study. Two pregnancies were terminated by an elective abortion with no complications, and 5 led to the birth of full-term infants with no malformations and no obstetric or perinatal complications. One male newborn had a neonatal jaundice that was reported as an unrelated adverse event and was assessed as physiological jaundice. One pregnancy case was lost to follow-up, and the outcome is unknown.</p>	<p>The text was updated based on the most recent data.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><u>Immunogenicity</u> Immunogenicity analysis showed that Anti-drug antibody ADA responses were observed in 3.3% to 11.8% of patients in the completed Phase 3 studies in patients with asthma (iv administration every 4 weeks, >1000 patients evaluated for ADA) ranged from 3.3% to 11.8% of patients in the different studies. In general, the ADA responses were low in titer and often transient, and were neithernot associated with an effect on reslizumab concentration, or eosinophil count, nor associated with specific clinical manifestations; (including hypersensitivity reactions).</p>	<p><u>Immunogenicity</u> Anti-drug antibody responses were observed in 3.3% to 11.8% of patients in the completed Phase 3 studies in patients with asthma (iv administration every 4 weeks, >1000 patients evaluated for ADA). In general, the ADA responses were low in titer and often transient, and were not associated with an effect on reslizumab concentration, eosinophil count, or specific clinical manifestations (including hypersensitivity reactions).</p>	<p>The text was updated based on the most recent data.</p>
<p>Section 1.4.1: Risks of Reslizumab:</p>		
<p><u>Most clinical safety data for reslizumab are based on the experience with iv administration of the drug.</u> As described in Section 1.3.2, iv reslizumab iv has been generally well tolerated over the range of doses evaluated (ie, from 0.03 through 3 mg/kg). <u>Systemic severe reactions (including Anaphylaxis)</u> and myalgia are considered ADRs of iv reslizumab. <u>There are limited safety data regarding sc administration of reslizumab.</u></p>	<p>Most clinical safety data for reslizumab are based on the experience with iv administration of the drug. As described in Section 1.3.2, iv reslizumab has been generally well tolerated over the range of doses evaluated (ie, from 0.03 through 3 mg/kg). Systemic severe reactions (including anaphylaxis) and myalgia are considered ADRs of iv reslizumab. There are limited safety data regarding sc administration of reslizumab.</p>	<p>The text was updated based on the most recent data.</p>

Original text with changes shown	New wording	Reason/Justification for change
Section 1.4.3: Overall Risk and Benefit Assessment for This Study:		
<p>The majority of adverse events in reslizumab-treated patients was<u>were</u> mild to moderate in severity; was considered to be unrelated to study drug treatment, as determined by the investigator; and, (as expected) was associated with underlying asthma disease. There were no significant differences in the adverse event profile between patients treated with reslizumab and patients treated with placebo, with the exception of <u>the following ADRs “systemic severe reactions (including anaphylaxis)” and “myalgia”.</u> Three of anaphylaxis reactions related to reslizumab infusions that were reported during the BREATH asthma program; None of these patients were positive for ADA. All cases resolved with standard treatment, and treatment with reslizumab was permanently discontinued. This is an expected ADR and is listed in the IB.</p> <p><u>Myalgia (without evidence for muscle injury) was reported at a slightly higher rate in the reslizumab 3.0-mg/kg group (1%) than in the placebo group (0.5%). The protocol includes measures to closely monitor and promptly address these ADRs, to mitigate any potential harm to patients.</u></p> <p>Overall, the nature and occurrence of the reported study drug related adverse events did not raise any specific safety concerns. For the full ADR list, please refer to the IB.</p>	<p>The majority of adverse events in reslizumab-treated patients were mild to moderate in severity; considered to be unrelated to study drug treatment, as determined by the investigator; and, (as expected) associated with underlying asthma disease. There were no significant differences in the adverse event profile between patients treated with reslizumab and patients treated with placebo, with the exception of the following ADRs “systemic severe reactions (including anaphylaxis)” and “myalgia”. Three anaphylaxis reactions related to reslizumab infusions were reported during the BREATH asthma program; none of the patients were positive for ADA. All cases resolved with standard treatment, and treatment with reslizumab was permanently discontinued. Myalgia (without evidence for muscle injury) was reported at a slightly higher rate in the reslizumab 3.0-mg/kg group (1%) than in the placebo group (0.5%). The protocol includes measures to closely monitor and promptly address these ADRs, to mitigate any potential harm to patients.</p>	<p>The additions further clarified the text.</p>
Section 1.7: Population to be Studied and Justification (Other sections affected by this change: Clinical Study Protocol Synopsis and Section 4.1):		
<p>Patients 12 to <18 years of age are excluded from participating in South Korea, the Netherlands, and Argentina, and patients 66 years of age and older are excluded from participating in South Korea.</p>	<p>Patients 12 to <18 years of age are excluded from participating in South Korea, the Netherlands, and Argentina, and patients 66 years of age and older are excluded from participating in South Korea.</p>	<p>Exclusion of pediatric patients is a local exclusion for the Netherlands</p>
Section 2.3.3: Other Prespecified Efficacy Endpoints (Other sections affected by this change: Clinical Study Protocol Synopsis and Section 9.5.3):		
<p>Change in total <u>inhalations of reliever bronchodilator medication (eg, SABA)</u> use (number of inhalations per 24 hours: day+night) from run-in baseline at each week through week 24 or early withdrawal</p>	<p>Change in total inhalations of reliever bronchodilator medication (eg, SABA) (number of inhalations per 24 hours: day+night) from run-in baseline at each week through week 24 or early withdrawal</p>	<p>This change accommodates inhaled rescue medications other than SABA.</p>

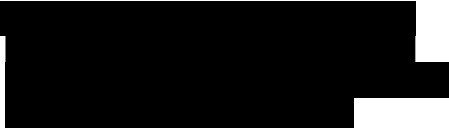

Original text with changes shown	New wording	Reason/Justification for change
<p>Change in <u>Number of</u> nighttime-awakenings due to asthma requiring rescue inhaler from run-in baseline at each week through week 24 or early withdrawal <u>over the 24-week treatment period</u></p>	<p>Number of nighttime-awakenings due to asthma over the 24-week treatment period</p>	<p>This text was updated to make this endpoint more general.</p>
<p>Section 2.3.6: Pharmacokinetic Endpoints (Other sections affected by this change: Clinical Study Protocol Synopsis and Section 2.3.5):</p>		
<p>Serum reslizumab concentrations will be determined from blood samples collected from each patient at DoR/baseline; <u>and prior to study drug administration at</u> weeks 4, 8 12, and 24 or early withdrawal; and at the follow-up visit (approximately week 32).</p>	<p>Serum reslizumab concentrations will be determined from blood samples collected from each patient at DoR/baseline; and prior to study drug administration at weeks 4, 8 12, and 24 or early withdrawal; and at the follow-up visit (approximately week 32).</p>	<p>This addition clarified that the sample collection was to be done prior to study drug administration at certain visits.</p>
<p>Section 3.1.1: Screening Period (Other sections affected by this change: Clinical Study Protocol Synopsis and Section 4.1)</p>		
<p>To be eligible to enroll in the study, a patient will have an airway FEV₁ reversibility of at least 12% and an absolute change of at least 200 mL to beta-agonist administration, a blood eosinophil count of at least 300/μL while on daily OCS or during the OCS optimization period or at the week -2 visit or a documented blood eosinophil level of at least 300/μL during the previous 12 months while on at least medium dose ICS (eg, ≥440 μg/day of fluticasone propionate or equivalent daily), a current fluticasone propionate dosage of at least 880 μg daily or equivalent plus another controller, and will have met all the inclusion and none of the exclusion criteria.</p>	<p>To be eligible to enroll in the study, a patient will have an airway FEV₁ reversibility of at least 12% to beta-agonist administration, a blood eosinophil count of at least 300/μL while on daily OCS or during the OCS optimization period or at the week -2 visit or a documented blood eosinophil level of at least 300/μL during the previous 12 months while on at least medium dose ICS, a current fluticasone propionate dosage of at least 880 μg daily or equivalent plus another controller, and will have met all the inclusion and none of the exclusion criteria.</p>	<p>This deletion was made for severe asthma patients on high GINA step therapy (i.e., ICS plus another controller (s) including OCS), it may be overly difficult to achieve both criteria..</p>
<p>Section 3.1.2: Optimization Period (Other sections affected by this change: Clinical Study Protocol Synopsis, Sections 2.3.3, 3.1.3, 3.1.4 [Table 2], 3.3.3, 4.1, 5.3, 6.9, and 9.5.3):</p>		
<p>At the beginning of the optimization period, an asthma symptom diary and electronic peak flow meter will be distributed where the patient will record asthma symptoms, number of reliever <u>bronchodilator</u> inhalations, of SABA, nighttime awakenings due to asthma requiring rescue inhaler, and AM and PM PEF.</p>	<p>At the beginning of the optimization period, an asthma symptom diary and electronic peak flow meter will be distributed where the patient will record asthma symptoms, number of reliever bronchodilator inhalations, nighttime awakenings due to asthma requiring rescue inhaler, and AM and PM PEF.</p>	<p>Added “bronchodilator” to “reliever inhalations,” or removed “SABA” to create more generalized wording.</p>
<p>Section 3.1.4: Treatment Period; Table 3: Oral Corticosteroid Decrements During the Treatment Period:</p>		
<p><< Edits made in Table 3 >></p>	<p>“0” (oral OCS dose mg/day) was added to the table.</p>	<p>These additions were made for clarification.</p>
<p>Section 3.1.4.1: Handling of Asthma Exacerbations During the Treatment Period (Other sections affected by this change: Section 3.16.4 and 9.5.6.1):</p>		

Original text with changes shown	New wording	Reason/Justification for change
<p>If a patient elects to withdraw (or is discontinued from treatment by the investigator), every attempt will be made to continue the assessments subsequent to his/her withdrawal from the study (<u>see Section 4.5</u>).</p>	<p>If a patient elects to withdraw (or is discontinued from treatment by the investigator), every attempt will be made to continue the assessments subsequent to his/her withdrawal from the study (see Section 4.5).</p>	<p>Section link added for clarification.</p>
<p>Section 3.3.3: Other Prespecified Efficacy Measures and Time Points (Other sections affected by this change: Clinical Study Protocol Synopsis):</p>		
<ul style="list-style-type: none"> • Total reliever bronchodilator inhalation SABA use (number of inhalations per 24 hours: day and night) based on the daily asthma control diary • Nighttime awakenings due to asthma requiring rescue inhaler based on the daily asthma control diary • Asthma symptoms based on the daily asthma control diary 	<ul style="list-style-type: none"> • Total reliever bronchodilator inhalation use (number of inhalations per 24 hours: day and night) based on the daily asthma control diary • Nighttime awakenings due to asthma requiring rescue inhaler based on the daily asthma control diary • Asthma symptoms based on the daily asthma control diary 	<p>This change clarified that the asthma control diary will measure asthma symptoms, reliever bronchodilator inhalation use, and nighttime awakenings due to asthma on a daily basis.</p>
<p>Section 3.9: Randomization and Blinding (Other sections affected by this change: Clinical Study Protocol Synopsis):</p>		
<p>The randomization list and treatment will be assigned to the relevant treatment groups through a qualified service providerCRO, eg, via Interactive Web Response System (IWRS). Generation of the medication list and management of the interactive response technology (IRT) system will be done by a qualified service providerCRO under the oversight of Teva’s Clinical Supply Chain.</p>	<p>The randomization list and treatment will be assigned to the relevant treatment groups through a qualified CRO, eg, via Interactive Web Response System (IWRS). Generation of the medication list and management of the interactive response technology (IRT) system will be done by a qualified CRO under the oversight of Teva’s Clinical Supply Chain.</p>	<p>Change wording from “service provider” to “CRO.”</p>
<p>In addition, tThe sponsor’s personnel involved in the study will also be blinded to the study drug identity after the run-in period until the database is locked for analysis and the treatment assignment is revealed, with the exception of the bioanalytical group (Global Bioassays and Technology), who, in order to facilitate PK and ADA sample analysis, will not be blinded. A third party vendor involved in PK and/or ADA data analysis may also be unblinded prior to database lock. Eosinophils and monocytes will be redacted from the post-baseline differential cell count reports to avoid the possibility of removing the blind.</p>	<p>The sponsor’s personnel involved in the study will also be blinded to the study drug identity after the run-in period until the database is locked for analysis and the treatment assignment is revealed, with the exception of the bioanalytical group (Global Bioassays and Technology), who, in order to facilitate PK and ADA sample analysis, will not be blinded. Eosinophils and monocytes will be redacted from the post-baseline differential cell count reports to avoid the possibility of removing the blind.</p>	<p>Removed from Section 3.9 and updated in 3.10.</p>

Original text with changes shown	New wording	Reason/Justification for change
Section 3.10.2: Blinding/Unblinding:		
<p>The individuals responsible for PK and ADA sample analysis will know which patients received the study drug and which patients received placebo. <u>In order to complete the data analysis for PK, it may be necessary to assay samples before database lock.</u> If so, the individuals responsible for sample analysis will know which patients received study drug and which patients received placebo. The randomization codes will be provided to personnel responsible for bioanalysis and PK data analysis according to a process that will be predefined in the unblinding plan form (GBP_RD_703_FRM_02) according to Teva standard operating procedure (SOP) GBP_RD_703. The form will be signed at the study initiation stage by Teva statistician, service provider CRO statistician, and randomization code generator. <u>After authorization has been obtained to release the codes, the randomization code generator at the CRO will provide the codes directly to the bioanalysis team; the statisticians (at Teva and the CRO) will not be unblinded.</u> Personnel responsible for bioanalysis and PK/ADA data analysis will not have access to clinical safety and efficacy data and will provide concentration data to any other personnel who may require it (including investigators) in a manner that will not identify individual patients (ie, a dummy patient identifier will be linked to an individual patient’s concentration data).</p>	<p>In order to complete the data analysis for PK, it may be necessary to assay samples before database lock. If so, the individuals responsible for sample analysis will know which patients received study drug and which patients received placebo. The randomization codes will be provided to personnel responsible for bioanalysis according to a process that will be predefined in the unblinding plan form (GBP_RD_703_FRM_02) according to the Teva standard operating procedure (SOP) GBP_RD_703. The form will be signed at the study initiation stage by Teva statistician, CRO statistician, and randomization code generator. After authorization has been obtained to release the codes, the randomization code generator at the CRO will provide the codes directly to the bioanalysis team; the statisticians (at Teva and the CRO) will not be unblinded. Personnel responsible for bioanalysis will not have access to clinical safety and efficacy data and will provide concentration data to any other personnel who may require it in a manner that will not identify individual patients (ie, a dummy patient identifier will be linked to an individual patient’s concentration data).</p>	<p>These updates were made to add clarity to the text.</p>
<p>For information about personnel who may be aware of treatment assignments, see Section 3.9. These individuals will not be involved in conduct of any study procedures or assessment of any adverse events, <u>safety, or efficacy data.</u></p>	<p>For information about personnel who may be aware of treatment assignments, see Section 3.9. These individuals will not be involved in conduct of any study procedures or assessment of any adverse events, safety, or efficacy data.</p>	<p>This addition clarifies that individuals aware of treatment assignments will also not be involved with assessment of safety or efficacy data.</p>
Section 3.14: Stopping Rules and Discontinuation Criteria:		
<p>Other than pregnancy, there are no formal rules for early withdrawal from this study.</p>	<p>Other than pregnancy, there are no formal rules for early withdrawal from this study.</p>	<p>These updates were made to add clarity to the text.</p>
Section 3.16: Study Procedures; Table 5: Study Procedures and Assessments: (Other sections affected by this change: Section 7.3.3.3):		
<p><u>X was added for pregnancy testing at V20</u></p>	<p>Additional day for pregnancy testing (V20)</p>	<p>This change creates consistency with text.</p>

