Clinical Study Protocol with Amendment 04

A 52-Week Double-Blind, Placebo-Controlled, Parallel-Group Efficacy and Safety Study of Reslizumab 110 mg Fixed, Subcutaneous Dosing in Patients with Uncontrolled Asthma and Elevated Blood Eosinophils

Study Number C38072-AS-30025

NCT02452190

Protocol with Amendment 04 Approval Date: 24 October 2016

Clinical Study Protocol with Amendment 04

Study Number C38072-AS-30025

A 52-Week Double-Blind, Placebo-Controlled, Parallel-Group Efficacy and Safety Study of Reslizumab 110 mg Fixed, Subcutaneous Dosing in Patients with Uncontrolled Asthma and Elevated Blood Eosinophils

Phase 3

IND number: 101,399 EudraCT number: 2015-000865-29

Protocol Approval Date: 24 October 2016

Sponsor	Monitor
Teva Branded Pharmaceutical Products R&D, Inc. 41 Moores Road Frazer, Pennsylvania 19355 United States	[redacted]

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 Code of Federal Regulations (CFR) and European Union 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.

AMENDMENT HISTORY

The protocol for Study C38072-AS-30025 (original protocol dated 26 March 2015) has been amended and reissued as follows:

Amendment 04	24 October 2016 468 patients enrolled to date
Amendment 03	25 July 2016 368 patients enrolled to date
Administrative Letter: Reiteration of eosinophil count	21 March 2016 85 patients enrolled to date
Administrative Letter: Change in Medical Monitor	08 March 2016 67 patients enrolled to date
Administrative Letter: Change in Sponsor's Medical Expert	26 February 2016 57 patients enrolled to date
Amendment 02	25 January 2016 24 patients enrolled to date
Administrative Letter: Contraception Use	22 July 2015 0 patients enrolled to date
Amendment 01	04 May 2015 0 patients enrolled to date
Addendum Letter: Change in estimated total blood volume taken	22 April 2015 0 patients enrolled to date
Administrative Letter : Change in Central Spirometry and ECG Vendor	14 April 2015 0 patients enrolled to date

INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 04

Original Protocol Dated 26 March 2015

IND Number: 101,399; EudraCT Number: 2015-000865-29

A 52-Week Double-Blind, Placebo-Controlled, Parallel-Group Efficacy and Safety Study of Reslizumab 110 mg Fixed, Subcutaneous Dosing in Patients with Uncontrolled Asthma and Elevated Blood Eosinophils

Phase 3

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol C38072-AS-30025 with Amendment 04 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	[redacted]	Date
[redacted]		Oct 24, 2016

COORDINATING INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 04

Original Protocol Dated 26 March 2015

IND Number: 101,399; EudraCT Number: 2015-000865-29

A 52-Week Double-Blind, Placebo-Controlled, Parallel-Group Efficacy and Safety Study of Reslizumab 110 mg Fixed, Subcutaneous Dosing in Patients with Uncontrolled Asthma and Elevated Blood Eosinophils

Phase 3

I have read the protocol C38072-AS-30025 with Amendment 04 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 and 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.

Coordinating Investigator: [redacted]

Title: [redacted]

Address of Investigational Center: [redacted]

Coordinating Investigator [redacted]	[redacted]	10/25/16

CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS

Central Institutional Review Board

[redacted]

Central Clinical Laboratory

[redacted]

Electronic Data Capture

[redacted]

Web and Phone Integrated Interactive Response Technology

[redacted]

Bioanalytical Pharmacokinetics Evaluation
Teva Pharmaceuticals
Global Bioassay and Technology
West Chester, PA 19380

Bioanalytical Immunogenicity Evaluation
Teva Pharmaceuticals
Global Bioassay and Technology
West Chester, PA 19380

Exploratory Asthma Biomarker Evaluation
Teva Pharmaceuticals
Global Bioassay and Technology
West Chester, PA 19380

Central Spirometry, e-diary and ECG
[redacted]

Spirometry and e-diary:
[redacted]

ECG:
[redacted]

CLINICAL STUDY PERSONNEL CONTACT INFORMATION

For medical issues, contact the physician listed below:

Oversight Lead Medical Monitor:

[redacted]

For centers in North America

[redacted]

For Centers in Latin America

[redacted]

For centers in Europe and countries outside the Americas

EMEA: [redacted]

APAC: [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 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-30025

Title of Study: A 52-Week Double-Blind, Placebo-Controlled, Parallel-Group Efficacy and Safety Study of Reslizumab 110 mg Fixed, Subcutaneous Dosing in Patients with Uncontrolled Asthma and Elevated Blood Eosinophils

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc

IND Number: 101,399 **EudraCT Number:** 2015-000865-29

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: ~275

Countries Planned: ~30

Planned Study Period: Q3 2015 to Q3 2017

Number of Patients Planned: Approximately 225 patients per treatment group for a total of 450 patients.

Study Population: Asthma patients 12 years of age and older (Patients 12 to <18 years of age are excluded from participating in South Korea 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 effect of reslizumab (110 mg) administered subcutaneously every 4 weeks on clinical asthma exacerbations (CAEs) in adults and adolescents with asthma and elevated blood eosinophils who are inadequately controlled on standard-of-care asthma therapy.

Secondary Objectives: Secondary efficacy objectives are to evaluate the effects of reslizumab compared with placebo on a range of clinical markers of asthma control including pulmonary function (forced expiratory volume in 1 second [FEV_1]).

Other Objectives: Other objectives of this study are to evaluate the safety, pharmacokinetics (PK), pharmacodynamics, and immunogenicity of reslizumab.

Study Endpoints:

Primary Efficacy Endpoint:

The primary efficacy endpoint is the frequency of CAEs per patient during the 52-week treatment period.

For this study, 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 (oral or injection) or at least a doubling from a stable maintenance oral corticosteroid 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.

Secondary Efficacy Endpoints:

The secondary efficacy endpoints are as follows:

- change in pre-bronchodilator FEV_1 from baseline/the day of randomization (DoR) at week 52

- change in Asthma Quality of Life Questionnaire for patients 12 years and older (AQLQ +12) score from baseline/DoR at week 52
- change in 6-item Asthma Control Questionnaire (ACQ-6) score from baseline/DoR at week 52
- change in total asthma symptom scores (day and night) from baseline at week 52
- percentage of asthma control days from baseline/DoR to week 52
- change in St. George's Respiratory Questionnaire (SGRQ) score from baseline/DoR at week 32
- time to first CAE during the 52-week treatment period
- frequency of exacerbations requiring hospitalization or emergency department visits per patient during the 52-week treatment period
- frequency of moderate exacerbations defined as exacerbations requiring additional asthma controller medication that was not a systemic corticosteroid and that did not result in an asthma-specific hospitalization or emergency department visit during the 52-week treatment period

Target Biomarker Endpoints: The target biomarker endpoints are the blood eosinophil counts at baseline/DoR; weeks 2, 4, 8, 12, 16, 32, 52 or early withdrawal; and the follow-up visit (approximately week 64).

Immunogenicity Endpoints: Samples for immunogenicity assessment for development of anti-drug antibodies will be obtained before the administration of study drug at DoR; weeks 4, 16, 32, 52 or early withdrawal; and the follow-up visit (approximately week 64). An additional sample will be obtained at the late follow-up visit (approximately week 76).

Pharmacokinetic Endpoints: The PK endpoints are the serum reslizumab concentrations at baseline/DoR; weeks 1 (patients in US study centers only), 2, and prior to study drug administration at weeks 4, 8, 12, 16, 20, 32, 48, 52 or early withdrawal; and the follow-up visit (approximately week 64). An additional PK sample will be taken at long term follow-up (approximately week 76) at the same time for anti-drug antibody (ADA) sample collection. (These data may be presented in a clinical study report addendum.)

[redacted]

Safety Endpoints

The safety endpoints for this study are as follows:

- adverse events throughout the study
- vital signs (pulse, respiratory rate, and blood pressure) throughout the study
- concomitant medication usage throughout the study
- physical examination findings throughout the study
- clinical laboratory evaluations at screening, baseline/DoR, and periodically throughout the study
- electrocardiogram (ECG) evaluation at screening and week 24, 36, and 52 or early withdrawal

General Design and Methodology: This is a 52-week, Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of reslizumab, at a fixed dose of 110 mg, administered subcutaneously every 4 weeks in patients aged 12 years and older with asthma and elevated blood eosinophils, who are inadequately controlled on at least a medium total daily ICS dose and a second asthma controller. Evidence of inadequate asthma control will include a history of at least 2 exacerbations requiring systemic corticosteroids (oral or injection) in the previous 12 months, a suboptimal screening ACQ score (≥1.5), and persistent symptoms during run-in on the patient's usual asthma controller regimen. The study's duration is approximately 69 weeks, including up to a 2-week (±3 days) screening period, a minimum 3-week run-in period, a 52-week treatment period. If the patient enrolls in an available open-label, long-term safety study, then adults (age 18 years and older) may wait to complete the early and late follow-up visits until the end of the open-label study; however, adolescents (ages 12 to <18 years) should complete the early follow-up visit at 12 weeks as part of this current study before starting an open-label study.

At the start of run-in, patients will begin daily self-monitoring at home using an asthma control diary and PEF meter, while taking their usual asthma medications, in order to establish their baseline level of asthma control based on the frequency of symptoms, use of reliever SABA, nighttime awakenings due to asthma, and ambulatory lung function measurement. Improvement in asthma control during the treatment period will primarily be assessed by a reduction in the rate of clinically significant asthma exacerbations with reslizumab versus placebo during the 52-week treatment period. Pulmonary function; AQLQ +12, ACQ, and SGRQ scores; asthma symptoms; use of reliever SABA; nighttime awakenings due to asthma; safety measures; PK; immunogenicity; and health care utilization events will be assessed periodically; final assessments will be made at the end of treatment visit (week 52) or at early withdrawal. Patients who withdraw from the study before completing the 52-week evaluation period will have visit-17 (week 52 or early withdrawal) procedures and assessments performed at their final visit. Patients will return 12 weeks after the end of treatment visit for follow-up hematology, PK, immunogenicity, and safety assessments. 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 their withdrawal from the study drug.

Method of Blinding and Randomization: This is a randomized, double-blind, placebo-controlled study. Patients who meet all inclusion criteria and none of the exclusion criteria will be randomly assigned to receive reslizumab 110 mg subcutaneously or matching placebo (approximately 225 patients per treatment group) in a 1:1 ratio. Randomization will be stratified by age (12 to <18 and ≥18 years), and blood eosinophil levels at screening (300/µL to <400/µL and ≥400/µL). Patients will be randomly assigned to the treatment groups by means of a computer-generated randomization list using interactive response technology after confirmation of all eligibility criteria. The sponsor's clinical personnel involved in the study will be blinded to the study drug identity until the database is locked for analysis and the treatment assignment is revealed, with the exception of the bioanalytical group, who will not be blinded to facilitate PK and ADA sample analysis. Eosinophils and monocytes will be redacted from the post-baseline differential cell count reports to avoid the possibility of unblinding patients. Both reslizumab and placebo will be provided as clear solutions essentially free of particulate matter.

Study Drug Dose, Mode of Administration, and Administration Rate: Reslizumab for subcutaneous injection 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. Reslizumab will be administered subcutaneously in a dose of 110 mg (1.0 mL) every 4 weeks.

Investigational Product: Reslizumab

Reference Therapy:

Placebo: Diluent solution administered subcutaneously

Comparison Drug: None

Duration of Patient Participation: Approximately 69 weeks, including up to a 2-week (±3 days) screening period, minimum 3-week run-in period, 52-week treatment period, and 12-week follow-up visit. An additional, late follow-up for immunogenicity testing will be performed 28 weeks (±2 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. Written informed consent is obtained. A patient 12 through <18 years of age must provide assent, and their parent(s) or legal guardian(s) must provide consent.

b. The patient is male or female, 12 years of age and older, with a diagnosis of asthma. (Patients 12 to <18 years of age are excluded from participating in South Korea and Argentina, and patients 66 years of age and older are excluded from participating in South Korea.)

c. The patient has had at least 2 documented asthma exacerbations requiring the use of systemic (oral, intramuscular, or intravenous) corticosteroids within 12 months of signing the Informed Assent Form/Informed Consent Form.

d. The patient has an ACQ-6 score of at least 1.5 at screening (visit 1).

e. The patient has a blood eosinophil level of at least 300/μL during the screening period (ie, before visit 2). (A maximum of 30% of the patients [60 patients per treatment group] with blood eosinophil levels of 300/μL to <400/μL will be enrolled. When this 30% threshold has been reached, only patients with blood eosinophil levels of ≥400/μL will then be enrolled.)

f. The patient has an FEV_1 reversibility of at least 12% after administration of inhaled SABA according to standard American Thoracic Society (ATS) or European Respiratory Society (ERS) protocol. Documented historical reversibility within 12 months of signing the Informed Assent Form/Informed Consent Form is acceptable.

g. The patient has required at least a medium total daily inhaled corticosteroid (ICS) dose based on Global Initiative for Asthma 2016 clinical comparability table (Protocol Appendix A) for at least 3 months. For ICS/LABA combination preparations, the mid-strength approved maintenance dose in the local country will meet this ICS criterion.

h. The patient has required an additional asthma controller medication (eg, long-acting beta-2-agonist [LABA], long-acting muscarinic antagonist [LAMA], leukotriene receptor antagonist [LTRA], or theophylline preparations), besides inhaled corticosteroids, for at least 3 months or a documented failure in the past 12 months of an additional asthma controller medication for at least 3 successive months.

i. 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. Contraception is further clarified in an administrative letter in Protocol Section 17.4.1.

j. The patient must be willing and able to comply with study restrictions, perform requisite procedures and remain at the clinic for the required duration during the study period, and be willing to return to the clinic for the follow-up evaluation as specified in this protocol.

k. The patient must maintain their usual asthma controller regimen without change throughout the screening and run-in periods. A patient who experiences an asthma exacerbation during this time that requires additional medication, beyond increased SABA use, will be considered to have failed screening/run-in and cannot undergo randomization. A patient may be rescreened for this reason 1 time only. The duration between the date of Screen Failure and the re-screening must be >30 days.

l. In order to be randomized, a patient must demonstrate the following:
   - inadequate asthma control at baseline/DoR as evidenced by:
     - daytime asthma symptom score >0 on >2 of the previous 7 days based on the asthma control diary received at run-in OR
     - need for reliever SABA use on >2 of the previous 7 days OR
     - ≥1 nighttime awakening due to asthma over the previous 7 days OR
     - pre-bronchodilator FEV_1 <80% predicted at baseline/DoR
     - AND
   - completion of at least 4 days of diary entries or equivalent during the last 7 days of run-in. A patient may be rescreened for this reason 1 time only.