Original text with changes shown	New wording	Reason/Justification for change
<u>Additional days for pre-bronchodilator spirometry at V2-11</u>	“X” was added for pre-bronchodilator spirometry at V2-V11.	This change creates consistency with text.
§ βHCG serum pregnancy tests will be performed at screening; urine pregnancy testing will be performed every 4 weeks thereafter until week 24 or early withdrawal (female patients who are not 2 years postmenopausal or surgically sterile) <u>and at the early follow-up visit (V20).</u>	§ βHCG serum pregnancy tests will be performed at screening; urine pregnancy testing will be performed every 4 weeks thereafter until week 24 or early withdrawal (female patients who are not 2 years postmenopausal or surgically sterile) and at the early follow-up visit (V20).	Footnote g was clarified to indicate that pregnancy testing will also be performed at visit 20.
Serum chemistry tests ⁱ <u>i CPK is collected with serum chemistry tests at scheduled visits. If potentially clinically significant CPK is reported, initiate CPK/myalgia CRF. Urinalysis and selected chemistries should be performed for 10x elevations as per CRF instructions, and CPK levels re-tested every 7 to 10 days until the elevation is resolved or if agreed with the medical monitor that no further testing is indicated.</u>	Serum chemistry tests ⁱ i CPK is collected with serum chemistry tests at scheduled visits. If potentially clinically significant CPK is reported, initiate CPK/myalgia CRF. Urinalysis and selected chemistries should be performed for 10x elevations as per CRF instructions, and CPK levels re-tested every 7 to 10 days until the elevation is resolved or if agreed with the medical monitor that no further testing is indicated.	Footnote i was added for the serum chemistry tests assessment.
<u>m Optional at visits 2-11.</u>	m Optional at visits 2-11.	Footnote m was added for pre-bronchodilator spirometry assessment, V2-V11 time point.
Post-bronchodilator spirometry ⁿ <u>n For post-bronchodilatory spirometry, short-acting beta-agonists, such as salbutamol or albuterol, administered via a metered dose inhaler should be used. Four separate doses (eg, albuterol 360 µg or salbutamol 100 µg ex-valve) should be given by a metered dose inhaler as tolerated. Post-bronchodilator spirometry should be completed a minimum of 15 minutes after dosing of short-acting beta-agonist.</u>	Post-bronchodilator spirometry ⁿ n For post-bronchodilatory spirometry, short-acting beta-agonists, such as salbutamol or albuterol, administered via a metered dose inhaler should be used. Four separate doses (eg, albuterol 360 µg or salbutamol 100 µg ex-valve) should be given by a metered dose inhaler as tolerated. Post-bronchodilator spirometry should be completed a minimum of 15 minutes after dosing of short-acting beta-agonist.	Footnote n was added for the post-bronchodilator spirometry assessment.
Blood for ADA ^p <u>p If possible, a blood sample for measurement of serum reslizumab concentrations will be obtained from patients experiencing an adverse event leading to withdrawal, a serious adverse event, an observation of any severe hypersensitivity reaction (eg, anaphylaxis), or an exacerbation of asthma symptoms.</u>	Blood for ADA ^p p If possible, a blood sample for measurement of serum reslizumab concentrations will be obtained from patients experiencing an adverse event leading to withdrawal, a serious adverse event, an observation of any severe hypersensitivity reaction (eg, anaphylaxis), or an exacerbation of asthma symptoms.	Footnote p was added for the blood for ADA assessment.

Original text with changes shown	New wording	Reason/Justification for change
<p>Adverse event inquiry^r <u>r Adverse event inquiry will occur before and after study drug administration at V3 to V16. Follow-up any prior messages from the post-injection eDiary symptom inquiry, as necessary. For systemic or severe hypersensitivity reactions possibly related to the study drug, initiate the anaphylaxis CRF. When such reactions are observed after study drug administration in the clinic, vital signs must be monitored using the unscheduled vital signs CRF. At the time of myalgia/muscular adverse events, CPK should be collected (initiate myalgia CRF).</u></p>	<p>Adverse event inquiry^r r Adverse event inquiry will occur before and after study drug administration at V3 to V16. Follow-up any prior messages from the post-injection eDiary symptom inquiry, as necessary. For systemic or severe hypersensitivity reactions possibly related to the study drug, initiate the anaphylaxis CRF. When such reactions are observed after study drug administration in the clinic, vital signs must be monitored using the unscheduled vital signs CRF. At the time of myalgia/muscular adverse events, CPK should be collected (initiate myalgia CRF).</p>	<p>Footnote r was added for the adverse event inquiry assessment.</p>
<p>Section 3.16.1: Procedures for Screening and Enrollment (Visit 1):</p>		
<p>Perform reversibility testing <u>if long-acting and short-acting inhaled bronchodilators were held for the specified time; if not, the patient should be brought back on another day to complete. Reversibility testing may be repeated once within the 2-week screening period. Airway reversibility will be demonstrated by measuring the change in FEV₁ before and after inhalation of SABA; reversibility testing should only be attempted after withholding short-acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long-acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule. SABAs, such as salbutamol or albuterol, administered via a metered dose inhaler should be used for reversibility testing. Four separate doses (eg, albuterol 360 µg or salbutamol 100 µg ex-valve) should be given by a metered dose inhaler, as tolerated. Post-bronchodilator spirometry should be completed a minimum of 15 minutes after dosing of SABA.</u>; reversibility testing may be repeated once within the 2-week screening period, and up to 4 puffs of SABA therapy are permitted for each airway reversibility test</p>	<p>Perform reversibility testing if long-acting and short-acting inhaled bronchodilators were held for the specified time; if not, the patient should be brought back on another day to complete. Reversibility testing may be repeated once within the 2-week screening period. Airway reversibility will be demonstrated by measuring the change in FEV₁ before and after inhalation of SABA; reversibility testing should only be attempted after withholding short-acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long-acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule. SABAs, such as salbutamol or albuterol, administered via a metered dose inhaler should be used for reversibility testing. Four separate doses (eg, albuterol 360 µg or salbutamol 100 µg ex-valve) should be given by a metered dose inhaler, as tolerated. Post-bronchodilator spirometry should be completed a minimum of 15 minutes after dosing of SABA.</p>	<p>To make consistent with the text provided in Table 5 Study Procedures and Assessments.</p>

Original text with changes shown	New wording	Reason/Justification for change
Section 3.16.3.1: Double-Blind Treatment Period (Weeks 1 Through 24 [Visits 13 Through 19]):		
Study drug will be administered at approximately 0800 (+2 hours) the same time in the morning on the days indicated in Table 5 .	Study drug will be administered at approximately the same time in the morning on the days indicated in Table 5 .	As this is an anti-inflammatory drug with a long half-life, the exact hour is not critical.
Section 3.16.3.1.1: Weeks 4, 8, 12, 16, 20, and 24 (Visits 14 Through 19):		
Section 3.16.3.1.1: Weeks 4, 8, 12, 16, 20, and 24 (Visits 14, 15, 16, 17, 18, Through 19)	Section 3.16.3.1.1: Weeks 4, 8, 12, 16, 20, and 24 (Visits 14 Through 19)	Change was made for consistency with the other section headings.
<p>The following procedures/assessments will be performed before prior to administration of study drug <u>unless otherwise indicated:</u></p> <p>...</p> <ul style="list-style-type: none"> • <u>Perform adverse event inquiry</u> • Complete asthma-specific tests <ul style="list-style-type: none"> – ... – AQLQ+12 at (weeks 4, 8, 12, 16, 20, and 24 or early withdrawal) <u>(may be completed after study drug administration during the 1-hour observation period)</u> – ACQ-6 at (weeks 4, 8, 12, 16, 20, and 24 or early withdrawal) <u>(may be completed after study drug administration during the 1-hour observation period)</u> • ... • Complete EQ-5D (week 24 or early withdrawal) <u>(may be completed after study drug administration during the 1-hour observation period)</u> •  • Complete SGRQ (weeks 12 and 24 or early withdrawal) <u>(may be completed after study drug administration during the 1-hour observation period)</u> 	<p>The following procedures/assessments will be performed before administration of study drug unless otherwise indicated:</p> <p>...</p> <ul style="list-style-type: none"> • Perform adverse event inquiry • Complete asthma-specific tests <ul style="list-style-type: none"> – ... – AQLQ+12 (weeks 4, 8, 12, 16, 20, and 24 or early withdrawal) (may be completed after study drug administration during the 1-hour observation period) – ACQ-6 (weeks 4, 8, 12, 16, 20, and 24 or early withdrawal) (may be completed after study drug administration during the 1-hour observation period) • ... • Complete EQ-5D (week 24 or early withdrawal) (may be completed after study drug administration during the 1-hour observation period) •  • Complete SGRQ (weeks 12 and 24 or early withdrawal) (may be completed after study drug administration during the 1-hour observation period) 	<p>This change was made to ensure consistency with Table 5 Study Procedures and Assessments.</p> <p>Clarification around timing of questionnaires was also added.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>The following procedures/assessments will be performed during and after administration of study drug:</p> <ul style="list-style-type: none"> • <u>Patients will be observed for 1 hour after study injection</u> • <u>Perform</u> A adverse event inquiry <ul style="list-style-type: none"> – <u>If, during post-study drug observation, the patient develops clinical symptoms, vital signs should be collected. The patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.7.</u> <p><u>Remind the patients that they will receive a post-injection symptom inquiry via the eDiary.</u></p>	<p>The following procedures/assessments will be performed during and after administration of study drug:</p> <ul style="list-style-type: none"> • Patients will be observed for 1 hour after study injection • Perform adverse event inquiry <ul style="list-style-type: none"> – If, during post-study drug observation, the patient develops clinical symptoms, vital signs should be collected. The patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.7. <p>Remind the patients that they will receive a post-injection symptom inquiry via the eDiary.</p>	<p>These updates were made to capture events during study drug administration.</p>
<p>Section 3.16.4: Procedures After Study Drug Treatment:</p>		
<ul style="list-style-type: none"> • <u>Perform urine pregnancy test</u> 	<ul style="list-style-type: none"> • Perform urine pregnancy test 	<p>These updates were made to capture events after study drug administration.</p>
<p>Section 4.1: Patient Inclusion Criteria (Other sections affected by this change: Clinical Study Protocol Synopsis):</p>		
<p>d. The patient has a documented blood eosinophil level of at least 300/μL during the previous 12 months while on at least medium <u>total daily</u> dose of ICS (based on Global Initiative for Asthma 2015 clinical comparability table (Appendix A) eg, \geq440 μg/day of fluticasone propionate or equivalent daily), or \geq300/μL at screening while on chronic OCS or that becomes manifest during the OCS optimization period or at the week -2 visit (end of optimization period/beginning of run-in period).</p>	<p>d. The patient has a documented blood eosinophil level of at least 300/μL during the previous 12 months while on at least medium total daily dose of ICS based on Global Initiative for Asthma 2015 clinical comparability table (Appendix A), or \geq300/μL at screening while on chronic OCS or that becomes manifest during the OCS optimization period or at the week -2 visit (end of optimization period/beginning of run-in period).</p>	<p>This update was added to encompass the medium (and higher) daily dose range for a given ICS formulation as per GINA 2015 BOX 3-6 as adapted in new Appendix A.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>e. The patient has required at least 880 µg of inhaled fluticasone propionate or equivalent daily PLUS another controller(s) (eg, long-acting beta-agonist [LABA], long-acting anti-muscarinic antagonist, leukotriene inhibitor, or theophylline), or documented intolerance to another controller, for at least 6 months before the screening visit. For a fixed-dose ICS/LABA preparation, the highest labeled dose in that region will satisfy this criterion. For patients 12 through <18 years of age, the ICS dose must ≥440 µg/day of fluticasone propionate or equivalent correspond to at least a medium total daily dose. Note: the dose and regimen of asthma controllers and any allergen immunotherapy should have been stable during the 30 days before signing the Informed Assent Form/Informed Consent Form (ICF).</p>	<p>The patient has required at least 880 µg of inhaled fluticasone propionate or equivalent daily PLUS another controller(s) (eg, long-acting beta-agonist [LABA], long-acting anti-muscarinic antagonist, leukotriene inhibitor, or theophylline), or documented intolerance to another controller, for at least 6 months before the screening visit. For a fixed-dose ICS/LABA preparation, the highest labeled dose in that region will satisfy this criterion. For patients 12 through <18 years of age, the ICS dose must correspond to at least a medium total daily ICS dose. Note: the dose and regimen of asthma controllers and any allergen immunotherapy should have been stable during the 30 days before signing the Informed Assent Form/Informed Consent Form (ICF).</p>	<p>This update was added to encompass the medium (and higher) daily dose range for a given ICS formulation as per GINA 2015 BOX 3-6 as adapted in new Appendix A.</p>
<p>Section 4.2: Patient Exclusion Criteria (Other sections affected by this change: Clinical Study Protocol Synopsis):</p>		
<p>e. The patient is pregnant or intends to become pregnant during the study <u>or within 5 months from last dose of study drug</u> or is lactating. Any woman becoming pregnant during the study will be withdrawn from the study.</p>	<p>e. The patient is pregnant or intends to become pregnant during the study or within 5 months from last dose of study drug or is lactating. Any woman becoming pregnant during the study will be withdrawn from the study.</p>	<p>Clarification added.</p>

Original text with changes shown	New wording	Reason/Justification for change
Section 4.5: Criteria and Procedures for Discontinuation of Study Treatment and/or Study Withdrawal:		
<p>4.5. <u>Withdrawal</u>–Criteria and Procedures for <u>Discontinuation of Study Treatment and/or Study Withdrawal</u></p> <p>In accordance with the Declaration of Helsinki (in accordance with the applicable country’s acceptance), each patient is free to<u>patients may voluntarily discontinue study treatment (ie, refuse study treatment but continue with study participation) or completely</u> withdraw from the study (ie, with no further study participation or contact) at any time.</p> <p>Each<u>The</u> investigator also has the right to <u>discontinue a patient from study treatment and/or</u> withdraw a patient from the study in the event of intercurrent illness, adverse events, pregnancy (see Section 7.2), or other reasons concerning the health or well-being of the patient, or in the event of lack of cooperation. In addition, a patient may be withdrawn from the study as described in Sections 3.10, 3.14, 3.16.4, 5.4, and 7.1.8.</p> <p>Should a patient decide to withdraw after administration of study drug(s), or should the investigator decide to withdraw the patient, all efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation at the time of the patient’s withdrawal should be made and an explanation should be given as to why the patient is withdrawing or being withdrawn from the study.</p> <p>The reason for and date of discontinuation from the study drug and the reasons for and date of withdrawal from the study must be recorded on the source documentation and transcribed onto the CRF. If a patient withdraws consent, every attempt will be made to determine the reasons. If the reason for withdrawal is an adverse event or a potentially clinically significant abnormal laboratory test result, monitoring will be continued until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made. The specific event or test result(s) must be recorded on the source documentation and transcribed onto the CRF.</p>	<p>4.5. Criteria and Procedures for Discontinuation of Study Treatment and/or Study Withdrawal</p> <p>In accordance with the Declaration of Helsinki (in accordance with the applicable country’s acceptance), patients may voluntarily discontinue study treatment (ie, refuse study treatment but continue with study participation) or completely withdraw from the study (ie, with no further study participation or contact) at any time. The investigator also has the right to discontinue a patient from study treatment and/or withdraw a patient from the study in the event of intercurrent illness, adverse events, pregnancy (see Section 7.2), or other reasons concerning the health or well-being of the patient, or in the event of lack of cooperation.</p> <p>If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event or a potentially clinically significant abnormal laboratory test result, monitoring will be continued until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made. The specific event or test result must be recorded on the source documentation and transcribed onto the CRF.</p>	<p>These edits clarified the procedures for discontinuation or withdrawal from the study.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>4.5.1 Discontinuation of Study Treatment</p> <p><u>If premature discontinuation of study treatment occurs for any reason, the patient should continue attending remaining study visits while off study treatment. The patient will continue to receive study provided OCS (prednisone) treatment for the remainder of their participation in the study. The patient should not be considered withdrawn from the study due to interruption or discontinuation of study treatment. For this study, it is very important to continue collecting data from all patients whether or not they complete treatment.</u></p> <p><u>If premature discontinuation of study treatment occurs, the patient should return to the clinic as soon as possible for a study treatment discontinuation visit.</u> All protocol-specified evaluations should be performed as <u>specified in the protocol for</u> the early termination <u>withdrawal</u> visit (see Table 5).</p> <p><u>The investigator must determine the reason for and the date of discontinuation of study treatment and record this information in both the source documentation and the Study Drug Treatment Completion CRF.</u></p> <p><u>The patient’s continued participation in the study must be discussed by the investigator and site staff with the patient; the investigator and site staff must also request the patient to continue attending study visits according to the study visit schedule with all assessments completed up to week 24 (visit 19). The OCS dose and safety assessments at week 24 (visit 19) are the priority assessments for patients that prematurely discontinue study treatment. At a minimum, the investigator should make every effort to obtain information regarding serious adverse events, OCS dose, and survival status at week 24. A safety follow-up visit (visit 20) should be conducted 8 weeks after visit 19.</u></p>	<p>4.5.1 Discontinuation of Study Treatment</p> <p>If premature discontinuation of study treatment occurs for any reason, the patient should continue attending remaining study visits while off study treatment. The patient will continue to receive study provided OCS (prednisone) treatment for the remainder of their participation in the study. The patient should not be considered withdrawn from the study due to interruption or discontinuation of study treatment. For this study, it is very important to continue collecting data from all patients whether or not they complete treatment.</p> <p>If premature discontinuation of study treatment occurs, the patient should return to the clinic as soon as possible for a study treatment discontinuation visit. All evaluations should be performed as specified in the protocol for the early withdrawal visit (see Table 5). The investigator must determine the reason for and the date of discontinuation of study treatment and record this information in both the source documentation and the Study Drug Treatment Completion CRF. The patient’s continued participation in the study must be discussed by the investigator and site staff with the patient; the investigator and site staff must also request the patient to continue attending study visits according to the study visit schedule with all assessments completed up to week 24 (visit 19). The OCS dose and safety assessments at week 24 (visit 19) are the priority assessments for patients that prematurely discontinue study treatment. At a minimum, the investigator should make every effort to obtain information regarding serious adverse events, OCS dose, and survival status at week 24. A safety follow-up visit (visit 20) should be conducted 8 weeks after visit 19.</p>	<p>This section was inserted to clarify discontinuation of study treatment.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>4.5.2 Complete Withdrawal from Study Patients who<u>If a patient decides to completely</u> withdraw from the study will be asked to return to the clinical site for a follow up visit 8 weeks (±7 days) after the early termination visit. All protocol specified evaluations should be performed at the follow up visit 8 weeks (±7 days) after the early termination visit (see Table 5).<u>refuses any further study participation or contact), all study participation for that patient will cease and all data to be collected at subsequent visits will be considered missing. If a patient decides to completely withdraw from the study, every effort should be made to complete and report the observations outlined in Section 4.5.1 (Discontinuation of Study Treatment) before withdrawal. A complete final evaluation at the time of the patient’s withdrawal should be made, including an explanation of why the patient is withdrawing from the study. The reason for and date of withdrawal from the study must be recorded in the source documentation and the Double-Blind Treatment Period Completion CRF. For patients who are lost to follow-up (ie, patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should make appropriate efforts to re-establish contact with patient; attempts to contact the patient should be documented in the source documents. If contact has not been re-established, efforts should still be made to locate the patient and obtain information regarding serious adverse events, OCS dose, and survival status at the end of the 24-week treatment period.</u> A patient should only be designated as lost to follow-up if the site is unable to establish contact with the subject<u>patient</u> after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc). If possible, a blood sample for measurement of serum reslizumab concentrations will be obtained from patients experiencing an adverse event leading to withdrawal, a serious adverse event, or an exacerbation of asthma symptoms. If the final visit is conducted more than 28 days after the final dose of study drug, all safety evaluations will be performed, but efficacy evaluations will not be made (see Section 3.16.4).</p>	<p>4.5.2 Complete Withdrawal from Study If a patient decides to completely withdraw from the study (ie, refuses any further study participation or contact), all study participation for that patient will cease and all data to be collected at subsequent visits will be considered missing. If a patient decides to completely withdraw from the study, every effort should be made to complete and report the observations outlined in Section 4.5.1 (Discontinuation of Study Treatment) before withdrawal. A complete final evaluation at the time of the patient’s withdrawal should be made, including an explanation of why the patient is withdrawing from the study. The reason for and date of withdrawal from the study must be recorded in the source documentation and the Double-Blind Treatment Period Completion CRF. For patients who are lost to follow-up (ie, patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should make appropriate efforts to re-establish contact with patient; attempts to contact the patient should be documented in the source documents. If contact has not been re-established, efforts should still be made to locate the patient and obtain information regarding serious adverse events, OCS dose, and survival status at the end of the 24-week treatment period. A patient should only be designated as lost to follow-up if the site is unable to establish contact with the patient after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).</p>	<p>This section was inserted to clarify complete withdrawal from the study.</p>

Original text with changes shown	New wording	Reason/Justification for change
Section 5.3: Prior and Concomitant Therapy or Medication:		
<u>Systemic corticosteroids and other medications will each be recorded in separate CRFs.</u> The sponsor will encode all therapy and medication according to the World Health Organization drug dictionary (WHO Drug).	Systemic corticosteroids and other medications will each be recorded in separate CRFs. The sponsor will encode all therapy and medication according to the World Health Organization drug dictionary (WHO Drug).	Clarification added.
Indication, dosage, and start and end dates should be entered on the <u>appropriate</u> CRF.	Indication, dosage, and start and end dates should be entered on the appropriate CRF.	Clarification added.
Section 6.2: Spirometry:		
<u>For post-bronchodilatory spirometry, SABAs, such as salbutamol or albuterol, administered via a metered dose inhaler should be used. Four separate doses (eg, albuterol 360 µg or salbutamol 100 µg ex-valve) should be given by a metered dose inhaler, as tolerated. Post-bronchodilator spirometry should be completed a minimum of 15 minutes after dosing of SABA.</u> Spirometry will be done according to ATS/ERS <u>2005</u> procedural guidelines.	For post-bronchodilatory spirometry, SABAs, such as salbutamol or albuterol, administered via a metered dose inhaler should be used. Four separate doses (eg, albuterol 360 µg or salbutamol 100 µg ex-valve) should be given by a metered dose inhaler, as tolerated. Post-bronchodilator spirometry should be completed a minimum of 15 minutes after dosing of SABA. Spirometry will be done according to ATS/ERS 2005 procedural guidelines.	The doses of various beta-agonists for spirometry were clarified by this addition. Year of guidance was specified for clarity.
Section 7.1.2: Recording and Reporting Adverse Events:		
At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open ended question such as, “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe.” <u>In addition, the eDiary will be programmed to query the patient about symptoms potentially consistent with hypersensitivity occurring during the 24 hour period following study drug injection.</u>	At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open ended question such as, “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe.” In addition, the eDiary will be programmed to query the patient about symptoms potentially consistent with hypersensitivity occurring during the 24 hour period following study drug injection.	This change was to clarify that the patient will be queried by the eDiary 24 hours after dosing with the study drug.
Section 7.1.6.3.1: Investigator Responsibility (Other sections affected by this change: Sections 3.16 [Table 5], 6.7, 7.1.8, and 8.1.1):		
If possible, a blood sample for measurement of serum reslizumab concentrations will be obtained from patients experiencing a serious adverse event, <u>an</u> adverse event leading to withdrawal, <u>an observation of any severe hypersensitivity reaction (eg, anaphylaxis),</u> or an exacerbation of asthma symptoms.	If possible, a blood sample for measurement of serum reslizumab concentrations will be obtained from patients experiencing a serious adverse event, an adverse event leading to withdrawal, an observation of any severe hypersensitivity reaction (eg, anaphylaxis), or an exacerbation of asthma symptoms.	The text was updated to reflect a new reason why blood samples for serum reslizumab concentrations will be obtained from patients.
Section 7.1.6.3.1: Investigator Responsibility (Other sections affected by this change: Section 1.4.3):		
cause of death (whether or not the death was related to study drug <u>as determined by the investigator</u>)	cause of death (whether or not the death was related to study drug as determined by the investigator)	Clarification added.

Original text with changes shown	New wording	Reason/Justification for change
Section 7.1.7: Specific Protocol-Defined Adverse Events:		
<p>7.1.7 <u>Specific</u> Protocol-Defined Adverse Events for Expedited Reporting</p> <p>7.1.7.1 Adrenal Insufficiency</p>	<p>7.1.7 Specific Protocol-Defined Adverse Events</p> <p>7.1.7.1 Adrenal Insufficiency</p>	<p>Headings were updated to clarify subsections.</p>
<p>7.1.7.2. Protocol-Defined Adverse Events for Expedited Reporting to Teva</p> <p>Additionally, fFor the purposes of this protocol, the following are considered protocol-defined adverse events for expedited reporting to Teva: anaphylaxis (possibly related to the study drug), newly diagnosed malignancy, and parasitic helminth infection. Hypersensitivity reactions will be monitored using the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis (Sampson et al 2006) (Appendix G). The process for reporting a protocol defined adverse event is the same as that for reporting a serious adverse event (see Section 7.1.6.3). Protocol defined adverse events for expedited reporting can be either serious or nonserious according to the criteria outlined in Section 7.1.6.1. The process for reporting a protocol-defined adverse event for expedited reporting is the same as that for reporting a serious adverse event (see Section 7.1.6.3).</p>	<p>7.1.7.2. Protocol-Defined Adverse Events for Expedited Reporting to Teva</p> <p>For the purposes of this protocol, the following are considered protocol-defined adverse events for expedited reporting to Teva: anaphylaxis, newly diagnosed malignancy, and parasitic helminth infection. Protocol defined adverse events for expedited reporting can be either serious or nonserious according to the criteria outlined in Section 7.1.6.1. The process for reporting a protocol-defined adverse event for expedited reporting is the same as that for reporting a serious adverse event (see Section 7.1.6.3).</p>	<p>Additional text added to clarify where all anaphylaxis are to be recorded.</p>
<p>7.1.7.3. Specific Adverse Event Case Report Form Capturing</p> <p>7.1.7.3.1. Anaphylaxis/Hypersensitivity Reactions Case Report Form</p> <p>Information about all suspected systemic reactions will be recorded on the Suspected Anaphylaxis/Hypersensitivity Reactions CRF, including the investigator's assessment if the event followed the definition of anaphylaxis based on the diagnostic criteria as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis (Sampson et al 2006) (Appendix G). The Anaphylaxis/Hypersensitivity Reactions CRF should be initiated in real time (along with vital sign assessment) for events occurring after study drug administration in the clinic or as soon as possible for suspect events outside the clinic.</p>	<p>7.1.7.3. Specific Adverse Event Case Report Form Capturing</p> <p>7.1.7.3.1. Anaphylaxis/Hypersensitivity Reactions Case Report Form</p> <p>Information about all suspected systemic reactions will be recorded on the Suspected Anaphylaxis/Hypersensitivity Reactions CRF, including the investigator's assessment if the event followed the definition of anaphylaxis based on the diagnostic criteria as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis (Sampson et al 2006) (Appendix G). The Anaphylaxis/Hypersensitivity Reactions CRF should be initiated in real time (along with vital sign assessment) for events occurring after study drug administration in the clinic or as soon as possible for suspect events outside the clinic.</p>	<p>Headings were updated to clarify subsections.</p> <p>Additional text added to clarify capturing of CRFs.</p>

Original text with changes shown	New wording	Reason/Justification for change
Section 7.1.7.3.2: Creatine Phosphokinase/Muscular Adverse Events CRF:		
<p><u>7.1.7.3.2. Creatine Phosphokinase/Muscular Adverse Events CRF</u> <u>Potentially clinically significant creatine phosphokinase (CPK) elevations (with or without associated symptoms) or myalgia/muscle symptoms will be recorded as an adverse event and documented using the potentially clinically significant CPK/myalgia case report form. A potentially clinically significant CPK is defined as $\geq 3.1 \times$ the upper limit of normal (Grade 3 based on the Food and Drug Administration [FDA] “Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials”).</u></p>	<p>7.1.7.3.2. Creatine Phosphokinase/Muscular Adverse Events CRF Potentially clinically significant creatine phosphokinase (CPK) elevations (with or without associated symptoms) or myalgia/muscle symptoms will be recorded as an adverse event and documented using the potentially clinically significant CPK/myalgia case report form. A potentially clinically significant CPK is defined as $\geq 3.1 \times$ the upper limit of normal (Grade 3 based on the Food and Drug Administration [FDA] “Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials”).</p>	<p>This section was added to address the reporting of muscular adverse events.</p>
Section 7.3.3.1: Urinalysis:		
<p>Urinalysis will <u>be performed at screening and will</u> include testing for the following:</p>	<p>Urinalysis will be performed at screening and will include testing for the following:</p>	<p>Text was added that urinalysis was to be collected for an elevated CPK level.</p>
Section 7.3.3.3: Human Chorionic Gonadotropin Tests:		
<p>Women of childbearing potential will have a blood <u>serum</u> βHCG test at screening (visit 1). <u>Human chorionic gonadotropin urine tests will be performed every 4 weeks thereafter until week 24 or early withdrawal, and at the early follow-up visit (visit 20)</u> and will be followed by urine tests monthly during the treatment period. Any patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.</p>	<p>Women of childbearing potential will have a serum βHCG test at screening (visit 1). Human chorionic gonadotropin urine tests will be performed every 4 weeks thereafter until week 24 or early withdrawal, and at the early follow-up visit (visit 20). Any patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.</p>	<p>The collection of pregnancy test results were clarified.</p>

Original text with changes shown	New wording	Reason/Justification for change
Section 7.4: Vital Signs:		
<p>Vital signs (pulse, blood pressure, body temperature, and respiratory rate) will be measured at time points specified in Table 5 and before^{prior to} other assessments (eg, blood draw and pulmonary function testing) and study drug administration. Vital signs include the following:</p> <ul style="list-style-type: none"> • pulse • blood pressure • body temperature • respiratory rate • height 	<p>Vital signs (pulse, blood pressure, body temperature, and respiratory rate) will be measured at time points specified in Table 5 and before other assessments (eg, blood draw and pulmonary function testing) and study drug administration. Vital signs include the following:</p> <ul style="list-style-type: none"> • pulse • blood pressure • body temperature • respiratory rate 	<p>Height was removed from the list of vital signs assessed, as it is not assessed at the same time as the other measurements.</p>
Section 9.2.2: Safety Analysis Set:		
<p>The safety population^{analysis set} will include all randomly assigned patients who receive at least 1 dose of study drug.</p>	<p>The safety analysis set will include all patients who receive at least 1 dose of study drug.</p>	<p>The description of the safety analysis set was updated based on feedback from the FDA.</p>
Section 9.2.3.1: Per-Protocol Analysis Set:		
<p>The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients without major protocol violations. In this analysis set, treatment will be assigned based on the treatment actually received, regardless of the treatment to which they were randomly assigned. Major violations will be defined in the statistical analysis plan.</p> <p>Additional analysis sets may be detailed in the statistical analysis plan.</p>	<p>The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients without major protocol violations.</p> <p>Additional analysis sets may be detailed in the statistical analysis plan.</p>	<p>The deletion adds clarity to the per-protocol analysis set.</p>