   Please refer to Protocol Section 3.16.1 and Section 3.16.2 for further guidance on rescreening if the above inclusion criteria are not met initially. The eosinophil count and reversibility test may each be repeated once during the Screening period, and subjects may also be rescreened for either of these reasons. The duration between the date of Screen Failure and the re-screening must be >30 days.

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, interpretation of efficacy results, or 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 [EGPA, also known as Churg-Strauss syndrome], or allergic bronchopulmonary aspergillosis [ABPA]).

c. The patient has a known hypereosinophilic syndrome.

d. The patient has a diagnosis of malignancy within 5 years of the screening visit, except for treated and cured non-melanoma skin cancers.

e. The patient is a pregnant or lactating woman, or intends to become pregnant during the study or within 5 months after the last dose of study drug. 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 or during the screening/run-in period.

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 or other monoclonal antibody [eg, mepolizumab] or soluble receptors) or non-biologic (eg, methotrexate or cyclosporine), except maintenance oral

corticosteroids for the treatment of asthma (up to and including 10 mg of prednisone daily or equivalent). Note: Previous use of such agents that occurred >5 half-lives from the initial screening visit may be allowed, if approved by the medical monitor.

i. The patient participated in a clinical trial 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 an immunodeficiency disorder including HIV.

m. The patient has current or suspected drug and alcohol abuse.

n. The patient has an active helminthic parasitic infection or was treated for one within 6 months of screening.

o. The patient has a history of allergic reaction 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.)

Measures and Time Points:

Primary Efficacy Measure and Time Point: The primary efficacy measure for this study is frequency of CAEs for each patient during the 52-week treatment period.

Secondary Efficacy Measures and Time Points: The secondary efficacy measures and their time points for this study include the following:

- pre-bronchodilator spirometry (at baseline/DoR and week 52 or early withdrawal)
- AQLQ +12 at baseline/DoR and week 52 or early withdrawal
- ACQ-6 at baseline/DoR and week 52 or early withdrawal
- asthma symptoms based on the daily asthma control diary at baseline and week 52 or early withdrawal
- asthma control days from baseline/DoR to week 52 or early withdrawal
- SGRQ at baseline/DoR and week 32

Safety Measures and Time Points: The following safety measures will be implemented throughout the study and evaluated at the following time points:

- inquiries about adverse events at every visit including screening, run-in, and follow-up
- clinical laboratory tests (serum chemistry at screening; baseline/DoR; and weeks 16, 32, and 52 or early withdrawal and hematology at screening; baseline/DoR; weeks 2, 4, 8, 12, 16, 32, 52 or early withdrawal; and follow-up (approximately week 64) (a sample for CPK measurement only, will also be collected on weeks 1, 2, 4, 8, 12, and 20).
- vital signs (respiratory rate, blood pressure, and pulse) at screening, run-in; baseline/DoR; and weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 or early withdrawal
- ECGs at screening and weeks 24, 36, and 52 or early withdrawal
- physical examinations, including body weight measurements. These will include both full physical examinations including height and weight (at screening and week 52 or early withdrawal) and brief physical examinations (at baseline/DoR and weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48).
- inquiries about concomitant medication usage at every visit including screening, run-in, and follow-up

Pharmacokinetics/Biomarkers/ Immunogenicity and Other Ancillary Studies Measures and Time Points:

Pharmacokinetics: Pharmacokinetic samples at baseline/DoR; weeks 1 (patients in US study centers only), 2, prior to study drug administration at weeks 4, 8, 12, 16, 20, 32, 48, and 52 or early withdrawal; and follow-up (approximately week 64). An additional PK sample will be taken at long term follow-up (approximately week 76) at the same time for ADA sample collection.

Target biomarkers: Blood eosinophils will be determined from blood samples at specified time points.

Immunogenicity: Serum anti-reslizumab antibodies will be determined from blood samples collected from each patient at baseline/DoR; prior to study drug administration at weeks 4, 16, 32, and 52 or early withdrawal; and follow-up (approximately week 64). An additional sample will be collected at late follow-up (approximately week 76).

Allowed and Disallowed Medications Before and During the Study: The following medications will not be allowed during this study: any immunosuppressive or immunomodulatory agents (excluding systemic corticosteroids prescribed for asthma and maintenance allergen immunotherapy), all biologic therapies, and all nonbiologic investigational drugs.

Statistical Considerations:

Sample Size Rationale:

Power calculations were based on the below assumptions:

- Negative binomial (NB) distribution for the number of exacerbations with a mean of 2.9 exacerbations per patient per year for the placebo group
- Dispersion parameter of 1.2
- Treatment effect of 45% between the reslizumab group and the placebo group
- Alpha level of 0.05

Based on the assumptions above, 225 patients per arm (450 total) will provide >99% power to detect significant treatment effect of reslizumab over placebo in the reduction of exacerbation rate. The sample size was increased beyond the minimal sample size required to provide 90% power in order to allow sufficient number of patients to assess safety and immunogenicity and to ensure adequate enrollment in the adolescent subset. The current sample size also provide higher power for other efficacy endpoints.

Analysis of Primary Endpoint: The primary analysis of frequency of CAEs will use the NB regression model. The primary NB model will include the treatment group, randomization stratification factors, and number of exacerbations in the previous year 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.

Data from all randomized patients will be used in the primary analyses regardless of whether they early withdrew from treatment or completed the treatment phase.

Analysis of Secondary Endpoints: Analysis of pulmonary function tests, AQLQ +12, ACQ-6, total asthma symptom scores, and SGRQ will use the mixed model repeated measures model with treatment group, visit,

treatment and visit interaction, baseline value, and stratification factors as fixed effects and patient as a random effect. Analysis of percentage of asthma control days will use an analysis of variance (ANOVA) model with treatment group and stratification factors.

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

The Kaplan-Meier (KM) method will be used to estimate and compare the distributions of time to first CAEs between treatment groups. Differences will be compared using a log rank test adjusting for the stratification factors. The frequency of exacerbations requiring hospitalization or emergency department visits and the frequency of moderate exacerbations will be examined separately. The analysis will use similar methodology to that described for the primary analysis.

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 two-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 until either all comparisons of interest are interpreted inferentially, or until the point at which the resulting two-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.

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

Analysis of Other Endpoints: All efficacy variables will be summarized by treatment group. For continuous variables, the summary statistics will include n, mean, SD, standard error (SE), median, minimum, and maximum. For categorical variables, counts and percentages will be provided. Categories for missing data will be presented if necessary.

[redacted] Reslizumab concentration data will be summarized by treatment group, and blood eosinophil count data will be listed by treatment group. An attempt will be made to correlate serum concentrations of reslizumab with measures of efficacy and/or safety. Anti-reslizumab antibody information will be described for subjects who test positive.

The baseline for diary variables will be the average of the run-in values over the 7 days preceding baseline/DoR. The baseline for clinic visit variables will be the last observed value before the first dose of study drug. The baseline for eosinophils levels analysis will be screening value.

Safety Analyses: Safety and PK data will be summarized using descriptive statistics by treatment group.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table of Abbreviations

Abbreviation	Term
ACQ	Asthma Control Questionnaire
ACQ-6	6-item Asthma Control Questionnaire
ADA	anti-drug antibody
ADR	adverse drug reaction
AQLQ +12	Asthma Quality of Life Questionnaire for patients 12 years and older
ANOVA	analysis of variance
AUC	area under the plasma drug concentration by time curve
$AUC_{0-\infty}$	area under the plasma drug concentration by time curve from time 0 to infinity
AUC_{0-t}	area under the plasma drug concentration by time curve from time 0 to the time of the last measurable drug concentration
BUN	blood urea nitrogen
CAE	clinical asthma exacerbation
CDMS	clinical data management system
CFR	Code of Federal Regulations
CPK	creatine phosphokinase
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
DoR	day of randomization
ECG	electrocardiogram
eDiary	electronic diary
EOT	end-of-treatment (visit)
[redacted]	
$FEF_{25\%-75\%}$	forced expiratory flow at the 25% point to the 75% point of forced vital capacity
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroids

Abbreviation	Term
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-5	Interleukin-5
IP	Investigational product
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
iv	intravenous
KM	Kaplan-Meier
LSLV	Last Subject Last Visit
LSO	local safety officer
mAb	monoclonal antibody
n	number
NB	negative binomial
PEF	peak expiratory flow
PK	pharmacokinetic(s)
SABA	short-acting beta-agonist
sc	subcutaneous
SD	standard deviation
SGRQ	St. George's Respiratory Questionnaire
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
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 334 million people in the world have asthma (Global Asthma Network 2014).

Asthma is a heterogeneous syndrome with distinct phenotypes and variable severity. Certain patients are prone to experiencing asthma exacerbations defined as an acute or sub-acute worsening in symptoms and lung function from the patient's usual status (Global Initiative for Asthma [GINA] 2014) in patients who are unable to achieve control despite chronic use of inhaled corticosteroids (ICS) and other asthma medications. These patients are considered at high risk because of the morbidity and potential mortality associated with exacerbations. During acute asthma exacerbations, patients often require additional therapy, such as a course of systemic corticosteroids, which have substantial adverse effects (Walsh LJ et al 2001, Wardlaw et al 2000).

Interleukin-5 (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 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; preliminary results are notable for a significant reduction in clinical asthma exacerbations (CAEs) as well as improved lung function.

1.2. Name and Description of Investigational Product

Reslizumab (CEP 38072) is a humanized anti-human IL-5 mAb of the IgG4/κ isotype. Reslizumab is 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 hyper-reactivity was suggested by studies in IL-5 gene knockout mice (Foster et al 1996). When sensitized and challenged with allergen, 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 hyper-responsiveness 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. Reslizumab's effects 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 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 no-observed-effect level of at least 25 mg/kg. The no-observed-effect level 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.

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 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.

1.3.2. Clinical Studies

1.3.2.1. Clinical Pharmacology 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.

Systemic exposure to reslizumab increases in a dose-proportional manner over the range of 0.03 to 3.0 mg/kg in patients with asthma and from 1.0 to 3.0 mg/kg in patients with nasal polyps. Serum concentration declines from peak in a biphasic manner with a mean elimination half-life ranging from 23 to 30 days. The volume of distribution for reslizumab is low (approximately 4 to 6 L), suggesting minimal distribution of reslizumab into extravascular tissues. Following a single 220 mg sc dose of reslizumab in adults, the bioavailability of reslizumab is approximately 67%, similar to other mAbs. Peak serum reslizumab concentrations are typically observed approximately 7 days after sc administration (range 12 hours to 20 days). As expected, the terminal 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 elimination half-life (approximately 26 days).

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

1.3.2.2. Clinical Safety and Efficacy Studies

The Phase 3 BREATH program in adult and adolescent asthma evaluated the safety and efficacy of reslizumab administered intravenously every 4 weeks at 3 mg/kg (16-week Studies C38072/3081 and C38072/3084, 52-week 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 ASUI) were observed for patients with eosinophilic asthma defined by a screening blood eosinophil count of ≥400/μL (Studies 3081, 3082, and 3083). In asthma patients without elevated blood eosinophils (Study 3084), reslizumab produced non-significant improvements in lung function and other measures of efficacy. In contrast in patients with blood eosinophil levels ≥400/μL, 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 Investigator's Brochure. 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 event 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 with 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: one 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 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

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 non-melanoma 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 a physiological jaundice. One pregnancy case was lost to follow-up, and the outcome is unknown.

Immunogenicity

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). 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 Investigator's Brochure.

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 as 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-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 FEV_1, and a medically meaningful decreased rate of CAEs with reslizumab.

1.4.3. Overall Risk and Benefit Assessment for This Study

Improvement in lung function has been confirmed in 3 Phase 3 clinical trials with the iv dosage form. In addition to improved lung function, 2 Phase 3 clinical trials demonstrated a significant reduction in CAEs over 52 weeks in patients with moderate to severe asthma and elevated blood eosinophils.

In completed studies, reslizumab was generally well-tolerated over the dosage range 0.03 to 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 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.

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

A detailed description of study drug administration is presented in Section 5.1.

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 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]). Please refer to the Investigator's Brochure for summary and comprehensive presentation of these data. Briefly, treatment with reslizumab 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) were slight. Improvements for patients in the reslizumab 0.3 mg/kg treatment group for FEV_1 were 0.129 L at week 16 (p=0.0481), but other efficacy endpoint results were more variable (eg, no treatment effect on FVC and $FEF_{25\%-75\%}$ was observed for patients in the reslizumab 0.3 mg/kg treatment group). Therefore, doses of ≥1 mg/kg are anticipated to be clinically effective in most patients. Based on these clinical and eosinophil pharmacodynamic data, Teva has chosen reslizumab 110 mg administered 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%, as determined by Study 1107). 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 FEV_1 in patients with eosinophilic asthma. Therefore, a fixed dose of 110 mg sc 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 [21CFR] Parts 11, 50, 54, 56, 312, and 314, European Union Directive 2001/20/EC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use). 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 in the country where each investigational center is located.

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 and requirements of the study and with the properties of the study drug(s) as described in the Investigator's Brochure 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

The study will enroll male and female patients, 12 years of age and older, with asthma and elevated blood eosinophils who are inadequately controlled on at least a medium total daily ICS dose and a second asthma controller. (Patients 12 to <18 years of age are excluded from participating in South Korea and Argentina, and patients 66 years of age and older are excluded from participating in South Korea.) Adolescents are included in this study because they follow the same treatment recommendations as adults according to widely cited asthma guidelines (GINA 2014, ERP-3 2007). Elevated blood eosinophils have been associated with poor asthma control and increased risk of exacerbation (Tran et al 2014, Zeiger et al 2014).

1.8. Location and Timing of Study

This study is planned to be conducted in approximately 30 countries at approximately 275 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 uncontrolled asthma and elevated blood eosinophils.

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective of this study is to determine the effect of reslizumab (110 mg) administered sc every 4 weeks on CAEs in adults and adolescents with asthma and elevated blood eosinophils who are inadequately controlled on standard-of-care asthma therapy.

2.2.2. Secondary Objectives

Secondary efficacy objectives are to evaluate the effects of reslizumab compared with placebo on a range of clinical markers of asthma control including pulmonary function (forced expiratory volume in 1 second [FEV_1]).

2.2.3. Other Objectives

Other objectives of this study are to evaluate the safety, PK, PD, and immunogenicity of reslizumab.

2.3. Study Endpoints

2.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the frequency of CAEs per patient during the 52-week treatment period. Refer to Section 6.1 for additional details regarding the definition of CAE.

2.3.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- change in pre-bronchodilator FEV_1 from baseline/the day of randomization (DoR) at week 52
- change in Asthma Quality of Life Questionnaire for patients 12 years and older (AQLQ +12) score from baseline/DoR at week 52
- change in 6-item Asthma Control Questionnaire (ACQ-6) score from baseline/DoR at week 52
- change in total asthma symptom scores (day and night) from baseline at week 52
- percentage of asthma control days from baseline/DoR to week 52
- change in St. George's Respiratory Questionnaire (SGRQ) from baseline/DoR at week 32

- time to first CAE during the 52-week treatment period
- frequency of exacerbations requiring hospitalization or emergency department visits per patient during the 52-week treatment period
- frequency of moderate exacerbations defined as exacerbations requiring additional asthma controller medication that was not a systemic corticosteroid and that did not result in an asthma-specific hospitalization or emergency department visit during the 52-week treatment period

2.3.4. Target Biomarker Endpoints

The target biomarker endpoints are the blood eosinophil counts at baseline/DoR; weeks 2, 4, 8, 12, 16, 32, 52 or early withdrawal; and the follow-up visit (approximately week 64).

2.3.5. Immunogenicity Endpoints

Samples for immunogenicity assessment for development of anti-drug antibodies will be obtained before the administration of study drug at DoR; prior to study drug administration at weeks 4, 16, 32, 52 or early withdrawal; and the follow-up visit (approximately week 64). Additional samples will be collected at the late follow-up visit (approximately week 76).

2.3.6. Pharmacokinetic Endpoints

The PK endpoints are the serum reslizumab concentrations at baseline/DoR; weeks 1 (patients in US study centers only), 2, and prior to study drug administration at weeks 4, 8, 12, 16, 20, 32, 48, 52 or early withdrawal; and the follow-up visit (approximately week 64). An additional PK sample will be taken at long term follow-up (approximately week 76) at the same time for ADA sample collection.

[redacted]

2.3.8. Safety Endpoints

The safety endpoints for this study are as follows:

- adverse events throughout the study
- vital signs (pulse, respiratory rate, and blood pressure) throughout the study
- concomitant medication usage throughout the study
- physical examination findings throughout the study
- clinical laboratory evaluations at screening, baseline/DoR, and periodically throughout the study
- ECG evaluation at screening and week 24, 36, and 52 or early withdrawal

3. STUDY DESIGN

3.1. General Design and Study Schema

This is a 52-week, Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of reslizumab, at a fixed dose of 110 mg, administered sc every 4 weeks in patients aged 12 years and older with asthma and elevated blood eosinophils, who are inadequately controlled on at least a medium total daily ICS dose and a second asthma controller.

Evidence of inadequate asthma control will include a history of at least 2 exacerbations requiring systemic corticosteroids (oral or injection) in the previous 12 months, a suboptimal screening ACQ-6 score (≥1.5), and persistent symptoms during run-in on the patient's usual asthma controller regimen. At least one of the historical exacerbations must have been previously documented in the medical or pharmacy record; additional exacerbations may have been documented in either the medical or pharmacy record, or may be documented by the study site at the time of screening history. For all exacerbations, which fulfill inclusion criterion 'c', the approximate dates of systemic corticosteroid therapy and the name of the systemic corticosteroid taken should be recorded in source documents. The study consists of a screening period of up to 2 weeks to satisfy essential screening inclusion criteria (ie, confirmation of asthma with elevated blood eosinophils), a minimum 3-week run-in period on usual care to establish the patient's baseline level of control and a 52-week double-blind treatment period. If the patient enrolls in an available open-label, long-term safety study, then adults (age 18 years and older) may wait to complete the early and late follow-up visits until the end of the open-label study; however, adolescents (ages 12 to <18 years) should complete the early follow-up visit at 12 weeks as part of this current study before starting an open-label study.

Patients will begin screening up to approximately 5 weeks (±1 week) before DoR. During the screening period, a signed and dated informed consent form (and an assent form for children ages 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 determined. If the patient's eosinophil count is 300 eosinophils/μL or greater, and if the patient's medication compliance and inhaler use technique are optimal, the patient will be eligible to continue in the study. Patient medical history, 12-lead ECG, physical examination, hematology and chemistry tests, urinalysis, vital signs measurements, beta-human chorionic gonadotropin serum pregnancy test (for all females of childbearing potential), and concomitant medication history will also be assessed at screening.

To be eligible to enroll in the study, a patient will have an ACQ-6 score of at least 1.5, airway FEV_1 reversibility of at least 12% to beta-agonist administration, blood eosinophil count of at least 300/μL, and a current fluticasone propionate dosage of at least a medium total daily ICS dose with a second asthma controller and will have met all the inclusion and none of the exclusion criteria at screening. The goal is to recruit a maximum of 30% of the patients (60 patients per treatment group) with eosinophil levels of 300/μL to <400/μL.

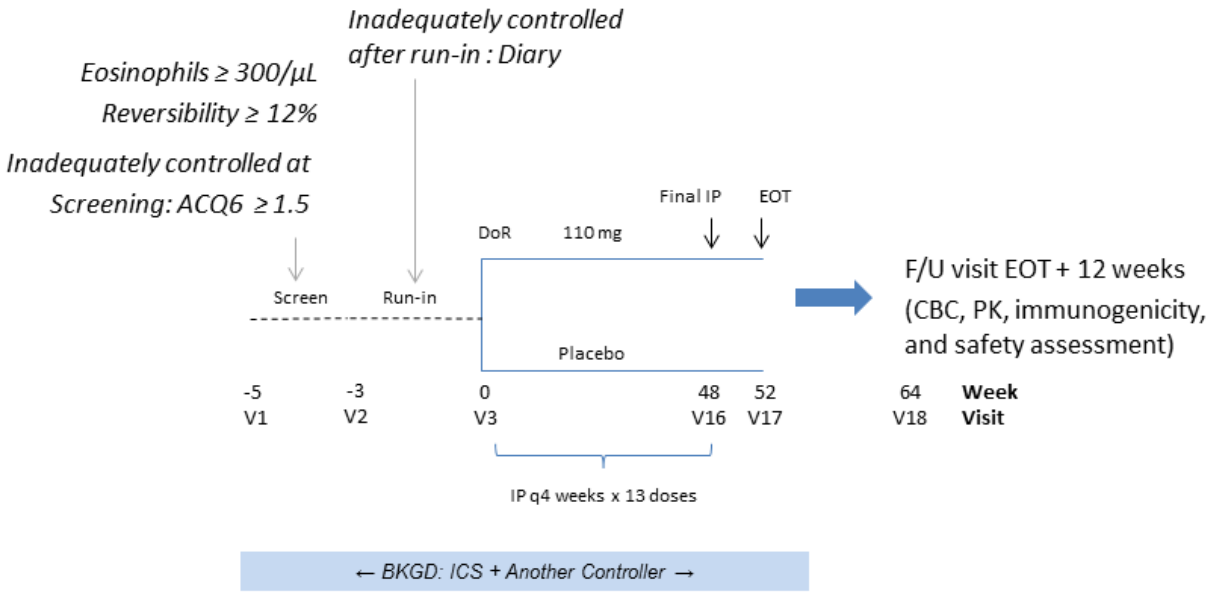
Patients who meet screening eligibility requirements will return to the research facility 3 weeks before baseline/DoR to confirm eligibility and begin the run-in period. At the start of run-in, patients will begin daily self-monitoring at home using an asthma control diary and PEF meter, while taking their usual asthma medications, in order to establish their baseline level of asthma control based on the frequency of symptoms, use of reliever SABA, nighttime awakenings due to asthma, and ambulatory lung function measurement. Improvement in asthma control during the treatment period will primarily be assessed by a reduction in the rate of clinically significant asthma exacerbations with reslizumab versus placebo over the 52-week treatment period. Pulmonary function; AQLQ +12, ACQ, and SGRQ scores; asthma symptoms; use of reliever SABA; nighttime awakenings due to asthma; safety measures; PK; immunogenicity; and health care utilization events will be assessed periodically; final assessments will be made at the EOT visit (week 52) or at early withdrawal. Patients who withdraw from the study before completing the 52-week evaluation period will have visit-17 (week 52 or early withdrawal) procedures and assessments performed at their final visit. Patients will return 12 weeks after the EOT visit for follow-up hematology, PK, immunogenicity, and safety assessments. An additional, late follow-up for immunogenicity testing will be performed 28 weeks (±2 weeks) after the last dose of study drug (ie, approximately week 76).

The assessments and procedures performed during each study visit are detailed in Table 2 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 their withdrawal from the study (see Section 4.4).

A total of 450 patients are planned to be randomized in a 1:1 ratio (approximately 225 patients within each treatment group) to receive reslizumab 110 mg or matching placebo every 4 weeks for 52 weeks.

The study schema is presented in Figure 1.

Figure 1: Overall Study Schema



*A maximum of 30% of the patients (60 patients per treatment group) with blood eosinophil levels of 300/µL to <400/µL will be enrolled. When this 30% threshold has been reached, only patients with blood eosinophil levels of ≥400/µL will then be enrolled.
Note: An additional, late follow-up for immunogenicity testing will be performed 28 weeks (±2 weeks) after the last dose of study drug (ie, approximately week 76).
ACQ6 = 6-item Asthma Control Questionnaire; BKGD = background; CBC = complete blood count; DoR = day of randomization; EOT = end of treatment; F/U = follow up; ICS = inhaled corticosteroid; IP = investigational product; PK = pharmacokinetic; q4 weeks = once every 4 weeks; V = visit.

3.2. Justification for Study Design

The rationale for the design of the study is summarized in Table 1.

Table 1: Rationale for Protocol

Area	Rationale
Study population	Representative of the uncontrolled asthma population with elevated blood eosinophils and history of exacerbations
Investigational product dosage regimen and duration of treatment	Subcutaneous dose and regimen are based on data and modeling from the BREATH intravenous program; fixed subcutaneous dosage form more convenient for patients
Choice of comparison drug(s) (placebo, active)	Placebo control is essential to establish efficacy
Number of patients (including number per treatment group)	Number of patients was based on power considerations and exacerbation data from BREATH Studies 3082 and 3083
Treatment blinding (ie, rationale for blinded or open-label design)	Double-blinding and randomized treatment allocation to prevent bias in pivotal efficacy trial

Area	Rationale
Primary analysis (measure, variable, time point, statistical test)	Reduction in the rate of asthma exacerbations is important to patients, health care professionals, and payers and constitutes the essential claim
Inclusion of ancillary studies: pharmacokinetics, target biomarker/pharmacodynamics, pharmacogenomics, and immunogenicity	• Pharmacokinetics and target blood eosinophil pharmacodynamics are important for correlating with efficacy results, and will provide a basis for future pediatric dosing. • [redacted]. • Immunogenicity assessments are essential to understanding the safety and efficacy of reslizumab.
Safety Assessments	Standard measures consistent with intravenous reslizumab studies in eosinophilic esophagitis and eosinophilic asthma

3.3. Primary and Secondary Efficacy Measures and Time Points

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

3.3.1. Primary Efficacy Measure and Time Points

The primary efficacy measure for this study is CAEs, which will be evaluated at the time points indicated in Table 2. 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. A diary alert, based on a sustained fall in peak flow from baseline, will also help support the patient's subjective experience. Procedures and assessments to be performed if an unscheduled visit occurs are described in Section 3.16.1. Refer to Section 6.1 for additional details regarding the definition of CAE.

3.3.2. Secondary Efficacy Measures and Time Points

The secondary efficacy measures for this study include the following. These measures will be evaluated at the time points indicated in Table 2.

- pre-bronchodilator spirometry
- AQLQ +12
- ACQ-6
- asthma symptoms based on the daily asthma control diary

- asthma control days
- SGRQ

[redacted]

3.4. Safety Measures and Time Points

The following safety measures will be implemented throughout the study and evaluated at the time points indicated in Table 2.

- inquiries about adverse events
- clinical laboratory (serum chemistry and hematology) tests
- vital signs (respiratory rate, blood pressure, and pulse)
- ECGs
- physical examinations, including body weight measurements. These will include both full physical examinations including height and weight and brief physical examinations.
- inquiries about concomitant medication usage

A description of the safety measures is provided in Section 7.

[redacted]

3.6. Pharmacokinetic Measures and Time Points

Serum reslizumab concentration will be determined from serum samples collected from drug-treated patients at the time points indicated in Table 2.

3.7. Target Biomarker Measures and Time Points

Blood eosinophils will be determined from blood samples collected at the time points indicated in Table 2.

3.8. Immunogenicity Measures and Time Points

Anti-reslizumab antibody responses will be determined from serum samples collected from drug-treated patients at the time points indicated in Table 2.

3.9. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Patients who meet all inclusion criteria and none of the exclusion criteria will be randomly assigned to receive reslizumab 110 mg sc or matching placebo (approximately 225 patients per treatment group) in a 1:1 ratio. Patients and investigators will remain blinded to treatment assignment during the study. Randomization will be stratified by age (12 to <18 and ≥18 years), and blood eosinophil levels at screening (300/µL to <400/µL and ≥400/µL). This system is used to ensure a balance across treatment groups. The goal is to recruit a maximum of 30% of the patients (60 patients per treatment group) with eosinophil levels of 300/µL to <400/µL.

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

The sponsor's clinical 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 who will not be blinded to facilitate PK and ADA sample analysis. Eosinophils and monocytes will be redacted from the post-baseline differential cell count reports to avoid the possibility of unblinding patients.

Each patient will receive either one 1.0-mL sc injection containing 110 mg of reslizumab or one 1.0-mL sc injection containing sterile placebo solution on each dosing day. Both reslizumab and placebo will be provided as clear solutions essentially free of particulate matter.