Original text with changes shown	New wording	Reason/Justification for change
Section 9.5.6.2: Sensitivity Analysis:		
<p>Other Ssensitivity analyses will include the following:</p> <ul style="list-style-type: none"> Analysis including data collected after early withdrawal from treatment. In this analysis, patients will be categorized according to the percent dose reduction at 24 weeks regardless of whether they withdrew early from treatment or completed treatment. For those patients from which the sponsor fails to retrieve data despite all attempts, multiple imputations method will be used. Repeating the primary analysis on the PP analysis set “Tipping point” multiple imputation analysis to assess deviations from missing at random (MAR); details regarding this analysis will be provided in the SAP <p>Additional sensitivity analyses may be included and will be detailed in the statistical analysis plan.</p>	<p>Other sensitivity analyses will include the following:</p> <ul style="list-style-type: none"> Repeating the primary analysis on the PP analysis set “Tipping point” multiple imputation analysis to assess deviations from missing at random (MAR); details regarding this analysis will be provided in the SAP <p>Additional sensitivity analyses may be included and will be detailed in the statistical analysis plan.</p>	<p>Revised so as to be updated in the statistical analysis plan.</p>
Section 9.5.6.3: Secondary Efficacy Analysis (Other sections affected by this change: Clinical Study Protocol Synopsis):		
<p>Additional covariates or factors may be added to the logistic regressionstatistical models. These will be detailed in the statistical analysis plan.</p>	<p>Additional covariates or factors may be added to the statistical models. These will be detailed in the statistical analysis plan.</p>	<p>Revised so as to be updated in the statistical analysis plan.</p>

Original text with changes shown	New wording	Reason/Justification for change
Section 9.7.2: Safety Analysis:		
<p>Summaries will be presented for all adverse events starting during or after first study drug administration (overall and by severity), adverse events determined by the investigator to be related to study treatment (ie, reasonable possibility; see Section 7.1.4, with missing relationship will be counted as related) (overall and by severity), serious adverse events, adverse events causing withdrawal from the study discontinuation from study treatment, adverse events with onset date after EOT visit during the follow-up period (ie, after the cessation of study treatment), and adverse events that begin within 24 hours after injection. Summaries will be presented by treatment group and for all patients. Patient listings of adverse events, serious adverse events, and adverse events leading to withdrawal discontinuation will be presented and will include all adverse events reported (including before first study drug administration).</p>	<p>Summaries will be presented for all adverse events starting after first study drug administration (overall and by severity), adverse events determined by the investigator to be related to study treatment (ie, reasonable possibility; see Section 7.1.4, with missing relationship will be counted as related) (overall and by severity), serious adverse events, adverse events causing discontinuation from study treatment, adverse events with onset during the follow-up period (ie, after the cessation of study treatment), and adverse events that begin within 24 hours after injection. Summaries will be presented by treatment group and for all patients. Patient listings of adverse events, serious adverse events, and adverse events leading to discontinuation will be presented and will include all adverse events reported (including before first study drug administration).</p>	<p>This text was clarified.</p>
Section 9.11: Immunogenicity Analysis (Other sections affected by this change: Clinical Study Protocol Synopsis):		
<p>ADA data information will be described for subjects who test positive listed at a patient level. Samples from placebo-treated patients will not be analyzed.</p>	<p>Anti-reslizumab antibody information will be described for subjects who test positive. Samples from placebo-treated patients will not be analyzed.</p>	<p>Clarification added.</p>
Section 11.1.2: Protocol Violations:		
11.1.2 Protocol Deviations Violations	11.1.2 Protocol Violations	Section title changed to match template.
<p>When a protocol violation is reported, the sponsor will determine whether to withdraw the patient from the study or permit the patient to continue in the study, with a documented approval decision from the Sponsor’s medical representative.</p>	<p>When a protocol violation is reported, the sponsor will determine whether to withdraw the patient from the study or permit the patient to continue in the study, with a documented decision from the Sponsor’s medical representative.</p>	<p>Clarification added.</p>
<p>If investigational center personnel learn that a patient who did not meet protocol eligibility criteria was entered into a study, they must immediately inform the sponsor of the protocol violation. If such patient has already completed the study or has withdrawn early, no action will be taken, but the violation incident will be recorded.</p>	<p>If investigational center personnel learn that a patient who did not meet protocol eligibility criteria was entered into a study, they must immediately inform the sponsor. If such patient has already completed the study or has withdrawn early, no action will be taken, but the incident will be recorded.</p>	<p>Clarification added.</p>

Original text with changes shown	New wording	Reason/Justification for change
Appendices A, B, C, D, E, and F:		
<u>(Sample provided in this appendix is for reference only.)</u>	(Sample provided in this appendix is for reference only.)	Clarification added.

APPENDIX A. GLOBAL INITIATIVE FOR ASTHMA ICS EQUIVALENCY TABLE

Medium or Higher Daily Doses of Inhaled Corticosteroids in Patients 12 Years and Older

Drug	Daily Dose (µg)	
	Medium	High
Beclomethasone dipropionate (CFC) ^a	>500	>1000
Beclomethasone dipropionate (HFA)	>200	>400
Budesonide (DPI)	>400	>800
Ciclesonide (HFA)	>160	>320
Fluticasone fuorate (DPI)	N/A	≥200
Fluticasone propionate (DPI)	>250	>500
Fluticasone propionate (HFA)	>250	>500
Mometasone furoate	>220	>440
Triamcinolone acetonide	>1000	>2000

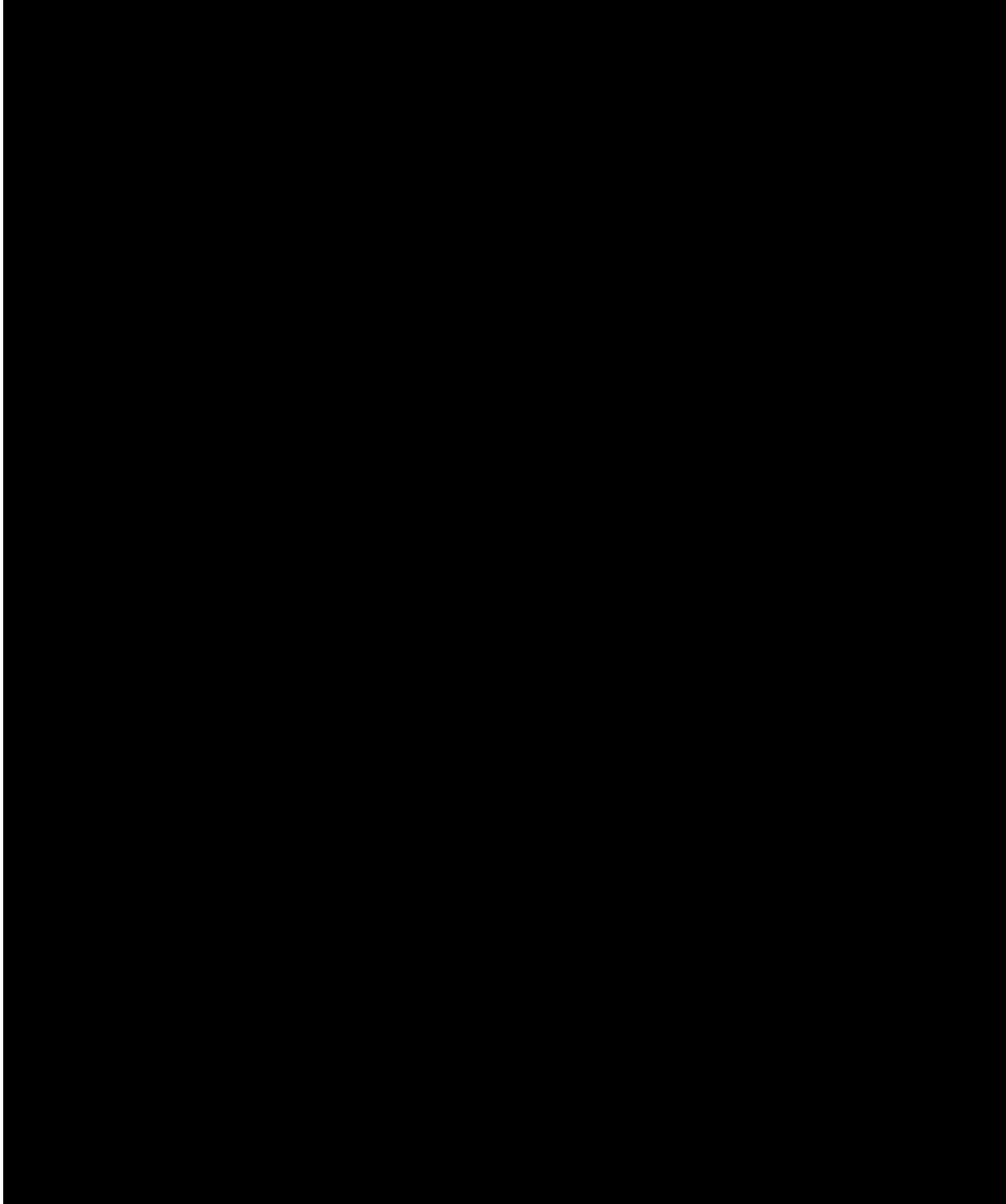
Source: Adapted from Box 8 in GINA 2016 Update (www.ginasthma.org).

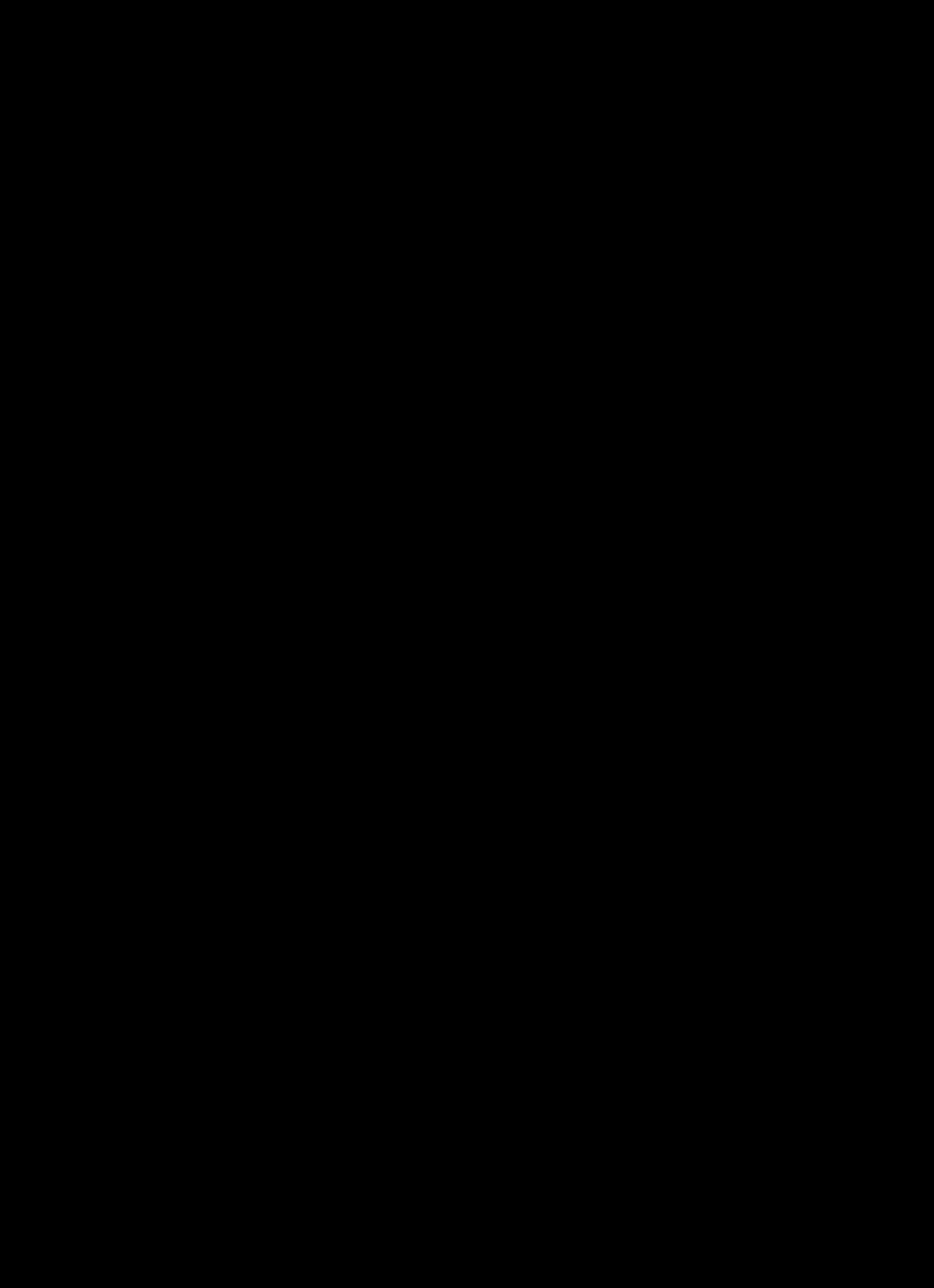
^a Beclomethasone dipropionate CFC is included for comparison with older literature.

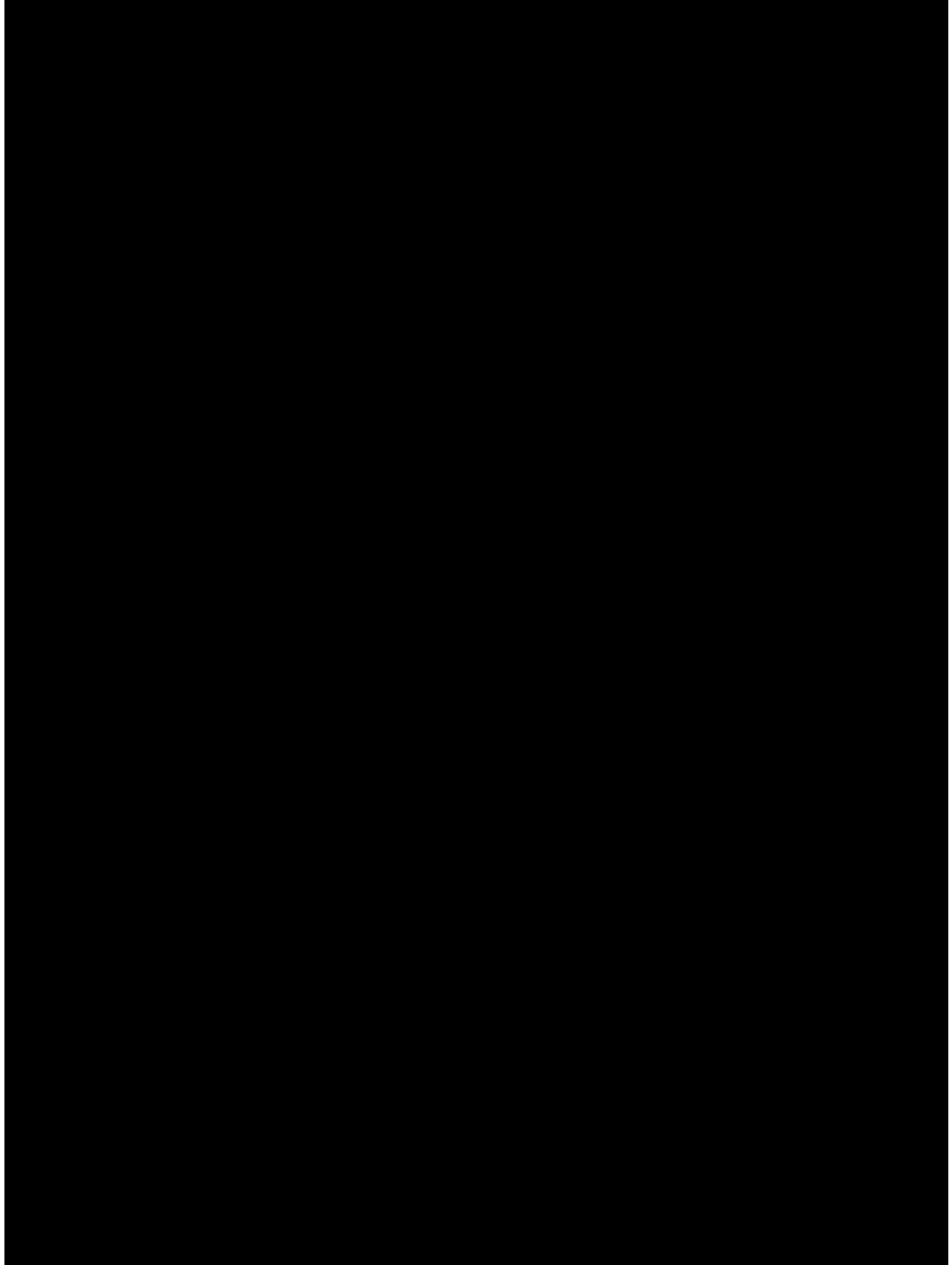
CFC = chlorofluorocarbon propellant; DPI = dry powder inhaler; HFA = hydrofluoroalkane propellant; N/A = not applicable.

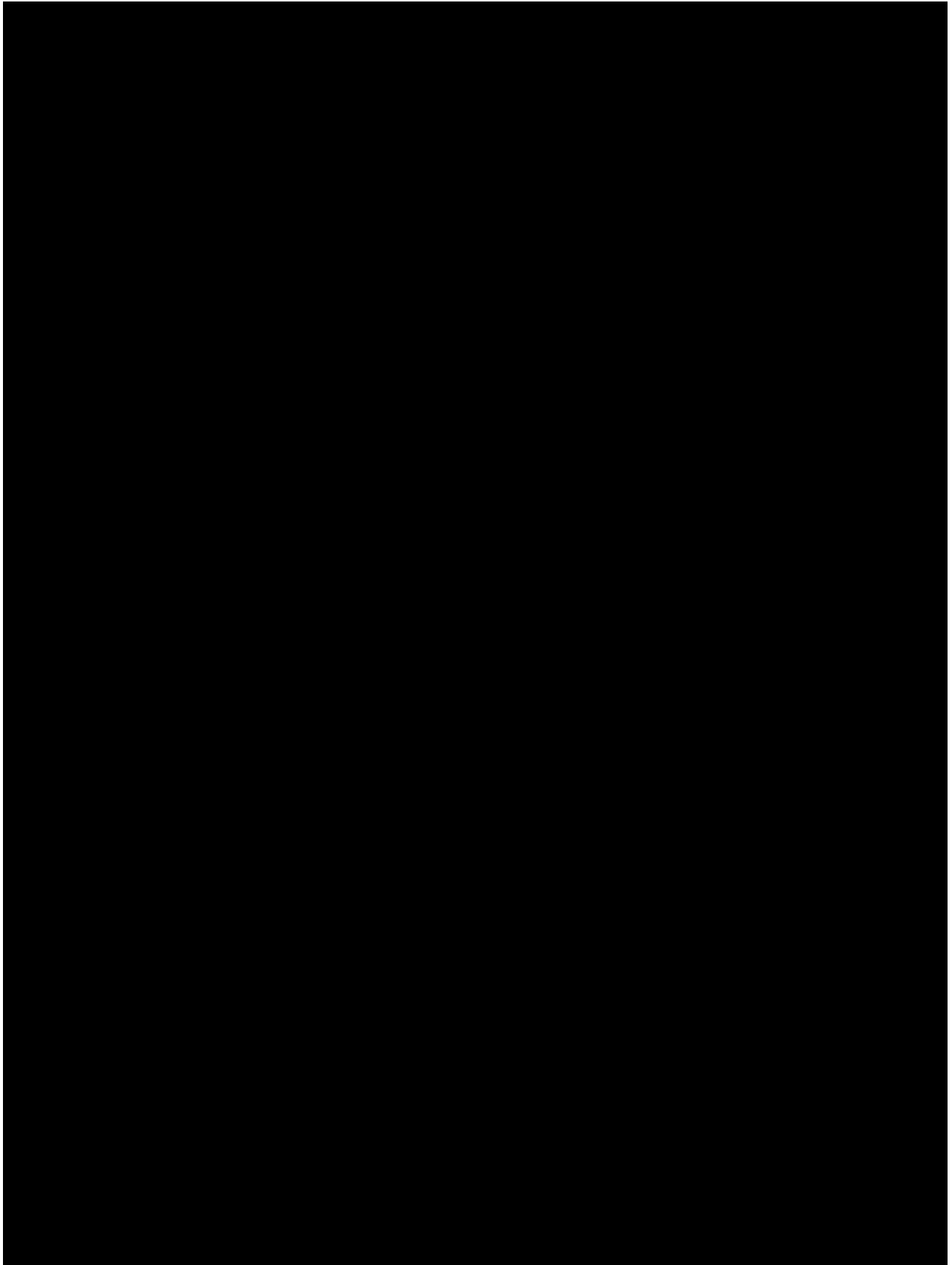
APPENDIX B. ASTHMA QUALITY OF LIFE QUESTIONNAIRE +12

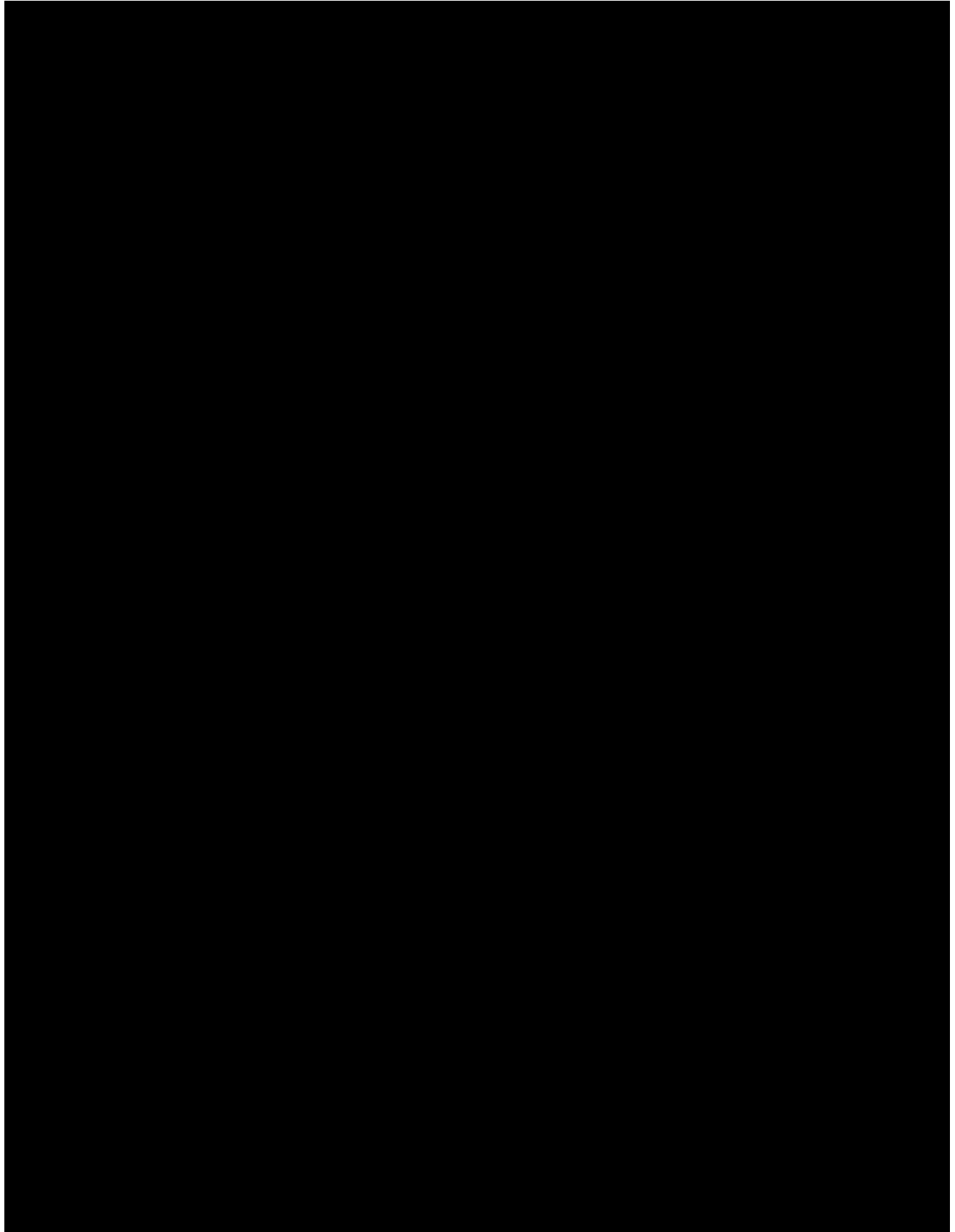
(Sample provided in this appendix is for reference only.)