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 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 randomized 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 afterwards, 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), Global Patient Safety and Pharmacovigilance 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) and the patient will not be withdrawn from the study.

3.10.3. Data Monitoring Committee

Not applicable.

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 Investigator's Brochure for reslizumab.

3.11.1. Investigational Product

Reslizumab for sc injection 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.

Reslizumab will be administered subcutaneously at a dose of 110 mg (1.0 mL) every 4 weeks. 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 of [redacted] sodium acetate, with [redacted] sucrose, [redacted] polysorbate 80, pH 5.5 buffer, presented as 1 mL per syringe. The needle shields of the prefilled syringes contain natural rubber latex.

Placebo will be administered subcutaneously as a 1.0-mL injection. 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) and should not be frozen and should be protected from light. Reslizumab and placebo supplies must 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 the contents of the shipment, a temperature monitoring device, and any applicable forms.

Each investigator is responsible for ensuring that deliveries of study drug and other study materials from Teva are correctly received and recorded, handled and stored safely and properly in accordance with the Code of Federal Regulations (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

This study will consist of up to a 2-week (±3 days) screening period, minimum 3-week run-in period and a 52-week double-blind treatment period**.** Patients are expected to participate in this study for approximately 69 weeks. An additional, late follow-up for immunogenicity testing will be performed 28 weeks after the last dose of study drug. If the patient enrolls in an available

open-label, long-term safety study, then adults (age 18 years and older) may wait to complete the early and late follow-up visits until the end of the open-label study; however, adolescents (ages 12 to <18 years) should complete the early follow-up visit at 12 weeks as part of this current study before starting an open-label study. See Section 12.4 for the definition of the end of the study.

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, adverse events will be reviewed by the sponsor (see Section 7.1.5) 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, and 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, 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 timing are summarized in Table 2. 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 7 (safety assessments), and Section 8 (PK and other assessments).

Table 2: Study Procedures and Assessments

Study period	**Pretreatment**		**Double-blind treatment period**																**Follow-up**	**Late follow-up**
Visit number	**V1 Start of screening period[a]**	**V2 Start of run-in period[b]**	**V3 DoR**	**V_{PK}**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17 EOT or early withdrawal**	**V18 EOS**	**V19**
Procedures and assessments	**Week -5 (±1 wk)**	**Week -3**	**0**	**W1 ±3d**	**W2 ±3d**	**W4 ±7d**	**W8 ±7d**	**W12 ±7d**	**W16 ±7d**	**W20 ±7d**	**W24 ±7d**	**W28 ±7d**	**W32 ±7d**	**W36 ±7d**	**W40 ±7d**	**W44 ±7d**	**W48 ±7d**	**W52 ±7d**	**EOT +12wk ±14d**	**W76 ±2wk**
Informed assent/consent	X																			
Medical history	X																			
Medication history	X																			
Inclusion and exclusion criteria	X	X	X[c]																	
Pregnancy testing[d]	X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CBC with differential[e]	X		X		X	X	X	X	X				X					X	X	
Serum chemistry tests[f]	X		X	X[g]	X[g]	X[g]	X[g]	X[g]	X	X[g]			X					X		
Urinalysis	X																			
Full physical examination[h]	X																	X		
Brief physical examination[h]			X		X	X	X	X	X	X	X	X	X	X	X	X	X			
Vital signs[h]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Height[i] and weight	X										X							X		

Table 2: Study Procedures and Assessments (Continued)

Study period	**Pretreatment**		**Double-blind treatment period**																**Follow-up**	**Late follow-up**
Visit number	**V1 Start of screening period[a]**	**V2 Start of run-in period[b]**	**V3 DoR**	**V_{PK}**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17 EOT or early withdrawal**	**V18 EOS**	**V19**
Procedures and assessments	**Week -5 (±1 wk)**	**Week -3**	**0**	**W1 ±3d**	**W2 ±3d**	**W4 ±7d**	**W8 ±7d**	**W12 ±7d**	**W16 ±7d**	**W20 ±7d**	**W24 ±7d**	**W28 ±7d**	**W32 ±7d**	**W36 ±7d**	**W40 ±7d**	**W44 ±7d**	**W48 ±7d**	**W52 ±7d**	**EOT +12wk ±14d**	**W76 ±2wk**
ECG[h]	X										X			X				X		
Reversibility testing[j]	X																			
Pre-bronchodilator spirometry[k]			X		X	X	X	X	X				X					X		
Post-bronchodilator spirometry			X						X				X					X		
Provide and collect PEF meter		X																X		
Provide/collect asthma control diary; reinforce diary and PEF compliance.		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ACQ[l]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AQLQ +12			X			X	X	X	X				X					X		
SGRQ			X										X					X		
[redacted]																				

Table 2: Study Procedures and Assessments (Continued)

Study period	**Pretreatment**		**Double-blind treatment period**																**Follow-up**	**Late follow-up**
Visit number	**V1 Start of screening period**[a]	**V2 Start of run-in period**[b]	**V3 DoR**	**V_{PK}**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17 EOT or early withdrawal**	**V18 EOS**	**V19**
Procedures and assessments	**Week -5 (±1 wk)**	**Week -3**	**0**	**W1 ±3d**	**W2 ±3d**	**W4 ±7d**	**W8 ±7d**	**W12 ±7d**	**W16 ±7d**	**W20 ±7d**	**W24 ±7d**	**W28 ±7d**	**W32 ±7d**	**W36 ±7d**	**W40 ±7d**	**W44 ±7d**	**W48 ±7d**	**W52 ±7d**	**EOT +12wk ±14d**	**W76 ±2wk**
Assess asthma exacerbations and related HCU[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK samples (ALL)			X	X[n]	X	X	X	X	X	X			X				X	X	X	X
Blood for ADA[o]			X			X			X				X					X	X	X
[redacted]																				
Blood for hepatitis B, hepatitis C, and HIV testing	X																			
Phadiatop allergy test and total serum IgE			X																	
Adverse event inquiry[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication inquiry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IP administration			X			X	X	X	X	X	X	X	X	X	X	X	X			
Injection site evaluation			X			X	X	X	X	X	X	X	X	X	X	X	X			

V = visit; DoR = day of randomization; PK = pharmacokinetic; EOT = end of treatment; EOS = end of study; TERM = termination; wk, W = week; d = day; ACQ = Asthma Control Questionnaire; ACQ-6 = 6-item Asthma Control Questionnaire; CBC = complete blood count; CPK = creatine phosphokinase; CRF = case report form; ECG = electrocardiogram; eDiary = electronic diary; PEF = peak expiratory flow; IP = investigational product; HCU = health care utilizations; AQLQ +12 = Asthma Quality of Life Questionnaire for patients 12 years and older; [redacted] SGRQ = St. George's Respiratory Questionnaire; [redacted] ADA = anti-drug antibody; HIV = human immunodeficiency virus; FEV_1 = forced expiratory volume in 1 second.

[a] The screening visit (visit 1) will take place approximately 5 weeks (±1 week) before the baseline/DoR visit. 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 (see note "k" for timing).

[b] A minimum of 3 weeks run-in (extension allowed up to 4 weeks) on stable doses of the patient's usual asthma medication is required to establish a baseline level of control before randomization.

[c] Diary control inclusion must be met at baseline/DoR in order for the patient to be randomized. If the control criteria are not met, the patient should not be randomized and should be discontinued at that time; the run-in may only be extended up to 4 weeks.

[d] Beta-human chorionic gonadotropin serum pregnancy tests will be performed at screening (female patients who are not 2 years postmenopausal or surgically sterile only). Urine pregnancy tests will be performed at baseline/DoR, before study drug injection at each administration visit and at week 52, or early withdrawal, and at follow-up V18. Pregnancy tests are not required for female patients who are 2 years postmenopausal or surgically sterile.

[e] The blood eosinophil count must meet the ≥300/μL inclusion criterion during the screening period. Given the known variability in this measure, the eosinophil count may be repeated once during screening (total of 2 attempts), at the discretion of the Investigator, in order to fulfill this inclusion criterion.

[f] CPK is collected with serum chemistry tests at scheduled visits. If a potentially clinically significant CPK level (≥3.1 × ULN) is reported, initiate the CPK/myalgia CRF and clinical monitoring as outlined in Protocol Section 7.1.7.2.

[g] CPK measurement only. CPK will be collected with PK sample.

[h] Physical examination, vital signs, and ECG should be obtained before spirometry procedures and IP administration.

[i] Patients aged 21 years and over will have their height and weight assessed at screening only. Patients aged 12 to 21 years will have height and weight assessed at screening, week 24, and EOT.

[j] A failed reversibility test may be repeated once, within the 2-week (±3 days) screening period. Reversibility testing will be confirmed before entering the run-in period. Documented historical reversibility within 12 months of signing the Informed Assent Form/Informed Consent Form is acceptable as per inclusion criterion f.

[k] 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.

[l] The ACQ will be completed by the patient at the clinic. ACQ should be completed through question 6. NOTE: The screening V1 ACQ-6 score must be ≥1.5 in order to continue in this study. A screening visit ACQ score <1.5 may not be repeated and the patient should be screen-failed at that time.

[m] 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. A diary alert, based on a sustained fall in peak flow from baseline, will also help support the patient's subjective experience. Procedures and assessments to be performed if an unscheduled visit occurs are described in Protocol Section 3.16.5.

[n] Patients at sites in the United States will return for a PK assessment at approximately 1 week, which corresponds approximately to maximum plasma drug concentration (Cmax) for subcutaneous reslizumab.
Note: All blood sampling (including hematology and chemistry) will be drawn before administration of IP unless otherwise indicated.

[o] Blood for ADA assessment will be collected at baseline/DoR, and other scheduled time points, and upon observation of any severe hypersensitivity reaction (eg, anaphylaxis). Blood for ADA assessment will be collected before dosing, if both occur on the same day. An additional, late follow-up for immunogenicity testing will be performed 28 weeks (±2 weeks) after the last dose of study drug (~week 76).

[p] 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).

3.16.1. Procedures for Screening and Start of Run-In Period (Visits 1 and 2)

A signed and dated informed consent form will be obtained from all patients 18 years of age or older before screening procedures commence (see Section 12.1). For patients 12 through <18 years of age, a signed and dated informed consent form will be obtained from each 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 before informed consent may be used for the study. Patients 18 years of age or older and parents/legal guardians for patients 12 through <18 years of age 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 3rd patient screened at center 5 would be given the number of 01005003).

Patients who do not initially meet the eosinophil or spirometry/reversibility criteria during the Screening period may have these tests repeated once, prior to excluding the subject from further study participation. A patient who is screened but not randomized (eg, because entry criteria were not met or enrollment did not occur within the specified time), may be considered in the future for screening again, once more, if, eg, there is a change in the patient's medical background or a modification of study entry criteria. The duration between the date of Screen Failure and re-screening must be >30 days.

The screening visit (visit 1) will take place approximately 5 weeks (±1 week) before the baseline/DoR visit. The following procedures will be performed at visit 1:

- Obtain written informed consent before any other study-related procedures are performed.
- Review medical history.
- Review medication history.
- Review inclusion/exclusion criteria.
- Perform serum pregnancy testing (female patients who are not 2 years postmenopausal or surgically sterile).
- Perform clinical laboratory tests (chemistry, hematology, urinalysis). Only those patients with an eosinophil count of 300 eosinophils/µL or greater at screening will be eligible to continue in the study. Eosinophil testing may be repeated once during the 2-week (±3 days) screening period.
- Perform full physical examination.

- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Measure height and weight.
- Perform ECG.
- Complete asthma-specific tests.
  - 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 (±3 days) screening period. Airway reversibility will be demonstrated by measuring the change in FEV_1 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 metered dose inhaler, as tolerated. Post-bronchodilator spirometry should be completed a minimum of 15 minutes after dosing of SABA. If a patient's FEV_1 improves at least 12% between the 2 tests, then they will be deemed as having airway reversibility and will continue the screening process.
  - Complete the ACQ-6.
  - Assess asthma exacerbations and related health care utilizations.
- Collect blood for human immunodeficiency virus (HIV) antigen/antibody, hepatitis B surface antigen, and hepatitis C antibody testing.
- Perform adverse event inquiry.
- Perform concomitant medication inquiry.

The start of run-in period visit (visit 2) will take place 3 weeks before the baseline/DoR visit. The following procedures will be performed at visit 2:

- Review inclusion/exclusion criteria.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Provide PEF meter to patient.
- Provide asthma control diary to patient.
- Assess asthma exacerbations and related health care utilizations.
- Perform concomitant medication inquiry.
- Perform adverse event inquiry

For a minimum of 3 weeks after visit 2, patients will continue on their usual asthma medications and complete daily self-monitoring of symptoms using an asthma control diary and PEF meter. Level of asthma control will be established based on the frequency of symptoms, use of a SABA, nighttime awakenings due to asthma, and ambulatory lung function.

3.16.2. Procedures Before Study Drug Treatment (Baseline/Day of Randomization [Week 0, Visit 3])

Patients who continue to meet the inclusion/exclusion criteria at visit 2 will continue to visit 3, when baseline/DoR evaluations will be conducted.

The following procedures will be performed at visit 3 before reslizumab or placebo administration:

- Review inclusion/exclusion 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 measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform concomitant medication inquiry.
- Perform adverse event inquiry.
- Complete asthma-specific tests.
  - If patient has withheld inhaled long acting and short-acting bronchodilators for the requisite time period, perform pre-bronchodilator spirometry, including FEV_1, FVC, and $FEF_{25\%-75\%}$, and post-bronchodilator spirometry, including FEV_1. If inhaled bronchodilators were used during the specified withhold window, lung function testing should be delayed until the withhold time is met if feasible, or the visit should be rescheduled.
  - Collect and review daily asthma control diary, and reinforce diary and PEF compliance. Patients must meet asthma control inclusion criteria.
  - Complete the ACQ-6.
  - Complete the AQLQ +12.
  - Complete the SGRQ.
  - [redacted]
  - Assess asthma exacerbations and related health care utilizations.
- Collect blood for serum reslizumab concentration determination (PK assessment) from all patients.

- Collect blood sample for immunogenicity (ADA) assessment.
- Collect blood for Phadiatop allergy test and total serum IgE (Vidal et al 2005).
- [redacted].