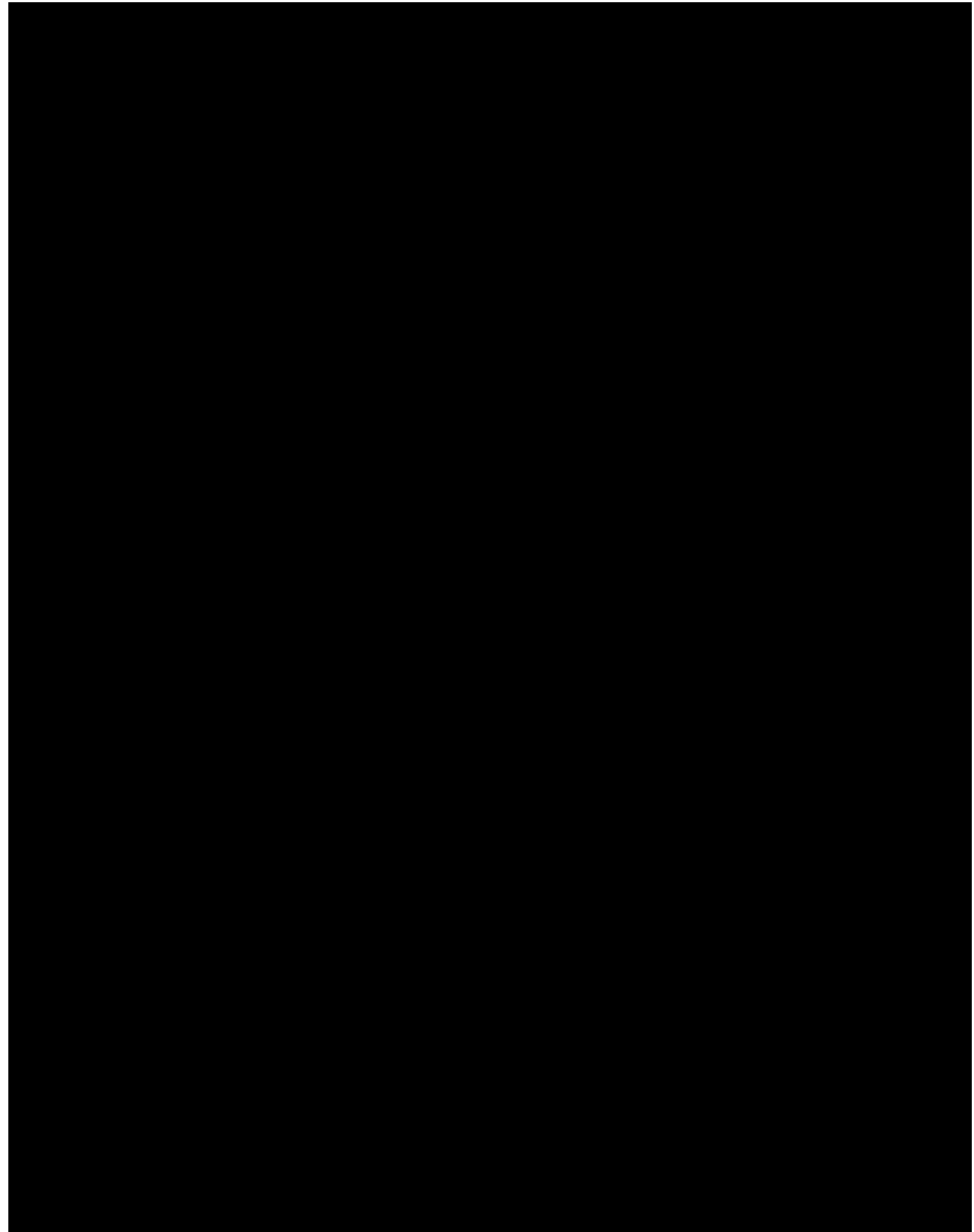








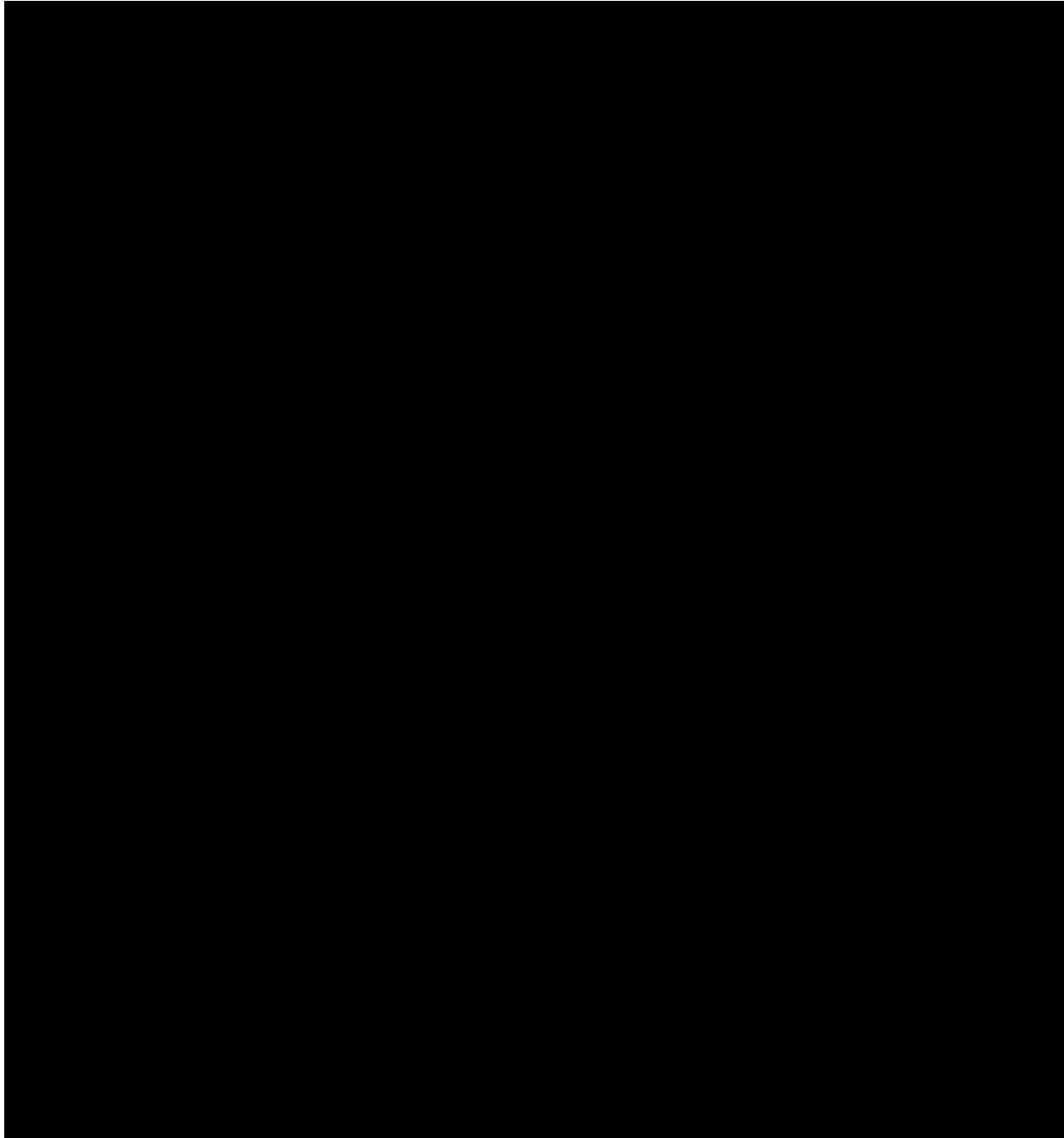




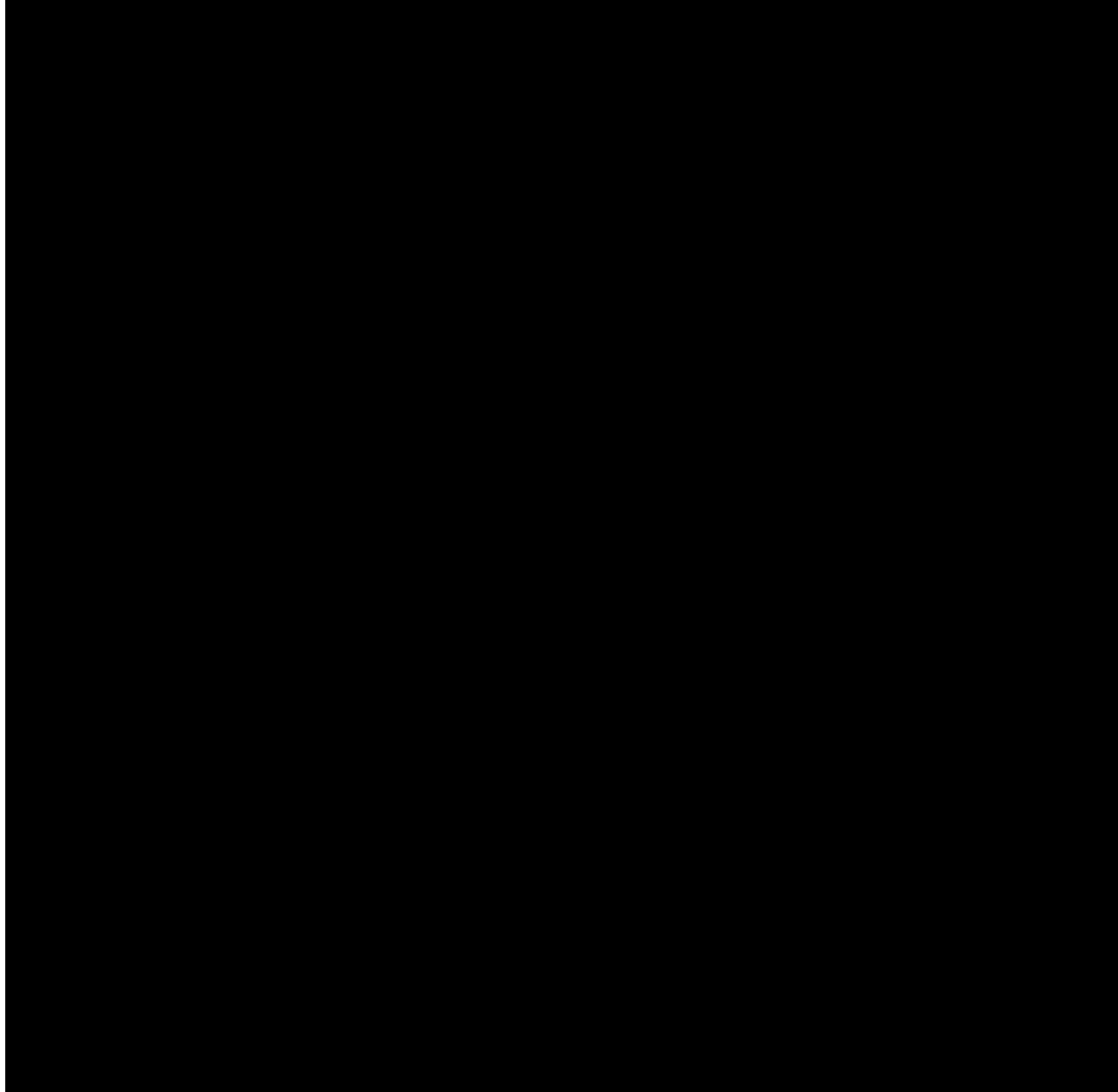
Source: Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health-related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992;47:76-83.

APPENDIX C. ASTHMA CONTROL QUESTIONNAIRE

(Sample provided in this appendix is for reference only.)



SOURCE: Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.



Source: Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.

APPENDIX D. ASTHMA CONTROL DIARY

(Sample provided in this appendix is for reference only.)

Asthma Symptom Score

Please enter a single number for the asthma symptom score below. This will be the score that describes all of your symptoms each morning and evening.

Each morning, indicate how you felt the previous night by recording your nighttime asthma symptom score in the box below.

Nighttime Asthma Symptom Score

(Determined in the morning)

0=No symptoms during the night

1=Symptoms causing me to wake once (or wake early)

2=Symptoms causing me to wake twice or more (including waking early)

3=Symptoms causing me to be awake for most of the night

4=Symptoms so severe that I did not sleep at all

Your nighttime symptom score:

Each evening, indicate how you felt during the day by recording your daytime asthma symptom score in the box below.

Daytime Asthma Symptom Score

(Determined in the evening)

0=No symptoms during the day

1=Symptoms for 1 short period during the day

2=Symptoms for 2 or more short periods during the day

3=Symptoms for most of the day that did not affect my normal daily activities

4=Symptoms for most of the day that did affect my normal daily activities

5=Symptoms so severe that I could not go to work or perform normal daily activities

Your daytime symptom score:

Peak Flow Meter

- You will need to record your peak expiratory flow (PEF) reading every morning and evening.
- Blow into your peak flow meter 3 times in the morning and 3 times in the evening.
- Write down the highest reading for the morning and the highest for the evening.

AM peak flow meter reading:

PM peak flow meter reading:

Time taken:

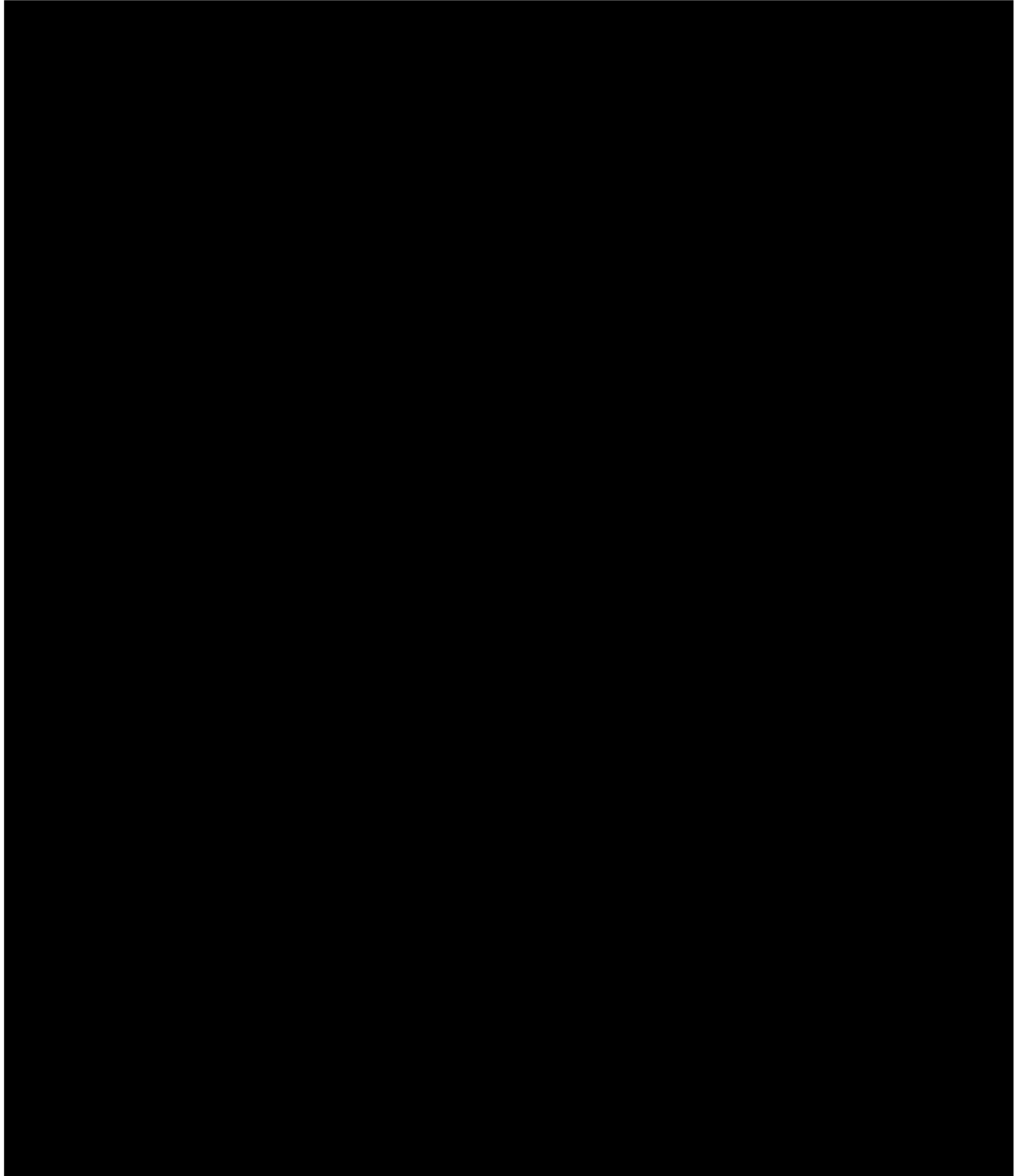
Time taken:

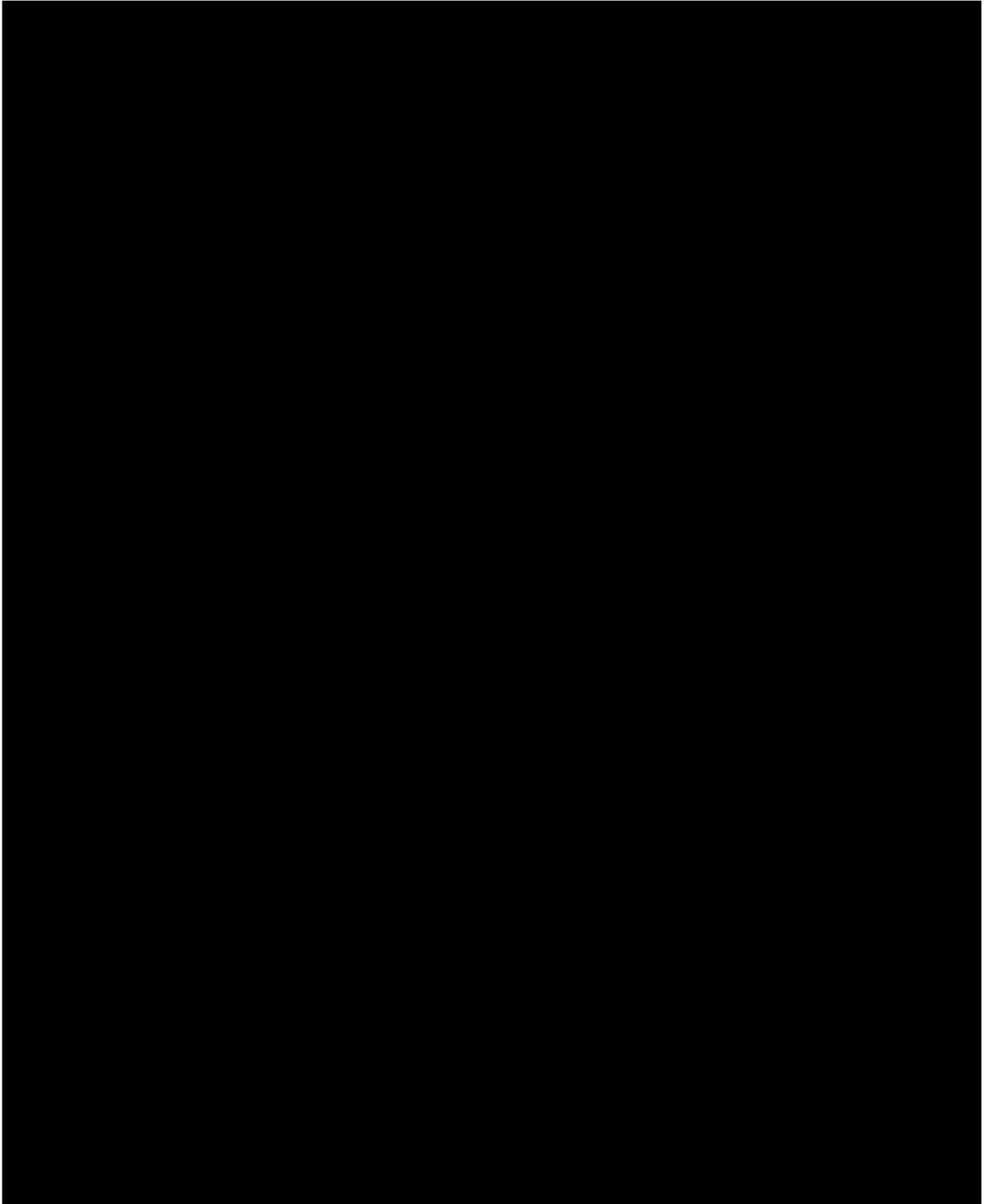
Rescue Medication (Do not record SABA use for exercise pretreatment!)