A patient who is not randomly assigned to treatment on the basis of 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 screening again if there is a change in the patient's medical background, a modification of study entry criteria, or other relevant change. A patient who does not complete at least 4 days of diary entries or equivalent during the last 7 days of run-in may also be considered for screening again. A patient may be rescreened for these reasons 1 time only. The duration between the date of Screen Failure and the re-screening must be >30 days. Patients may be screened again if they did not meet spirometry/reversibility criteria initially, and they may also be screened again if they did not meet the eosinophil criterion during the initial Screening.

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 two 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:

- 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

Study drug will be administered at approximately the same time in the morning on the days indicated in Table 2. (Note: Patients must be observed for a minimum of 1 hour after study drug administration.)

3.16.3.1.1. Week 1 (Pharmacokinetic Visit)

Patients at sites in the US will return to the research facility approximately 1 week after administration of the first dose of study drug. A blood sample will be collected for serum reslizumab concentration determination and measurement of CPK at this visit. Adverse events, concomitant medications, and asthma exacerbations and related health care utilizations will also be assessed.

3.16.3.1.2. Other On-Treatment Visits (Visits 4 through 17 [EOT])

During the double-blind treatment period, patients will return to the study center at week 2 and week 4 and then once every 4 weeks (±7 days) thereafter (relative to baseline/DoR) for administration of study drug and assessments until 4 weeks after the final administration of study drug (week 52 or early withdrawal).

The following procedures/assessments will be performed before administration of study drug at each of these visits, unless otherwise indicated:

- Perform urine pregnancy testing (female patients who are not 2 years postmenopausal or surgically sterile only) (excluding week 2 [visit 4]).
- Perform hematology tests (weeks 2, 4, 8, 12, 16, 32, and 52 or early withdrawal only).
- Perform serum chemistry tests (weeks 16, 32, and 52 or early withdrawal only) (a sample for CPK measurement only, will also be collected on weeks 2, 4, 8, 12, and 20).
- Perform full physical examination (week 52 or early withdrawal only).
- Perform brief physical examination (excluding week 52 or early withdrawal).
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Measure height and weight (weeks 24 and 52 or early withdrawal only; patients 12 to 21 years of age only).
- Perform ECG (week 24, 36, and 52 or early withdrawal only).
- Perform concomitant medication inquiry.
- Perform adverse event inquiry.
- Complete asthma-specific tests.
  - If patient has withheld inhaled long acting and short-acting bronchodilators for the requisite time period, perform pre-bronchodilator spirometry, including FEV_1, FVC, and $FEF_{25\%-75\%}$ (weeks 2, 4, 8, 12, 16, 32, and 52 or early withdrawal only).
  - Perform post-bronchodilator spirometry, including FEV_1 (weeks 16, 32, and 52 or early withdrawal only). If inhaled bronchodilators were used within the specified withhold window, lung function testing should be delayed until the withhold time is met if feasible, or the visit should be rescheduled. If neither option is feasible for the patient, the test may proceed and the deviation recorded.
  - Collect PEF meter (week 52 or early withdrawal only).
  - Collect and review daily asthma control diary, and reinforce diary and PEF compliance (excluding week 2).
  - Complete the ACQ-6 (may be completed after study drug administration during the 1-hour observation period.)
  - Complete the AQLQ +12 (weeks 4, 8, 12, 16, 32, and 52 or early withdrawal only) (AQLQ+12 may be completed after study drug administration during the 1-hour observation period.)
  - Complete the SGRQ (weeks 32 and 52) (may be completed after study drug administration during the 1-hour observation period.)

[redacted]

  - Assess asthma exacerbations and related health care utilizations.
- Collect blood for serum reslizumab concentration determination (PK assessment) from all patients (weeks 2, 4, 8, 12, 16, 20, 32, 48, and 52 or early withdrawal only).
- Collect blood sample for immunogenicity (ADA) assessment (weeks 4, 16, 32, and 52 or early withdrawal only).
- [redacted]

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 52 weeks of double-blind treatment will be considered to have completed the treatment period. Patients who complete the follow-up visit (week 64) will be considered as having completed the study. An exception to this may be adult patients who enroll in an available open-label, long-term safety study and complete the early and late follow-up visits as part of that study. These adult patients may be considered as having completed the current study at the time of the 52-week visit (end of treatment period). See Section 12.4 for the definition of the end of the study.

For patients who complete the treatment period, final evaluations will be performed at the end-of treatment/week 52 visit and the follow-up visit.

Patients who discontinue treatment prematurely must be encouraged to continue to attend the regular scheduled visits, and complete the prescribed safety and efficacy evaluations through the end-of-treatment/early withdrawal visit and the follow-up visit, if at all possible (see Section 4.4).

Patients who both discontinue treatment and also withdrawal from the study should have final evaluations performed on the last day the patient receives the study drug, or as soon as possible thereafter. The patient should also return for the follow-up visit and procedures if at all possible (see Section 4.4).

Procedures for patients who withdraw prematurely from the study are described in Section 4.4. 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.

The following procedures/assessments will be performed at the follow-up visit (EOT +12 weeks ±14 days, end of study visit):

- Perform hematology tests.
- Assess asthma exacerbations and related health care utilizations.
- Collect blood for serum reslizumab concentration determination (PK assessment) from all patients.
- Collect blood sample for immunogenicity (ADA) assessment.
- Perform adverse event inquiry.
- Perform concomitant medication inquiry.
- Perform urine pregnancy test.

3.16.5. Unscheduled Visits

An unscheduled visit may be performed at any time during the study at the patient'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 noted within the patient's source notes.

Procedures performed during unscheduled visits include the following:

- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform adverse event inquiry.
- Perform concomitant medication inquiry.
- Perform study compliance review.

Other procedures may be performed at the discretion of the investigator. As outlined in Section 4.4, subjects who discontinue study treatment will have all visit 17 procedures performed at an unscheduled visit. This visit should be scheduled as soon as possible after the time of treatment discontinuation.

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 this study only if they meet all of the following criteria:

a. Written informed consent is obtained. A patient 12 through <18 years of age must provide assent, and their parent(s) or legal guardian(s) must provide consent.

b. The patient is male or female, 12 years of age and older, with a diagnosis of asthma. (Patients 12 to <18 years of age are excluded from participating in South Korea and Argentina, and patients 66 years of age and older are excluded from participating in South Korea.)

c. The patient has had at least 2 documented asthma exacerbations requiring the use of systemic (oral, intramuscular, or iv) corticosteroids within 12 months of signing the Informed Assent Form/Informed Consent Form.

d. The patient has an ACQ-6 score of at least 1.5 at screening (visit 1).

e. The patient has a blood eosinophil level of at least 300/µL during the screening period (ie, before visit 2). (A maximum of 30% of the patients [60 patients per treatment group] with blood eosinophil levels of 300/µL to <400/µL will be enrolled. When this 30% threshold has been reached, only patients with blood eosinophil levels of ≥400/µL will then be enrolled.)

f. The patient has an FEV_1 reversibility of at least 12% after administration of inhaled SABA according to standard American Thoracic Society (ATS) or European Respiratory Society (ERS) protocol. Documented historical reversibility within 12 months of signing the Informed Assent Form/Informed Consent Form is acceptable.

g. The patient has required at least a medium total daily ICS dose based on GINA 2016 clinical comparability table (Appendix A) for at least 3 months. For ICS/LABA combination preparations, the mid-strength approved maintenance dose in the local country will meet this ICS criterion.

h. The patient has required an additional asthma controller medication (eg, long-acting beta-2-agonist [LABA], long-acting muscarinic antagonist [LAMA], leukotriene receptor antagonist [LTRA], or theophylline preparations), besides ICS, for at least 3 months or a documented failure in the past 12 months of an additional asthma controller medication for at least 3 successive months.

i. 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. Contraception is further clarified in an administrative letter in Section 17.5.1.

j. The patient must be willing and able to comply with study restrictions, 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.

k. The patient must maintain their usual asthma controller regimen without change throughout the screening and run-in periods. A patient who experiences an asthma exacerbation during this time that requires additional medication, beyond increased SABA use, will be considered to have failed screening/run-in and cannot undergo randomization. A patient may be rescreened for this reason 1 time only. The duration between the date of Screen Failure and the re-screening must be >30 days.

l. In order to be randomized, a patient must demonstrate the following:

- inadequate asthma control at baseline/DoR as evidenced by 1 of the 4 criteria below:
  - daytime asthma symptom score >0 on >2 of the previous 7 days based on the asthma control diary received at run-in OR
  - need for reliever SABA use on >2 of the previous 7 days OR
  - ≥1 nighttime awakening due to asthma over the previous 7 days OR
  - pre-bronchodilator FEV_1 <80% predicted at baseline/DoR

AND

- completion of at least 4 days of diary entries or equivalent during the last 7 days of run-in. A patient may be rescreened for this reason 1 time only.

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, interpretation of efficacy results, or 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 [EGPA, also known as Churg-Strauss syndrome], or allergic bronchopulmonary aspergillosis [ABPA]).

c. The patient has a known hypereosinophilic syndrome.

d. The patient has a diagnosis of malignancy within 5 years of the screening visit, except for treated and cured non-melanoma skin cancers.

e. The patient is a pregnant or lactating woman, or intends to become pregnant during the study or within 5 months after the last dose of study drug. 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 or during the screening/run-in period.

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 mAb or other mAb or soluble receptors) or other monoclonal antibody [eg, mepolizumab] or soluble receptors) or non-biologic (eg, methotrexate or cyclosporine), except maintenance oral corticosteroids for the treatment of asthma (up to and including 10 mg of prednisone daily or equivalent). Note: Previous use of such agents that occurred >5 half-lives from the initial screening visit may be allowed, if approved by the medical monitor.

i. The patient participated in a clinical trial 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 an immunodeficiency disorder including HIV.

m. The patient has current or suspected drug and alcohol abuse.

n. The patient has an active helminthic parasitic infection or was treated for one within 6 months of screening.

o. The patient has a history of allergic reaction 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 asthma phenotype that remains uncontrolled on standard of care asthma medications that may benefit from a targeted therapy such as reslizumab, while also ensuring that enrolled patients are of sufficient overall health to safely participate in this study and not assume unnecessary risk.

4.4. 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 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.

4.4.1. 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 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 an unscheduled visit and include all the assessments specified in the protocol for the early withdrawal visit (see Table 2). 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 52 (visit 17). The CAE event status and safety assessments at week 52 (visit 17) 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, CAE events, and survival status at week 52. A safety follow-up visit (visit 18) should be conducted 12 weeks after visit 17.

4.4.2. 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, the patient should return to the clinic as soon as possible to complete the early withdrawal visit (see Table 2). 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, CAE

events, and survival status at the end of the 52-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 blood eosinophil count (300/µL to <400/µL or ≥400/µL) and age (12 to <18 years or ≥18 years) at baseline/DoR, using IRT, which utilizes computerized central randomization. Study drug will be administered by qualified study personnel as a sc injection every 4 weeks for a total of 13 doses. Patients within each treatment group (placebo and 110 mg) will be randomly allocated to a particular sequence of injection sites:

a. upper arm (A)→abdomen (B)→thigh (C)

b. abdomen (B)→thigh (C)→upper arm (A)

c. thigh (C)→upper arm (A)→abdomen (B)

Study drug will be administered as a single sc injection containing either placebo (1.0 mL) or 110 mg of reslizumab (1.0 mL).

The pre-filled syringe has a staked 27G ½" 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. 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. 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 in regard to sexual activity and required laboratory values 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 4 weeks before study drug administration and 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. The sponsor will encode all therapy and medication according to the World Health Organization drug dictionary (WHO Drug).

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 the study unless patient safety is at risk. Any changes in background maintenance therapy must be discussed with the medical monitor.

The following medications will not be allowed during this study:

- 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

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. 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

The estimated total blood volume withdrawn over the entire study (including screening) is approximately 120 mL per patient. To further reduce the volume of blood withdrawn, pediatric tubes will be used when possible.

6. ASSESSMENT OF EFFICACY

6.1. Primary Efficacy Measure and Justification

For this study, 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 (oral or injection) or at least a doubling from a stable maintenance oral corticosteroid dose for at least 3 days[1]
- 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 [oral or injection] or at least a doubling from a stable maintenance oral corticosteroid 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 or the last day of an asthma-specific hospitalization or emergency department visit, whichever is later. For patients who are on a stable maintenance oral corticosteroid dose and receive at least a doubling of that dose for 3 days, the stop date is when they return to their baseline dose. For patients receiving a new use of oral corticosteroids or at least a doubling from their stable maintenance oral corticosteroid dose for at least 3 days that did not return to baseline, a CAE stop date will be the day that they have been on a stable dose for at least 10 days.

6.2. Spirometry

Pre-bronchodilator FEV_1, FVC, and $FEF_{25\%-75\%}$ and post-bronchodilator FEV_1 will be measured using spirometry. The FEV_1 is the volume of air which 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 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 American Thoracic Society/European

[1] A single depot corticosteroid injection would fulfill this criterion.

Respiratory Society 2005 procedural guidelines. The National Health and Nutrition Survey (NHANES) III reference equations will be used.

6.3. PEF Monitoring

AM (morning) ambulatory and PM (evening) ambulatory PEF will be measured. PEF will be measured using a PEF meter. PEF is the maximum speed of exhalation. AM (morning) ambulatory and PM (evening) 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, which was developed to measure functional impairments experienced by adults ≥17 years of age. The AQLQ +12 is valid for patients aged 12 to 70 years 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 is a validated asthma assessment tool that has been widely used (Juniper et al 1999). Six questions are self-assessments (completed by the patient). Each item on the ACQ 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 G.

6.7. Asthma Control Days

An asthma control day is defined as a day on which the patient used ≤2 puffs of inhaled SABA, had no nighttime awakenings, and experienced no asthma exacerbations as defined in the protocol (Baumgartner et al 2003, Schulpher and Buxton 1993).

6.8. St. George's Respiratory Questionnaire

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

[redacted]

6.10. Asthma Rescue Medication Use

The number of times asthma rescue medication (number of inhalations/puffs) is used will be assessed by reviewing the asthma control diary. Note: SABA therapy used for exercise pretreatment should not be recorded.

6.11. Nighttime Awakenings

Patients will record nighttime awakenings due to asthma as indicated in the asthma control diary.

[redacted]

7. ASSESSMENT OF SAFETY

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

- adverse events throughout the study
- vital signs (pulse, respiratory rate, blood pressure) assessments throughout the study
- concomitant medication usage throughout the study
- physical examination findings throughout the study
- laboratory evaluations at screening, the baseline visit/DoR, and periodically throughout the study
- ECG at screening and week 24, 36, and 52

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 informed consent form 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 7.1.5. 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 the disease under study or other 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, or 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.)

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 informed consent form through the end of the follow-up period. For this study, the follow-up period is defined as 12 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 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events once the study has ended. Serious adverse events that occur to a patient after the end of study should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

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 that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to adverse events that, 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: • It does not follow a reasonable temporal sequence from the administration of the study 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 study drug. • It does not reappear or worsen when the study 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 study drug administration cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the study 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 study drug, yet a drug relationship clearly exists. • It follows a known pattern of response to the study drug.

7.1.5. Serious Adverse Events

7.1.5.1. 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.

7.1.5.2. 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 Investigator's Brochure. All serious adverse events will be evaluated for expectedness by the sponsor.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events (as described in Section 7.1.5.1, 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. The event must be reported 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 patients for adverse events once this study has ended. Serious adverse events occurring to a patient after the end of 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 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
- onset date and detailed 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
- explanation of assessment of relatedness
- 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 (CIOMS) 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 IEC/IRB is also informed of the event, in accordance with local regulations.

The 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 PhV 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.

7.1.5.3.2. 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

7.1.6. 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 7.1.5.1. 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 7.1.5.3). A list of potential opportunistic infections is found in Appendix I.

7.1.7. Specific Adverse Event Case Report Form Capturing

7.1.7.1. Anaphylaxis/Hypersensitivity Reactions Case Report Form

Information about all suspected anaphylaxis events will be recorded on the Suspected Anaphylaxis/Hypersensitivity Reactions CRF, which is based on 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. The process for reporting a protocol-defined adverse event is the same as that for reporting a serious adverse event (see Section 7.1.5.3). These events can be either serious or nonserious, according to the criteria outlined in Section 7.1.5.1.

7.1.7.2. Creatine Phosphokinase/Muscular Adverse Events Case Report Form

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 ≥3.1× 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 (≥3.1 × 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 ≥10 × 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 ≥10 × 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 medical monitor 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 which in the opinion of the investigator is not severe enough to warrant discontinuation but which requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In

such a case, the reason for discontinuation would be the need to take a prohibited medication, not the adverse event.

A subject 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 investigational product (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 7.1.5.3).

Any patient becoming pregnant during the study will be withdrawn. All patients who become pregnant after first IP administration and within 5 months after last IP injection 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 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.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and presence or absence of any birth defect, congenital abnormalities or maternal and newborn complications. Pregnancy follow-up reports, like pregnancy reports, should be forwarded to Pharmacovigilance for data-entry to the global safety database and are also recorded on a specific CRF provided by Local Clinical Management.

The pregnancies reporting procedure should be the same as the serious adverse event reporting procedure.

7.3. Clinical Laboratory Tests

A laboratory test result that has significantly worsened (according to investigator's medical judgment) from the baseline/DoR result will be recorded on the source documentation and should be repeated. An adverse investigational 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. And adverse clinical laboratory should be monitored as described in Section 7.1.2. See Section 7.1.1 for a description of laboratory results that will be reported as adverse events.

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

Clinical laboratory tests (serum chemistry, hematology, serology, and urinalysis) will be performed before IP administration at the time points detailed in Table 2. 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:

- calcium
- phosphorus
- sodium
- potassium
- chloride
- creatine phosphokinase (at scheduled visits as noted in Table 2)
- bicarbonate or carbon dioxide
- glucose
- blood urea nitrogen (BUN)
- creatine
- cholesterol (at screening and week 52 or early withdrawal only)
- uric acid (at screening and week 52 or early withdrawal only)

- alanine aminotransferase
- aspartate aminotransferase
- lactic dehydrogenase
- alkaline phosphatase
- creatine phosphokinase
- total protein
- albumin
- total bilirubin
- direct bilirubin (only if total bilirubin is elevated)
- indirect bilirubin (only if total bilirubin is elevated)

7.3.2. Hematology and Serology

The following hematology tests will be performed:

- hemoglobin
- hematocrit
- platelet count
- absolute neutrophil count
- white blood cell count and differential count
  - polymorphonuclear leukocytes (neutrophils)
  - lymphocytes
  - eosinophils (blinded)
  - monocytes (blinded)
  - basophils

7.3.3. 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
- white blood cells
- casts
- crystals

7.3.4. Other Clinical Laboratory Tests

At screening, patients will be tested for hepatitis B surface antigen, hepatitis C antibody, and HIV.

7.3.4.1. Human Chorionic Gonadotropin Tests

Human chorionic gonadotropin serum tests will be performed for all females of childbearing potential at screening (visit 1). Urine pregnancy tests will be performed at baseline/DoR, before study drug injection at each administration visit and at week 52, or early withdrawal, and at follow-up V18. 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 will be measured at time points specified in Table 2, 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 (visit 1), week 24 (visit 10), week 36 (visit 13), and EOT or early withdrawal. 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 baseline/DoR and 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 baseline/DoR 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 2. 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 clinical project physician/medical monitor according to the safety monitoring plan (eg, scheduled safety reviews for study drug) 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, BIOMARKERS, AND IMMUNOGENICITY

8.1. Pharmacokinetic Variables

Serum reslizumab concentration will be measured at the time points indicated in Table 2.

8.1.1. Specimen Sampling and Handling

Blood samples (3 mL) will be collected via venipuncture or indwelling catheter at the time points detailed in Table 2 for serum concentration measurements of reslizumab.

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, patient number, period, and nominal collection time. Blood samples will be left standing upright at room temperature (20°C to 25°C) to clot for approximately 30-60 minutes. Samples should then be centrifuged at a minimum of 1500 g for approximately 10 minutes at 4°C (if available, or ambient if 4°C centrifuge is not available) until clot and serum are well separated. Samples may be centrifuged at ambient temperature at 1500 g for 10 minutes as long as measures are be 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 (Aliquot A and B), immediately frozen in an upright position at a temperature within the range of –60ºC to –90ºC, and stored under these conditions until shipped to the bioanalytical facility. Storage at -15 to -25°C is acceptable for a period of up to 60 days if a ≤-65°C freezer is not available. The listed temperatures must be maintained. Labels for samples should include study number, patient number, period, nominal collection time, set (A or B), and indication that they are PK samples.

The dates and exact times of study drug administration and of each PK sample will be recorded on the source documentation and transcribed onto 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 shipped to the sponsor or its designee for analysis. 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 either be sent to the same laboratory as that for set A on a later day by next-day courier, or be retained at the investigational center until the study is completed (unless shipment to another facility is requested by the sponsor).

Samples from reslizumab-treated patients will be analyzed using an appropriate validated method. Samples from placebo-treated patients will not be analyzed. 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.

8.2. Biomarker Variables

8.2.1. Blood Eosinophil Counts

Biomarker measures will include blood eosinophils and [redacted] measured at the time points indicated in Table 2. Details of blood sampling and preparation are described in the Laboratory Manual provided in the study file documents.

8.2.2. [redacted]

[redacted]

8.3. Immunogenicity

Blood samples (5 mL) for assessment of ADA response will be taken before dosing at the time points indicated in Table 2. Unscheduled blood samples for anti-reslizumab antibody 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, patient number, period, and nominal collection time. Blood samples will be left standing upright at room temperature (20°C to 25°C) to clot for approximately 30-60 minutes. Samples should then be centrifuged at a minimum of 1500 g for approximately 10 minutes at 4°C until clot and serum are well separated. Samples may be centrifuged at ambient temperature at 1500 g 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 two labeled cryovial tubes (primary aliquot A and back-up aliquot B) and stored in an ultralow freezer at ≤-65°C until shipped to a central or bioanalytical laboratory with temperature monitoring. Sample labels should include patient number, study number, collection date, and indication that it is an ADA sample aliquot (A or B). Storage at -15 to -20°C is acceptable for a period of up to 1 month if a ≤-65°C freezer is not available. The listed temperatures must be maintained. The actual times and dates of sampling will be recorded on the CRF.

8.3.1. 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 shipped to the sponsor or its designee for analysis. Samples will be stored in an upright position at ≤–65ºC 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 either be sent to the same laboratory as that for set A on a later day by next-day courier, or be retained at the investigational center until the study is completed (unless shipment to another facility is requested by the sponsor).

Samples from reslizumab-treated patients will be analyzed using appropriate validated methods. Timing of the initiation of sample analysis will be determined by the Teva Pharmaceuticals bioanalytical department representative responsible for the bioanalysis. The bioanalytical team will not be blinded for this analysis.

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

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 for this study is the frequency of CAEs per patient during the 52-week treatment period. The study will be considered positive if the primary efficacy measure indicates a statistically significant treatment effect of reslizumab versus placebo at the respective predefined significance level.

Power calculations were based on the below assumptions:

- Negative binomial (NB) distribution for the number of exacerbations with a mean of 2.9 exacerbations per patient per year for the placebo group
- Dispersion parameter of 1.2
- Treatment effect of 45% between the reslizumab group and the placebo group
- Alpha level of 0.05

Based on the assumptions above, 225 patients per arm (450 total) will provide >90% power to detect significant treatment effect of reslizumab over placebo in the reduction of exacerbation rate. The sample size was increased beyond the sample size required to provide 90% power in order to allow sufficient number of patients to assess safety and immunogenicity and to ensure adequate enrollment in the adolescent subset. The current sample size also provides higher power for other efficacy endpoints.

Patients with blood eosinophil levels of 300/μL to <400/μL will be limited to no more than 30% of patients (60 patients per treatment group).

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized 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 randomized, 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 randomized.

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

The primary analysis will include multiple imputations for missing data as detailed in Section 9.5.6.1.

The methodology and algorithm to be used for imputations will be detailed in the Statistical Analysis Plan. For all other variables, 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 randomized, patients randomized to treatment in the study, patients randomized but not treated, patients in the safety analysis set, patients in the per-protocol analysis set, patients who completed treatment period (week 52), and patients who complete the study (see Section 3.16.4 for definition of study completion), patients that 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 treatment but continue to attend study visits will be tabulated.

9.4.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, prior 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, 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 variable for this study is the frequency of CAEs per patient during the 52-week treatment period.

9.5.2. Secondary Endpoints

Secondary efficacy endpoints are as follows:

- change in pre-bronchodilator FEV_1 from baseline/DoR at week 52
- change in AQLQ +12 score from baseline/DoR at week 52
- change in ACQ-6 score from baseline/DoR at week 52
- change in total asthma symptom scores (day and night) from baseline at week 52
- percentage of asthma control days from baseline/DoR to week 52
- change in SGRQ score from baseline/DoR at week 32
- time to first CAE during the 52-week treatment period
- frequency of exacerbations requiring hospitalization or emergency department visits per patient during the 52-week treatment period
- frequency of moderate exacerbations defined as exacerbations requiring additional asthma controller medication that was not a systemic corticosteroid and did not result in an asthma-specific hospitalization or emergency department visit during the 52-week treatment period

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.

9.5.5. Target Biomarker Endpoints

The target biomarker endpoints are the blood eosinophil counts at baseline/DoR; weeks 2, 4, 8, 12, 16, 32, 52 or early withdrawal; and the follow-up visit (approximately week 64).

9.5.6. Planned Method of Analysis

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

The baseline for diary variables will be the average of the run-in values over the 7 days preceding baseline/DoR. The baseline for clinic visit variables will be the last observed value before the first dose of study drug. The baseline for eosinophils levels analysis will be screening value.

9.5.6.1. Primary Efficacy Analysis

The primary analysis of frequency of CAEs will use the NB regression model. The primary NB model will include the treatment group, randomization stratification factors, and number of exacerbations in the previous year 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.

CAEs that occur between the completion of the 1st dose of study drug and 2 weeks after the end of treatment/early withdrawal visit will be counted towards the CAEs for analysis.

The primary analysis will incorporate data from all randomized patients. The analysis will include the frequency of all exacerbations observed in 52 weeks, for patients completed the 52 weeks treatment period and for patients withdrew from treatment earlier than 52 weeks. For early withdrawal patients that the sponsor will fail to retrieve data after withdrawal despite all

attempts to contact the patient, a multiple imputation will be performed for the frequency of exacerbation after withdrawal. The multiple imputations will utilize the post-withdrawal data observed for patients who withdrew 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.

Sensitivity analyses will include:

- Analysis including the frequency of all exacerbations observed until treatment completion or until withdrawal from treatment, excluding exacerbations observed after withdrawing from treatment.
- Repeating the primary analysis using an offset variable in the NB model calculated as the logarithm of total follow-up duration (not excluding the summed duration of exacerbations).
- Repeating the primary analysis on the Per-protocol analysis set.
- "Tipping point" multiple imputation analysis to assess deviations from missing at random (MAR). The details regarding this analysis will be provided in the SAP.

Additional sensitivity analyses will be detailed in statistical analysis plan.

In addition, to the analysis described above, subgroup analyses will be performed for:

1. Age categories. Patients at ages 12 to <18 and patients ≥18 will be analyzed separately.
2. [redacted]
3. Eosinophil levels at baseline categories. Patients with blood eosinophil levels at baseline of 300/µL to <400/µL and ≥400/µL will be analyzed separately.

Additional subgroup analyses may be performed. These will be described and detailed in the statistical analysis plan.

9.5.6.2. Secondary Efficacy Analysis

All efficacy variables will be summarized by treatment group. For continuous variables, the summary statistics will include n, mean, SD, standard error (SE), median, minimum, and maximum.

Analysis of pulmonary function tests, AQLQ +12, ACQ-6, total asthma symptom scores, and SGRQ use will use the mixed model repeated measures model with treatment group, visit, treatment and visit interaction, baseline value, and stratification factors as fixed effects and patient as a random effect.

Analysis of percentage of asthma control days will use an analysis of variance (ANOVA) model with treatment group and stratification factors.

The Kaplan-Meier (KM) method will be used to estimate and compare the distributions of time to first CAE between treatment groups. Differences will be compared using a log rank test adjusting for the stratification factors.

The frequency of exacerbations requiring hospitalization or emergency department visits and the frequency of moderate exacerbations will be examined separately. The analysis will use similar methodology to that described for the primary analysis.