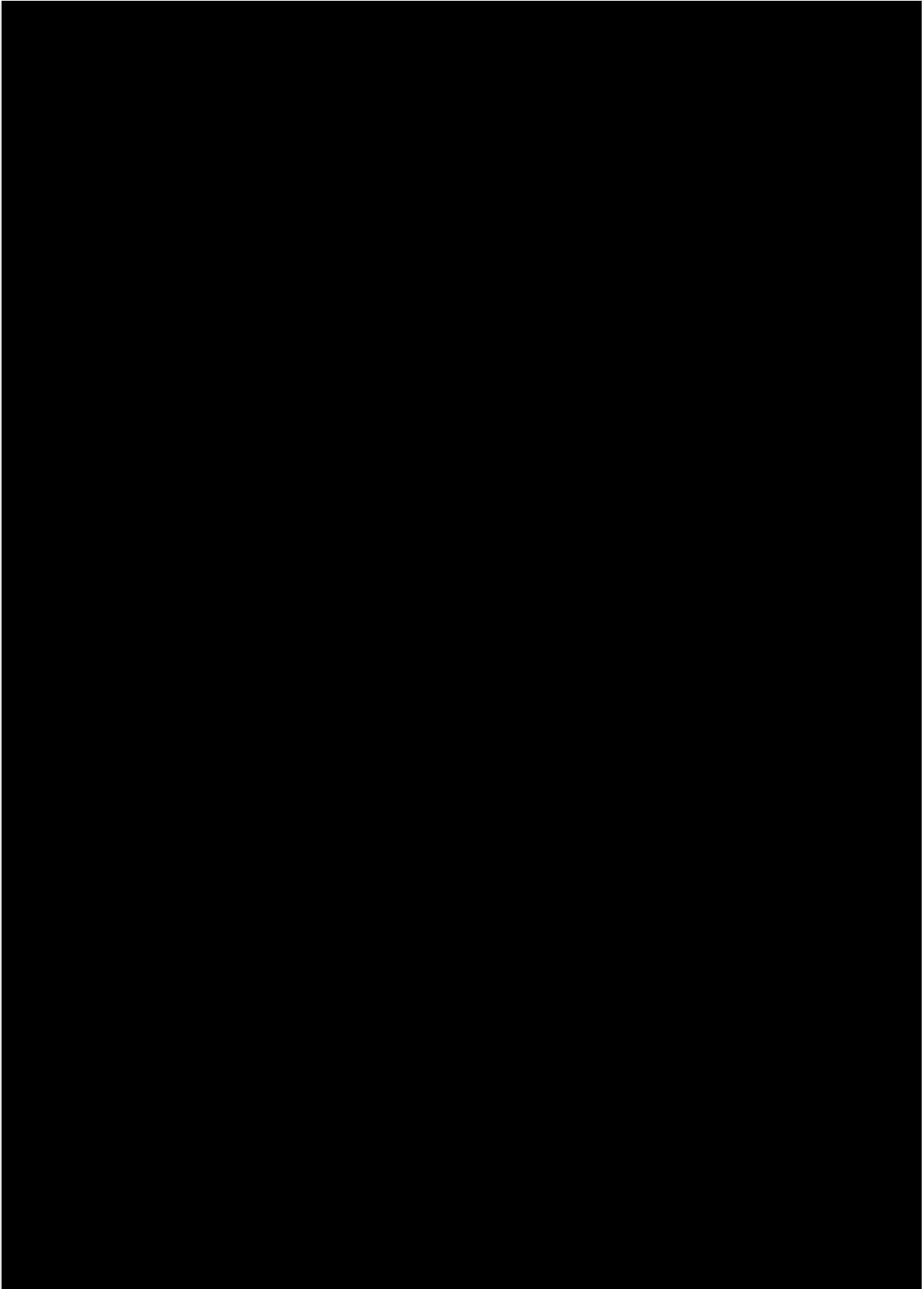
Total number of puffs (daily)

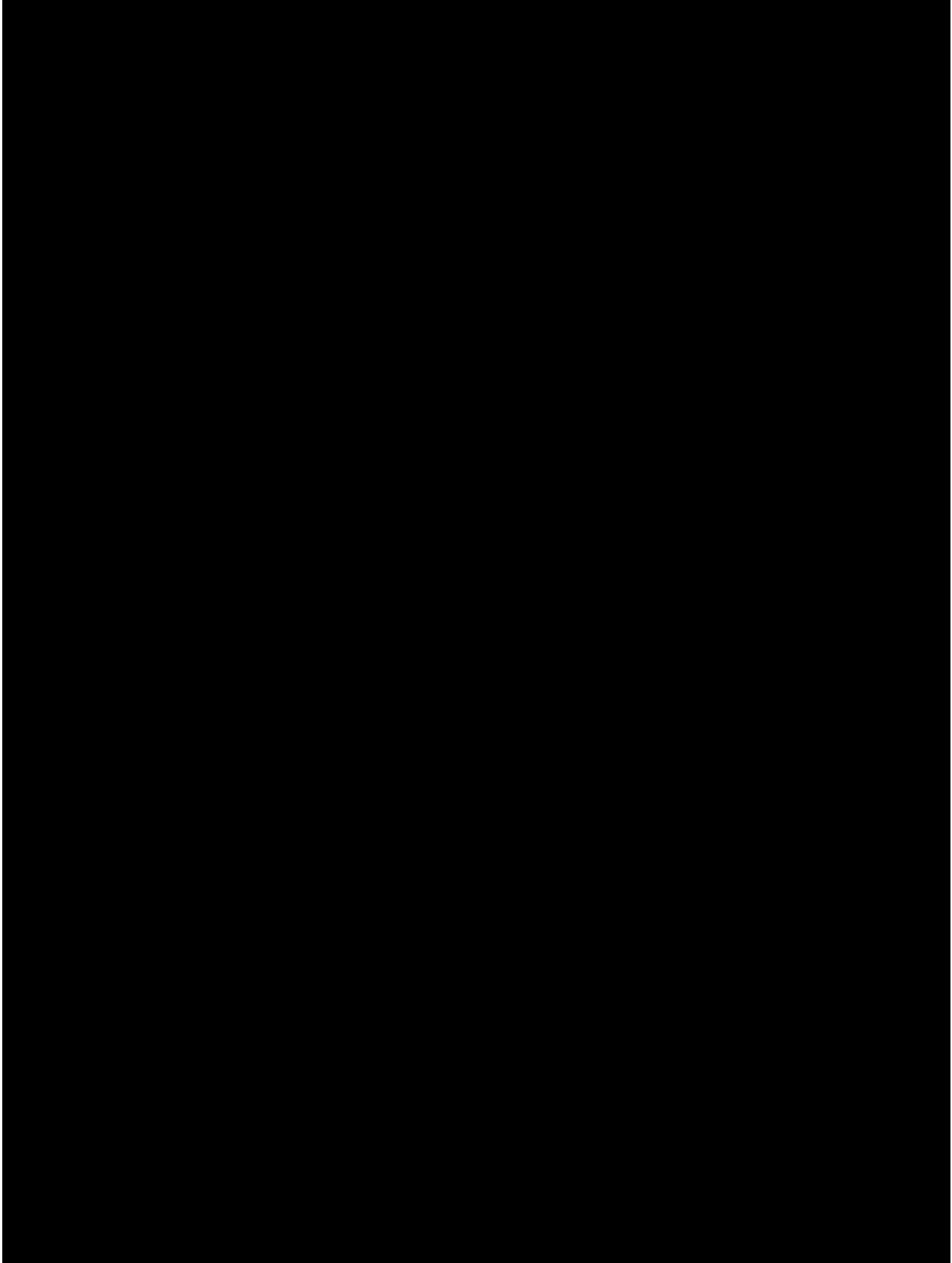
APPENDIX E. EUROPEAN QUALITY OF LIFE 5-DIMENSION HEALTH STATE UTILITY INDEX

(Sample provided in this appendix is for reference only.)



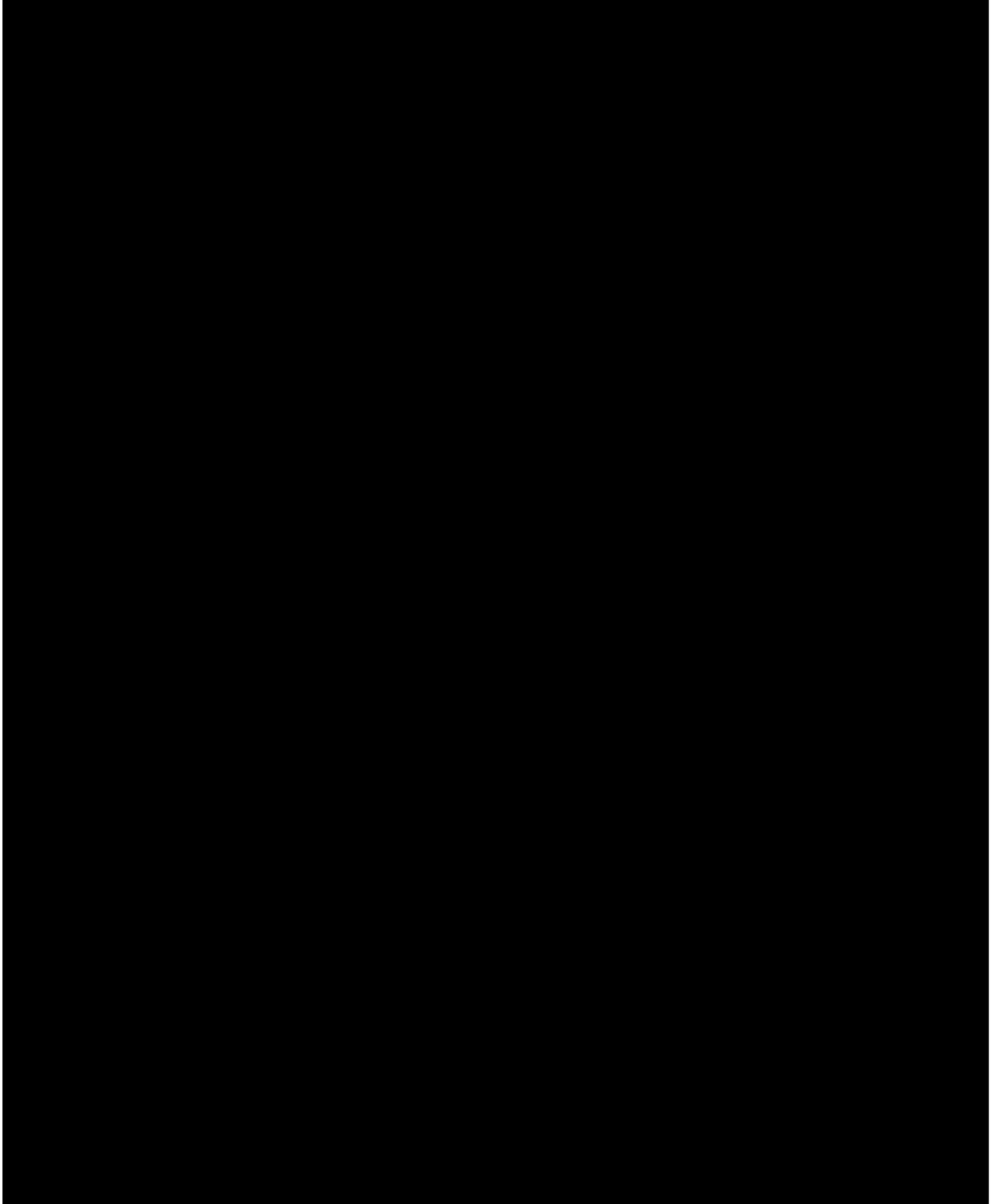


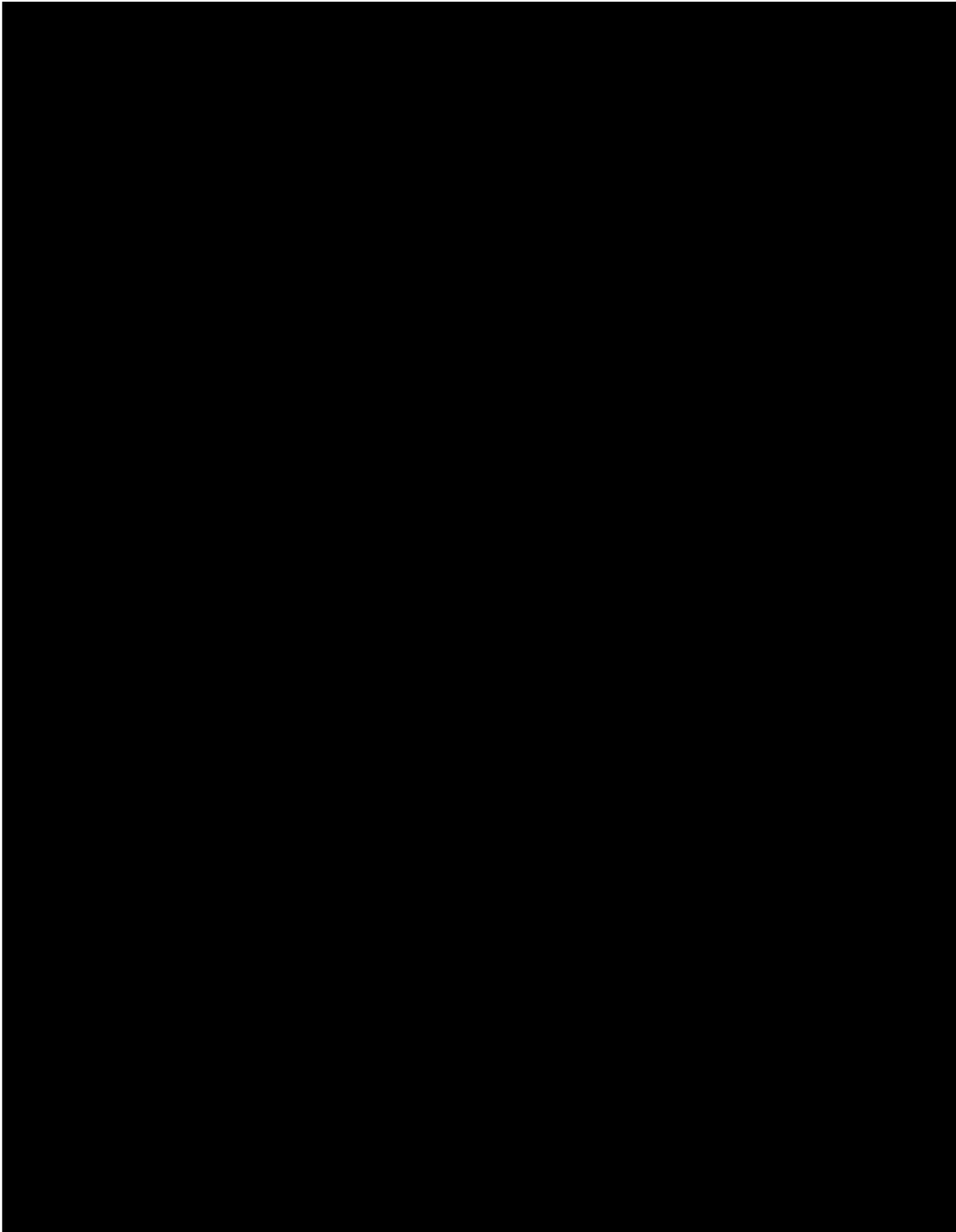


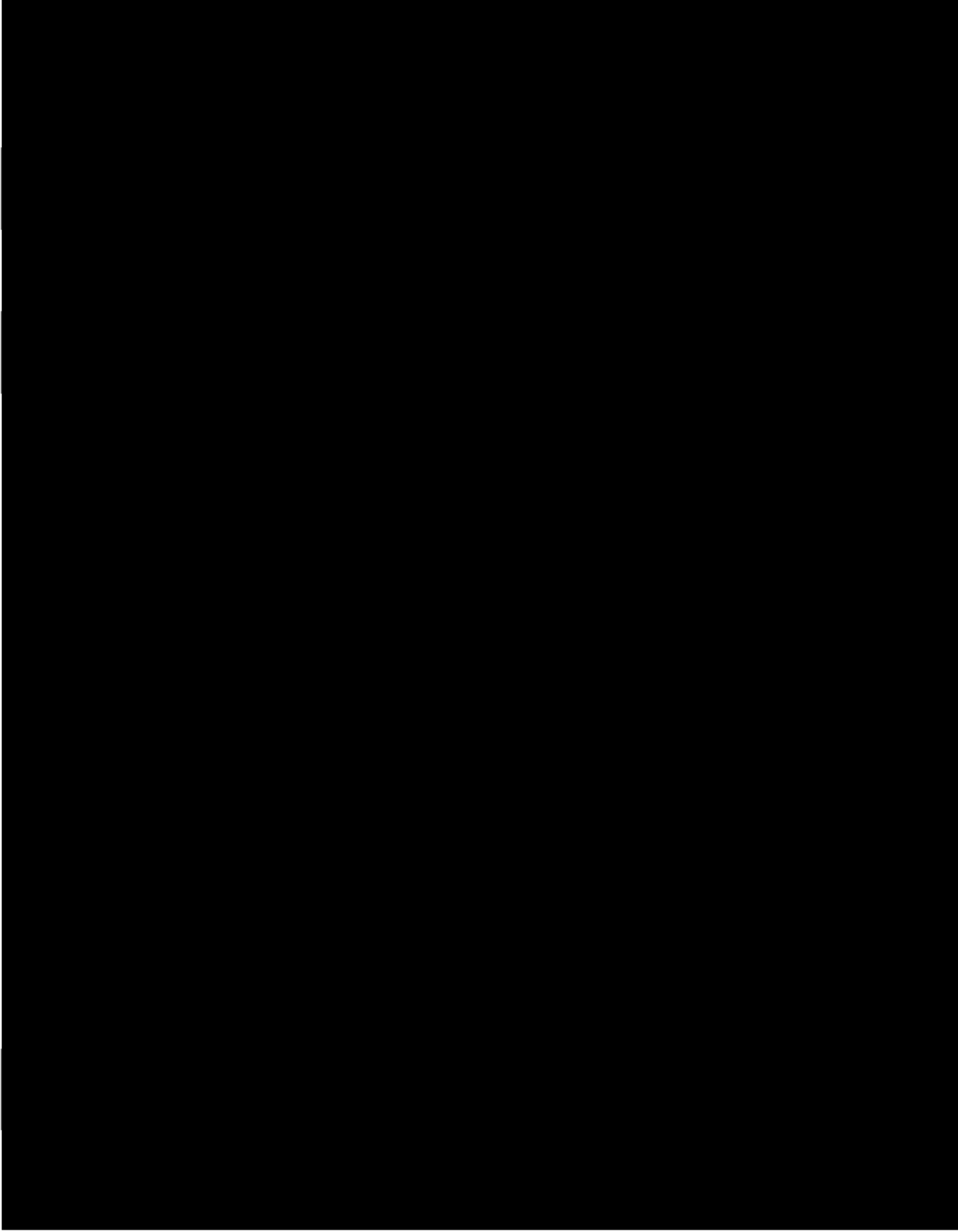


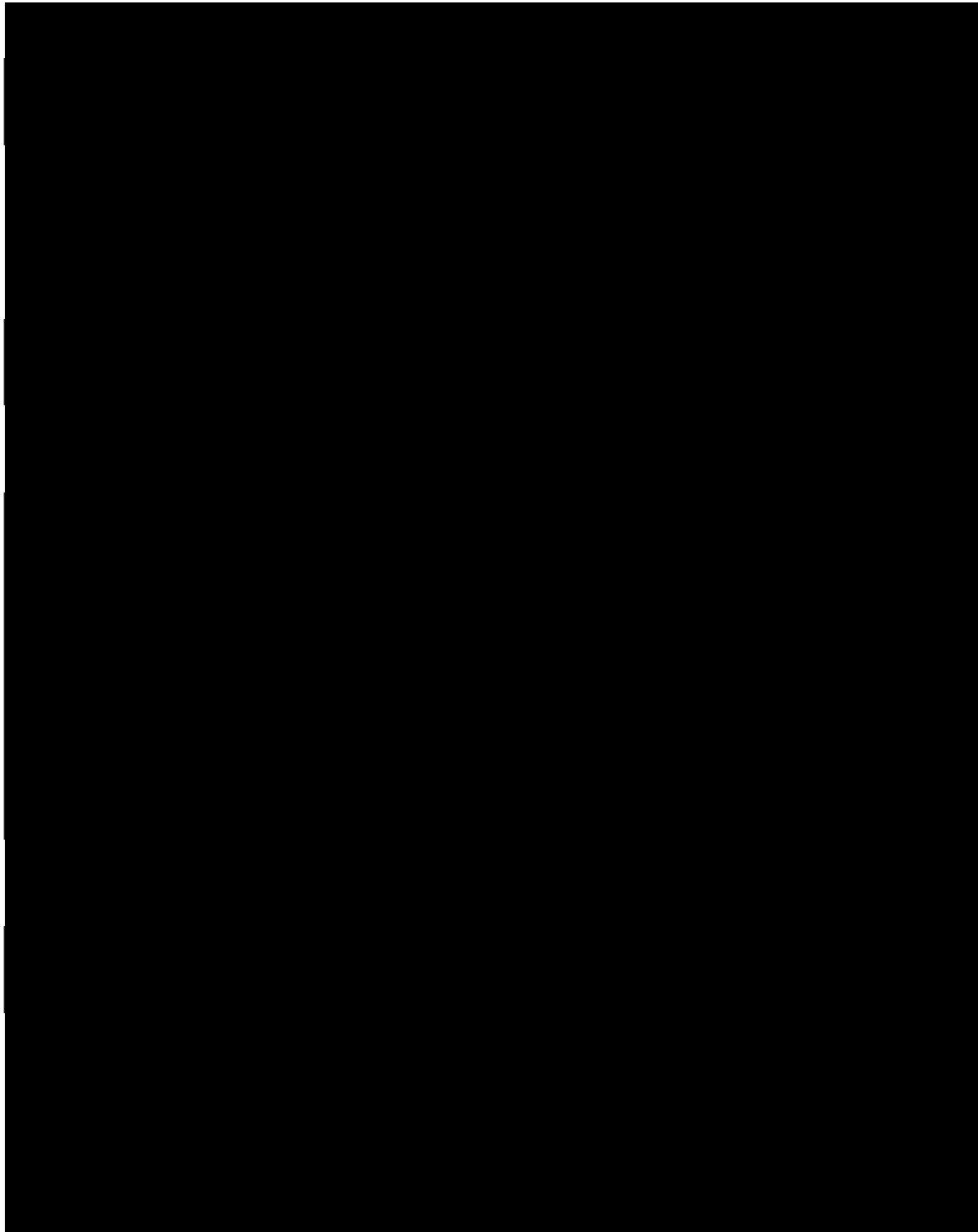
APPENDIX G. ST. GEORGE’S RESPIRATORY QUESTIONNAIRE

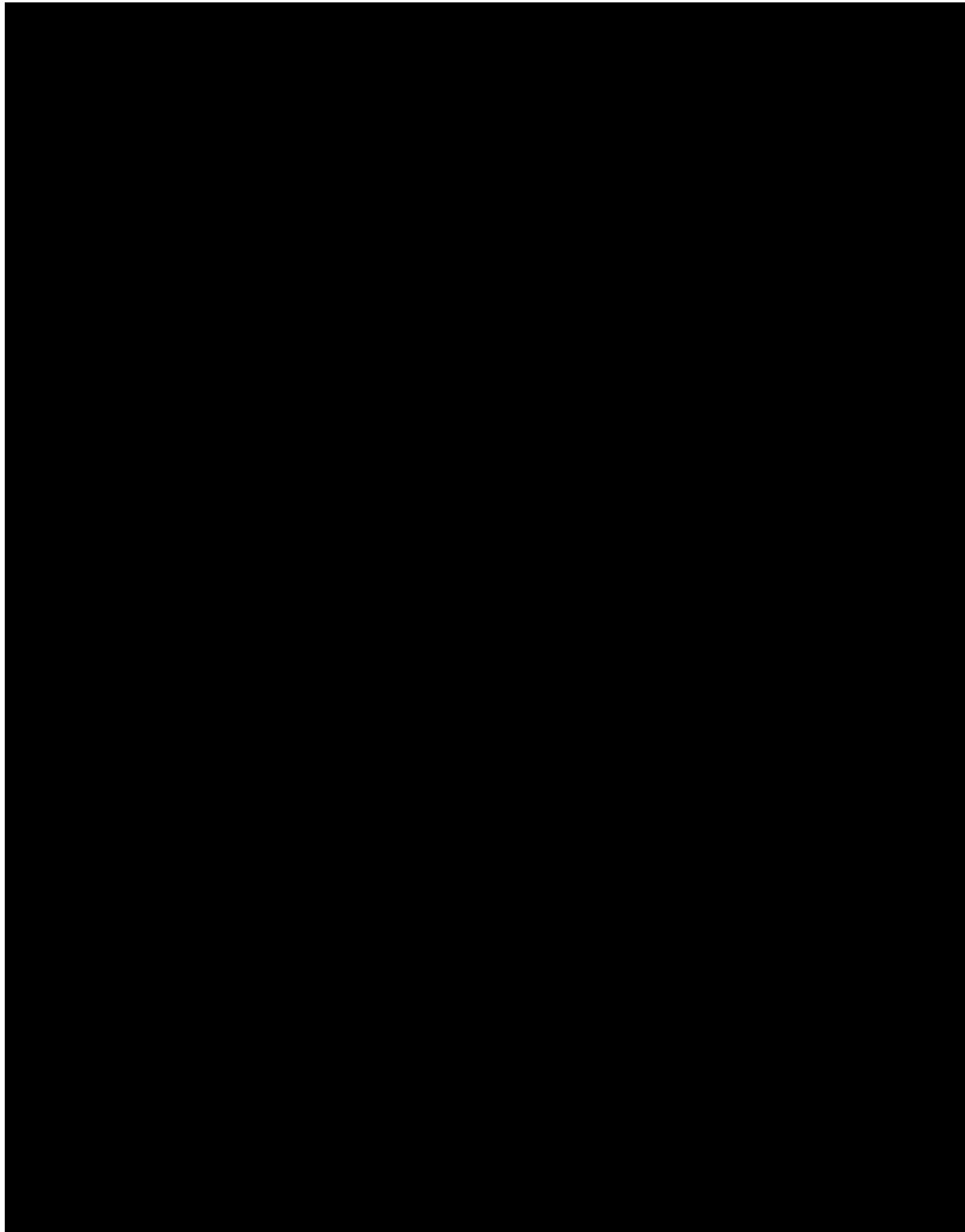
(Sample provided in this appendix is for reference only.)

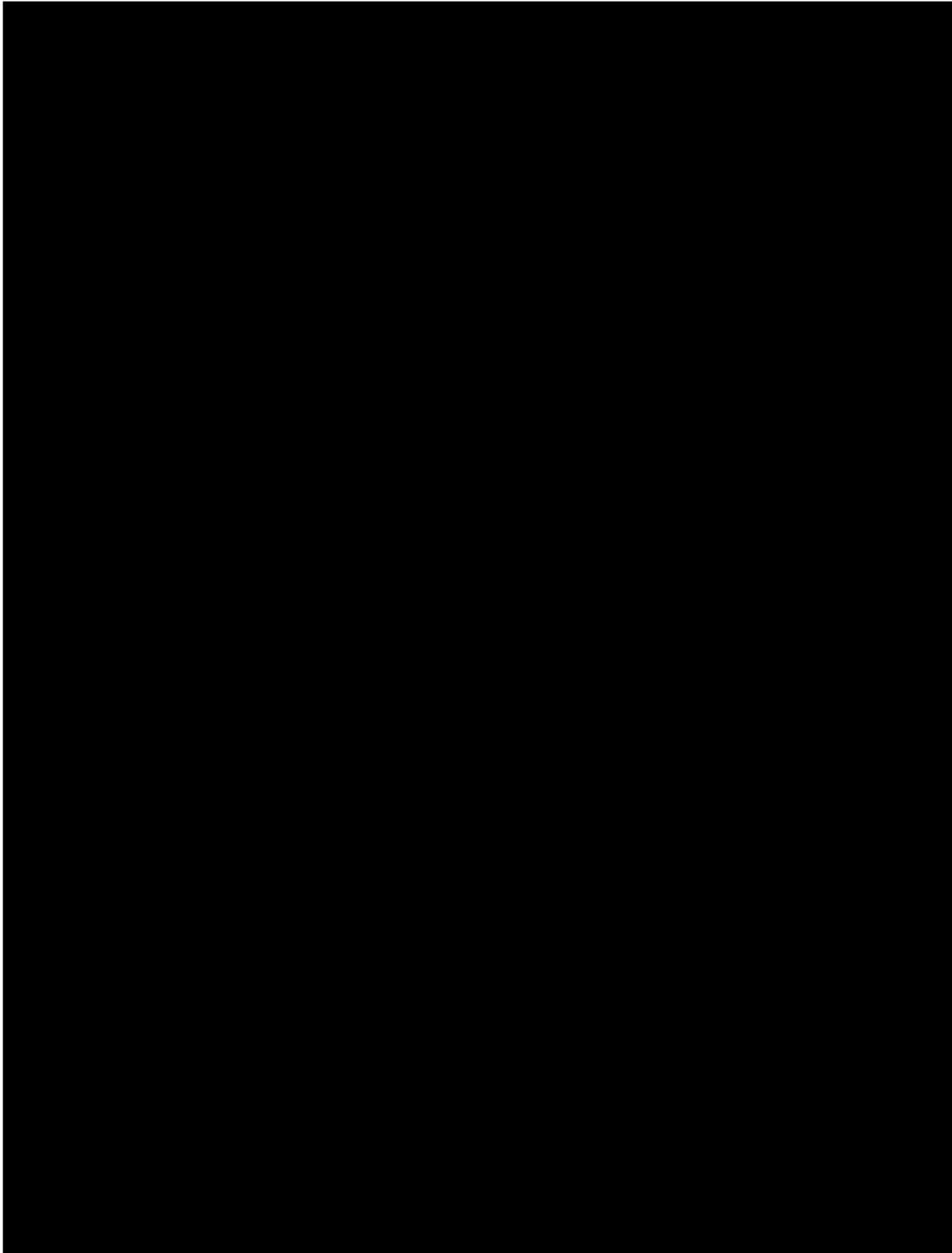












APPENDIX H. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

- a. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
 - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
 - Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
- b. 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 (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
 - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
- c. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
 - Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
 - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Source: Modified from Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, 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 [reprint in *Ann Emerg Med* 2006;47(4):373-80; PMID: 16546624]. *J Allergy Clin Immunol* 2006;117(2):391-7.

APPENDIX I. OPPORTUNISTIC INFECTIONS

Potential opportunistic infections include, but are not limited to, the following:

- Acinetobacter infection
- Aspergillosis
- Blastomycosis, extrapulmonary
- Burkitt's lymphoma
- Candidiasis of esophagus, bronchi, trachea, or lungs
- Cervical cancer invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis infection, chronic intestinal (>1 month duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Hepatitis B and C
- Herpes simplex bronchitis, pneumonitis, or esophagitis
- Herpes simplex ulcers chronic (>1 month)
- Herpes zoster (Shingles) when 2 distinct episodes or more than 1 dermatome
- Histoplasmosis disseminated or extrapulmonary
- Human polyomavirus infection
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Listeriosis
- Lymphoid interstitial pneumonia
- Lymphoma immunoblastic
- Lymphoma primary of brain
- Mycobacterium avium complex or *M. kansasii*, disseminated or extrapulmonary Mycobacterium infections, other species or unidentified species, disseminated or extrapulmonary (eg, *M. haemophilium*, *M. fortuitum*, or *M. marinum*)
- Mycobacterium tuberculosis, any site, latent or active
- Nocardiosis
- Pneumocystis jiroveci infection
- Pneumonia, recurrent

- Polyomavirus (JC virus or BK virus)-associated nephropathy (including progressive multifocal leukoencephalopathy)
- Salmonella sepsis
- Salmonella septicemia, recurrent
- Shingles
- Toxoplasmosis of brain
- Any active tuberculosis
- Wasting secondary to human immunodeficiency virus (HIV)

Source: Modified from the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Disease Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.