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

[redacted]

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 two-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 until either all comparisons of interest are interpreted inferentially, or until the point at which the resulting two-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 3.4. The overall safety of reslizumab treatment will be assessed throughout the study by evaluating adverse events and the following additional safety variables:

- adverse events throughout the study
- vital signs (pulse, respiratory rate, and blood pressure) throughout the study
- concomitant medication usage throughout the study
- physical examination findings throughout the study
- clinical laboratory evaluations at screening, baseline/DoR, and periodically throughout the study
- ECG at screening and week 24, 36, and 52 or early withdrawal

9.7.2. Safety Analysis

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 that started after first study dosing (overall and by severity), adverse events determined by the investigator to be related to study treatment (ie, reasonable possibility; see Section 7.1.4) (defined as related or with missing relationship) (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. In addition, summaries of adverse events will be presented separately for patients with ADA positive status and patients with ADA negative status. Patient listings of adverse events, serious adverse events, and adverse events leading to discontinuation will be presented.

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

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, median, minimum, and maximum) will be provided for actual values and changes from baseline/DoR 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.

9.7.3. Immunogenicity Endpoints

Samples for immunogenicity assessment for development of anti-drug antibodies will be obtained before the administration of study drug at DoR; prior to study drug administration at weeks 4, 16, 32, 52 or early withdrawal; and the follow-up visit (approximately week 64). Additional samples will be collected at the late follow-up visit (approximately week 76). These data may be presented in a clinical study report addendum.

9.8. Pharmacokinetic Analysis

Reslizumab concentration data will be summarized by treatment group and time point. 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 population PK and PK/PD analysis and reported in a separate report. An additional, a PK sample will be collected 28 weeks (±2 weeks) after the last dose of study drug (~week 76) for validation of the ADA assessment.

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. 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.

9.11. Planned Interim Analysis

No interim analysis is planned for this study.

9.12. 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 statistical analysis 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 nonsubstantial 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 impact 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 trial.

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 discontinue 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 informed consent form 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(s) 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(s) will contact the 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, including 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 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. The 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's 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 or 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 informed consent form 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 ensure 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 (ie, 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 (week 52). LSLV late follow up for immunogenicity testing only, will be performed 28 weeks (±2 weeks) after the last dose of study drug (approximately week 76). 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 CONTROL, 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 21CFR 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 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. 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.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, eDiary data, ePRO Tablet), 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 entry 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 control, 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 control, will be described in a data management plan.

Case report forms 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
- case report forms 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 patient 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 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.

Baumgartner RA, Martinez G, Edelman JM, Rodriguez Gomez GG, Bernstein M, Bird S, et al. Montelukast Asthma Study Group. Distribution of therapeutic response in asthma control between oral montelukast and inhaled beclomethasone. Eur Respir J 2003;21(1):123-8.

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.

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.

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]

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.

Sculpher MJ1, Buxton MJ. The episode-free day as a composite measure of effectiveness: an illustrative economic evaluation of formoterol versus salbutamol in asthma therapy. Pharmacoeconomics 1993;4(5):345-52.

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.

Tran TN, Khatry 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.

US Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program Expert Panel Report 3 (ERP-3). Guidelines for the diagnosis and management of asthma. NIH publication number 08-5846. October 2007.

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, Oborne 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, Chen W, Khatry DB, Gossage D, et al. High blood eosinophil count is a risk factor for future asthma exacerbations in adult persistent asthma. J Allergy Clin Immunol Pract 2014;2(6):741-50.e4.

17. SUMMARY OF CHANGES TO PROTOCOL

17.1. Amendment 04 Dated 24 October 2016

The revisions listed below have been made to the protocol Study C38072-AS-30025 and are considered substantial by the Teva Authorized Representative.

Table 3: Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
Cover Page (Other sections affected by this change: Investigator Agreement page)		
[redacted] **Teva Branded Pharmaceutical Products R&D, Inc.** [redacted] ~~Teva Branded Pharmaceutical Products R&D, Inc.~~	[redacted] Teva Branded Pharmaceutical Products R&D, Inc.	Change in Sponsor Authorized Representative
Cover Page		
[redacted] Teva Global R&D [redacted]	[redacted] Teva Global R&D [redacted]	Change in Sponsor's medical expert phone number
Section 2.3.4 Target Biomarker Endpoints (Other sections affected by this change: Synopsis, Section 2.3.5 Immunogenicity Endpoints, Section 2.3.6 Pharmacokinetic Endpoints, Section 3.1 General Design and Study Schema, Figure 1 Overall Study Schema, Section 3.13 Duration of Patient Participation and Justification, Table 2 Study Procedures and Assessments, Section 3.16.4 Procedures After Study Drug Treatment, Section 4.4.1 Discontinuation of Study Treatment, Section 7.1.2 Recording and Reporting Adverse Events, Section 9.5.5 Target Biomarker Endpoints, and Section 9.7.3 Immunogenicity Endpoints)		
The target biomarker endpoints are the blood eosinophil counts at baseline/DoR; weeks 2, 4, 8, 12, 16, 32, 52 or early withdrawal; and the follow-up visit (approximately week ~~60~~**64**).	The target biomarker endpoints are the blood eosinophil counts at baseline/DoR; weeks 2, 4, 8, 12, 16, 32, 52 or early withdrawal; and the follow-up visit (approximately week 64).	Early follow-up visit was changed from 8 to 12 weeks after end of treatment based on the European Medicines Agency Decision, P/0256/2016, dated 05 October 2016, on Pediatric Investigational Plan (PIP) modification EMEA-001202-PIP02-13-M01.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.1 General Design and Study Schema (Other sections affected by this change: Synopsis, Section 3.13 Duration of Patient Participation and Justification, and Section 3.16.4 Procedures After Study Drug Treatment)		
~~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.~~ **If the patient enrolls in an available open-label, long-term safety study, then adults (age 18 years and older) may wait to complete the early and late follow-up visits until the end of the open-label study; however, adolescents (ages 12 to <18 years) should complete the early follow-up visit at 12 weeks as part of this current study before starting an open-label study.**	If the patient enrolls in an available open-label, long-term safety study, then adults (age 18 years and older) may wait to complete the early and late follow-up visits until the end of the open-label study; however, adolescents (ages 12 to <18 years) should complete the early follow-up visit at 12 weeks as part of this current study before starting an open-label study.	Revised per the European Medicines Agency Decision, P/0256/2016, dated 05 October 2016, on PIP modification EMEA-001202-PIP02-13-M01.

17.2. Amendment 03 Dated 25 July 2016

The revisions listed below have been made to the protocol Study C38072-AS-30025 and are considered substantial by the Teva Authorized Representative.

Table 4: Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
Cover Page		
[redacted] Teva Global R&D [redacted]	[redacted] Teva Global R&D [redacted]	Sponsor Medical Expert changed.
Clinical Study Personnel Contact Information		
For centers in North America [redacted] *For Centers in Latin America* [redacted]	*For centers in North America* [redacted] *For Centers in Latin America* [redacted]	Per administrative letter, the contact physicians for North American and Latin America were updated/clarified.

Original text with changes shown	New wording	Reason/Justification for change
Study Synopsis - Number of Patients Planned; page 8 (Other sections affected by this change: Synopsis page 10, 11, 14; Section 3.1 Study Design; Section 3.9 Randomization and Blinding; Section 4.1 Patient Inclusion Criteria; Section 9.1 Sample Size and Power Considerations)		
Number of Patients Planned: Approximately ~~200~~**225** patients per treatment group for a total of ~~400~~**450** patients.	**Number of Patients Planned:** Approximately 225 patients per treatment group for a total of 450 patients.	The total enrollment of the study was increased in order to ensure adequate adolescent enrollment.
Study Synopsis - Criteria for Inclusion; page 12		
l. In order to be randomized, a patient must demonstrate the following: … … **Please refer to Section 3.16.1 and Section 3.16.2 for further guidance on rescreening if the above inclusion criteria are not met initially. The eosinophil count and reversibility test may each be repeated once during the Screening period, and subjects may also be rescreened for either of these reasons. The duration between the date of Screen Failure and the re-screening must be >30 days.**	l. In order to be randomized, a patient must demonstrate the following: … … Please refer to Section 3.16.1 and Section 3.16.2 for further guidance on rescreening if the above inclusion criteria are not met initially. The eosinophil count and reversibility test may each be repeated once during the Screening period, and subjects may also be rescreened for either of these reasons. The duration between the date of Screen Failure and the re-screening must be >30 days.	Clarification to study synopsis added for completeness and to further articulate the rescreening possibilities.
Section 1.3.2: Clinical Studies		
Additional Safety ~~Issues~~ Considerations	**Additional Safety Considerations**	Section renamed for clarity and inclusiveness.
Malignancy 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.**	*Malignancy* 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**.**	Language was added to clarify that the number of reported events includes patients who received placebo in the overall clinical program.
Malignancy 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.	*Malignancy* 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.	The number of cases with previous medical history of malignancy was corrected.

Original text with changes shown	New wording	Reason/Justification for change
<u>New Text</u>	*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.	Additional safety consideration for infections added for clarity.
Section 3: Study Design		
3.1 General Design and Study Schema (Other sections affected by this change: Synopsis)		

Original text with changes shown	New wording	Reason/Justification for change
Evidence of inadequate asthma control will include a history ~~of recent exacerbation (~~ **of** at least 2 **exacerbations requiring systemic corticosteroids (oral or injection)** in the previous 12 months~~)~~, a suboptimal screening ACQ-6 score (≥1.5), and persistent symptoms during run-in on the patient's usual asthma controller regimen. **At least one of the historical exacerbations must have been previously documented in the medical or pharmacy record; additional exacerbations may be documented in either the medical or pharmacy record, or documented by the study site at the time of screening history. For all exacerbations, which fulfill inclusion criterion 'c', the approximate dates of systemic corticosteroid therapy and the name of the systemic corticosteroid taken should be recorded in source documents**. The study consists of up to 2 weeks to satisfy essential screening inclusion criteria (ie, confirmation of asthma with elevated blood eosinophils), a minimum 3-week run-in period on usual care to establish the patient's baseline level of control **and**~~,~~ a 52-week double-blind treatment period**.** ~~, and follow-up evaluation approximately 8 weeks after the end of treatment (EOT) visit.~~ **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.**	Evidence of inadequate asthma control will include a history of at least 2 exacerbations requiring systemic corticosteroids (oral or injection) in the previous 12 months, a suboptimal screening ACQ-6 score (≥1.5), and persistent symptoms during run-in on the patient's usual asthma controller regimen. At least one of the historical exacerbations must have been previously documented in the medical or pharmacy record; additional exacerbations may be documented in either the medical or pharmacy record, or documented by the study site at the time of screening history. For all exacerbations, which fulfill inclusion criterion 'c', the approximate dates of systemic corticosteroid therapy and the name of the systemic corticosteroid taken should be recorded in source documents. The study consists of up to 2 weeks to satisfy essential screening inclusion criteria (ie, confirmation of asthma with elevated blood eosinophils), a minimum 3-week run-in period on usual care to establish the patient's baseline level of control and a 52-week double-blind treatment period. 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.	Rewording of study design to provide clarification of screening and enrollment. 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.
Patients will return 8 weeks after the EOT visit for follow-up hematology, PK, immunogenicity, and safety assessments. **An additional, late follow-up for immunogenicity testing will be performed 28 weeks (±2 weeks) after the last dose of study drug (ie, approximately week 76).**	Patients will return 8 weeks after the EOT visit for follow-up hematology, PK, immunogenicity, and safety assessments. An additional, late follow-up for immunogenicity testing will be performed 28 weeks (±2 weeks) after the last dose of study drug (ie, approximately week 76).	Clarification of study duration and milestones.
Section 3.11: Drugs Used in the Study **(Other sections affected by this change: Section 5.1)**		
Section 3.11.1 Investigational Product Reslizumab for sc injection 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.**	***Section 3.11.1 Investigational Product*** Reslizumab for sc injection 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.	Information regarding the natural rubber component of the prefilled syringe was added for transparency.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.11.2 Placebo Placebo will be provided as a sterile solution of [redacted] sodium acetate, with [redacted] sucrose, [redacted] polysorbate 80, pH 5.5 buffer, presented as 1 mL per syringe. **The needle shields of the prefilled syringes contain natural rubber latex.**	***Section 3.11.2 Placebo*** Placebo will be provided as a sterile solution of [redacted] sodium acetate, with [redacted] sucrose, [redacted] polysorbate 80, pH 5.5 buffer, presented as 1 mL per syringe. The needle shields of the prefilled syringes contain natural rubber latex.	Information regarding the natural rubber component of the prefilled syringe was added for transparency.
3.13 Duration of Patient Participation and Justification		
This study will consist of up to a 2-week (±3 days) screening period, minimum 3-week run-in period~~,~~ and a 52- week double-blind treatment period**.** ~~, and 8-week follow-up visit. Patients are expected to participate in this study for approximately 65 weeks. An additional, late follow-up for immunogenicity testing will be performed 28 weeks after the last dose of study drug.~~ **Patients are expected to participate in this study for approximately 65 weeks. An additional, late follow-up for immunogenicity testing will be performed 28 weeks after the last dose of study drug. 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.**	This study will consist of up to a 2-week (±3 days) screening period, minimum 3-week run-in period and a 52- week double-blind treatment period. Patients are expected to participate in this study for approximately 65 weeks. An additional, late follow-up for immunogenicity testing will be performed 28 weeks after the last dose of study drug. 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.	Clarification of study duration and milestones.
3.14 Stopping Rules and Discontinuation Criteria		
Other than pregnancy, there are no formal rules ~~for early withdrawal from this study~~ **for study drug discontinuation in this study**. During the conduct of the study, adverse events will be reviewed by the sponsor (see Section 7.1.5) 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, and 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 (e.g. pregnancy, a related severe hypersensitivity**, or related severe myalgia/muscle event**), a protocol violation or deviation as defined in Section 11.1.2, or noncompliance.	Other than pregnancy, there are no formal rules for study drug discontinuation in this study. During the conduct of the study, adverse events will be reviewed by the sponsor (see Section 7.1.5) 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, and 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 (e.g. pregnancy, a related severe hypersensitivity, or related severe myalgia/muscle event), a protocol violation or deviation as defined in Section 11.1.2, or noncompliance.	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. Additional language was added to describe reasons for patient withdrawal.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.16: Study Procedures; Table 2: Study Procedures and Assessments (Other sections affected by this change: Sections 3.16.3.1.1 and 3.16.3.1.2).		
W76 **+2wk**	W76 +2wk	Time window added to Week 76 visit. Only upper limit so ensure ADA titer is obtained without residual drug on board.
Addition of CPK assessments at Day 7, Weeks 2-12, and Week 20	Addition of CPK assessments at Day 7, Weeks 2-12 and Week 20.	Clarification added based on request by Health Authorities.
Removal of Phadiatop allergy test and total serum IgE at Visit 17 (Week 52)	Phadiatop allergy test and total serum IgE at Visit 17 (Week 52) was removed.	The phadiatop assessment at Week 52 was removed because it is exclusively a baseline assessment.
Addition of Injection site evaluation at Visit 3 and Weeks 4-48.	Injection site evaluation addition at Visit 3 and Weeks 4-48.	Row added aligning with IP visits for clarification of evaluation.
f. CPK is collected with serum chemistry tests at scheduled visits. If potentially clinically significant CPK **(≥3.1x ULN)** is reported, 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 7.1.7.2.**	f. CPK is collected with serum chemistry tests at scheduled visits. If a potentially clinically significant CPK level (≥3.1x ULN) is reported, initiate the CPK/myalgia CRF and clinical monitoring required as outlined in Protocol Section 7.1.7.2.	Footnote modified for clarity.
--	g. CPK measurement only. CPK will be collected with PK sample.	New footnote added to support the additional CPK collection.

Original text with changes shown	New wording	Reason/Justification for change
k. 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**	k. 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	Clarification of timing for spirometry.
3.16.1 Procedures for Screening and Start of Run-In Period (Visits 1 and 2)		
Patients who do not initially meet the eosinophil or spirometry/reversibility criteria during the Screening period may have these tests repeated once, prior to excluding the subject from further study participation. A patient who is screened but not **randomized (**eg, because entry criteria were not met or enrollment did not occur within the specified time**)**, may be considered **in the future** for screening again, once more, if, eg, 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 ~~first visit during the screening period and the~~ **date of Screen Failure and** re-screening must be >30 days.	Patients who do not initially meet the eosinophil or spirometry/reversibility criteria during the Screening period may have these tests repeated once, prior to excluding the subject from further study participation. A patient who is screened but not randomized, eg, because entry criteria were not met or enrollment did not occur within the specified time, may be considered in the future for screening again, once more, if, eg, there is a change in the patient's medical background or a modification of study entry criteria. The duration between the date of Screen Failure and re-screening must be >30 days.	Screening and re-screening details clarified.
• Perform clinical laboratory tests (chemistry, hematology, urinalysis). Only those patients with an eosinophil count of 300 eosinophils/µL or greater at screening will be eligible to continue in the study~~; .patients with historic eosinophil counts of 400 eosinophils/µL or greater will not be eligible.~~ Eosinophil testing may be repeated once during the 2-week (±3 days) screening period.	• Perform clinical laboratory tests (chemistry, hematology, urinalysis). Only those patients with an eosinophil count of 300 eosinophils/µL or greater at screening will be eligible to continue in the study. Eosinophil testing may be repeated once during the 2-week (±3 days) screening period.	Change made to protocol reflecting changes from administrative letter issued previously.

Original text with changes shown	New wording	Reason/Justification for change
3.16.2 Procedures Before Study Drug Treatment (Baseline/Day of Randomization [Week 0, Visit 3])		
The duration between the first visit during the screening period and the re-screening must be >30 days. Patients may be screened again if they did not meet spirometry/reversibility criteria initially**, and they may also be screened again if they did not meet the eosinophil criterion during the initial Screening.**	The duration between the first visit during the screening period and the re-screening must be >30 days. Patients may be screened again if they did not meet spirometry/reversibility criteria initially, and they may also be screened again if they did not meet the eosinophil criterion during the initial Screening.	Screening and re-screening details clarified.
These two 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:** • **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.**	These two 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: • 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.	Clarification of study procedures to reflect the schedule of assessments.
3.16.3.1.1 Week 1 (Pharmacokinetic Visit)		
Patients at sites in the US will return to the research facility approximately 1 week after administration of the first dose of study drug. A blood sample will be collected for serum reslizumab concentration determination **and measurement of CPK** at this visit. Adverse events, concomitant medications, and asthma exacerbations and related health care utilizations will also be assessed.	Patients at sites in the US will return to the research facility approximately 1 week after administration of the first dose of study drug. A blood sample will be collected for serum reslizumab concentration determination and measurement of CPK at this visit. Adverse events, concomitant medications, and asthma exacerbations and related health care utilizations will also be assessed.	Edited to align with modification to schedule of assessments.

Original text with changes shown	New wording	Reason/Justification for change
3.16.3.1.2 Other On-Treatment Visits (Visits 4 through 17 [EOT])		
Perform serum chemistry tests (weeks 16, 32, and 52 or early withdrawal only) **(a sample for CPK measurement only, will also be collected on weeks 2, 4, 8, 12, and 20).**	Perform serum chemistry tests (weeks 16, 32, and 52 or early withdrawal only) (a sample for CPK measurement only, will also be collected on weeks 2, 4, 8, 12, and 20).	Edited to align with modification to schedule of assessments.
~~Collect blood for Phadiatop allergy test and total serum IgE (week 52 or early withdrawal only; Vidal et al 2005).~~	- [removed]	Removed to align with modification to schedule of assessments.
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.** • ~~Perform adverse event inquiry.~~ – 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 ~~7.1.6~~**7.1.7**. Remind the patients that they will receive a post-injection symptom inquiry via the eDiary.	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.	Added to align with modification to schedule of assessments and to fully outline the assessments required.
4.1 Patient Inclusion Criteria (Other sections affected by these changes: Study Synopsis)		
g. The patient has required at least a medium total daily ICS dose based on GINA ~~2015~~**2016** clinical comparability table (Appendix A) for at least 3 months. For ICS/LABA combination preparations, the mid-strength approved maintenance dose in the local country will meet this ICS criterion	g. The patient has required at least a medium total daily ICS dose based on GINA 2016 clinical comparability table (Appendix A) for at least 3 months. For ICS/LABA combination preparations, the mid-strength approved maintenance dose in the local country will meet this ICS criterion	GINA Guidance version updated.

Original text with changes shown	New wording	Reason/Justification for change
i. 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. Contraception is further clarified in an administrative letter in Section 17.4.1.	i. 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. Contraception is further clarified in an administrative letter in Section 17.4.1.	Criterion revised for clarity and alignment with case report form.
k. The patient must maintain their usual asthma controller regimen without change throughout the screening and run-in periods. A patient who experiences an asthma exacerbation during this time that requires additional medication, beyond increased SABA use, will be considered to have failed screening/run-in and cannot undergo randomization. A patient may be rescreened for this reason 1 time only. **The duration between the date of Screen Failure and the re-screening must be >30 days. Patients may be screened again if they did not meet spirometry/reversibility criteria initially.**	k. The patient must maintain their usual asthma controller regimen without change throughout the screening and run-in periods. A patient who experiences an asthma exacerbation during this time that requires additional medication, beyond increased SABA use, will be considered to have failed screening/run-in and cannot undergo randomization. A patient may be rescreened for this reason 1 time only. The duration between the date of Screen Failure and the re-screening must be >30 days. Patients may be screened again if they did not meet spirometry/reversibility criteria initially.	Criterion revised for clarity and alignment with case report form instructions.
4.4.1 Disconinutation of Study Treatment (Other sections affected by these changes: 3.16.5)		
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 **an unscheduled visit and include all the assessments** specified in the protocol for the early withdrawal visit.	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 an unscheduled visit and include all the assessments specified in the protocol for the early withdrawal visit.	Clarification of assessments for an unscheduled visit.

Original text with changes shown	New wording	Reason/Justification for change
4.4.2 Complete Withdrawal from Study (Other sections affected by these changes: 3.16.5)		
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**, the patient should return to the clinic as soon as possible to complete the early withdrawal visit (see Table 2)**.	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, the patient should return to the clinic as soon as possible to complete the early withdrawal visit (see Table 2).	Clarification of assessments for an unscheduled visit.
5.5 Total Blood Volume		
The estimated total blood volume withdrawn over the entire study (including screening) is approximately ~~115~~**120** mL per patient	The estimated total blood volume withdrawn over the entire study (including screening) is approximately 120 mL per patient	Increased to account for additional CPK draws.
Section 7.1: Adverse Events		
7.1.1. Definition of 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 Section7.1.5.** 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:	**7.1.1. Definition of 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 Section7.1.5. 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:	Clarification of the reporting of the disease under study as an adverse event.

Original text with changes shown	New wording	Reason/Justification for change
• 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… ~~Worsening of the disease under study (ie, 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.~~	• 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…	
Section 7.1.5.1 Definition of a Serious Adverse Event • 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 ~~only~~ if the presentation or outcome is more severe than the patient's known course of asthma.	***Section 7.1.5.1 Definition of a Serious Adverse Event*** • 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	Alignment between protocol language, adverse event reporting instructions, and processes.

Original text with changes shown	New wording	Reason/Justification for change
7.1.6: Protocol-Defined Adverse Events for Expedited Reporting to Teva (Other sections affected by this change: Appendix I)		
7.1.6: 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 7.1.5.1. 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 7.1.5.3). **A list of potential opportunistic infections is found in Appendix I.**	*7.1.6: 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 7.1.5.1. 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 7.1.5.3). A list of potential opportunistic infections is found in Appendix I.	A list of opportunistic infections was provided to increase investigators' awareness of the potential for opportunistic infection during reslizumab treatment.
7.1.7.2. Creatine Phosphokinase/Muscular Adverse Events Case Report Form		
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 ≥3.1× 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"). **If a potentially clinically significant CPK level (≥3.1 × 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 ≥10 × 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**	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 ≥3.1× 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"). If a potentially clinically significant CPK level (≥3.1 × 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 ≥10 × ULN elevations in CPK, repeat CPK level, urinalysis (including microscopy), serum electrolytes, BUN, and creatinine will be performed as soon as possible after receipt	Requested edits from Health Authority and for overall clarity.

Original text with changes shown	New wording	Reason/Justification for change
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, urine alkalinization) should be considered by the investigator. **In cases deemed by the investigator to be treatment-related elevations in CPK ≥10 × ULN (eg, potentially rhabdomyolysis), study drug discontinuation should occur at least until CPK normalization or longer based on investigator clinical assessment.**	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, urine alkalinization) should be considered by the investigator. In cases deemed by the investigator to be treatment-related elevations in CPK ≥10 × ULN (eg, potentially rhabdomyolysis), study drug discontinuation should occur at least until CPK normalization or longer based on investigator clinical assessment.	
9.10 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 study**. Summaries will be provided if appropriate.	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.	Updated to accommodate baseline ADA testing in previous placebo patients.
17.4.4. Administrative Letter Dated February 2016	17.4.4. Administrative Letter Dated February 2016	Letter added as reference.
17.4.5. Administrative Letter Dated 08 March 2016	17.4.5. Administrative Letter Dated 08 March 2016	Letter added as reference.
17.4.6. Administrative Letter Dated 21 March 2016	17.4.6. Administrative Letter Dated 21 March 2016	Letter added as reference.
Appendix A		
Global Initiative for Asthma **ICS** Equivalency Table and **Row added for fluticasone fuorate total daily dose**	Global Initiative for Asthma ICS Equivalency Table and Row added for fluticasone fuorate total daily dose	Title amended for clarity. Additional row added to account for fluticasone fuorate total daily dose as per GINA 2016 guidance.

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.

17.3. Amendment 02 Dated 25 January 2016

The revisions listed below have been made to the protocol Study C38072-AS-30025 and are considered substantial by the Teva Authorized Representative.

Table 5: Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
Title Page:		
[redacted] Teva Branded Pharmaceutical Products R&D, Inc [redacted]	[redacted] Teva Branded Pharmaceutical Products R&D, Inc [redacted]	Sponsor's Safety Representative was changed.
Clinical Study Personnel Contact Information:		
[redacted]	[redacted]	Medical Monitor for North America was changed.
EMEA: [redacted]	EMEA: [redacted]	The spelling of the EMEA Medical Monitor was corrected.
Section 1: BACKGROUND INFORMATION		
Section 1.3.2.2: Clinical Safety and Efficacy Studies:		
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.	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.	IV was removed as the 2195 subjects also included 45 patients who received sc reslizumab in Study 1107.
Serious adverse event**s** and death cases from the ~~ongoing~~ open-label ~~s~~**S**tudy ~~(~~3085~~)~~ are also included in the relevant sections	Serious adverse events and death cases from the open-label Study 3085 are also included in the relevant sections	The language was updated, as Study 3085 has been completed since the last version of the protocol.

Original text with changes shown	New wording	Reason/Justification for change
Serious Adverse Events … **Deaths** … **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 ~~or~~**of** reslizumab. ~~Mild~~**Small** decreases in the mean value**s** of total white blood cell counts ~~was~~**were** also observed in some studies and ~~has~~**have** been assessed as reflecting the decrease in the eosinophil **component of differential cell** count**s** ~~in hypereosinophilic patients~~. The mean values of eosinophil and ~~WBC~~**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** A~~s expected with administration of a monoclonal antibody, hypersensitivity/ anaphylactic injection reactions/~~**Anaphylaxis were related to reslizumab infusion has been** reported and **is** ~~are~~ considered **an** adverse drug reaction~~s~~ **(ADR).** 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 infusion-related anaphylaxis reactions ~~related to~~ **reported as anaphylaxis that occurred during or shortly after** reslizumab **infusion** in the reactions **reported as anaphylaxis that occurred during or shortly after** reslizumab **infusion** in the BREATH studies~~:~~ **that were characterized variously by skin or mucosal involvement, dyspnea, wheezing, gastrointestinal symptoms, and chills.** ~~a~~**A**ll 3 were treated at the study site and the patients were ~~discontinued~~ **withdrawn** from the study. M**yalgia 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.**	**Serious Adverse Events** … **Deaths** … **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 differential cell counts. The mean values of eosinophil andwhite 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. There were 3 infusion-related anaphylaxis reactions reported as anaphylaxis that occurred during or shortly after reslizumab infusion in the BREATH studies that were characterized variously by skin or mucosal involvement, dyspnea, wheezing, gastrointestinal symptoms, and chills. All 3 were treated at the study site and the patients were withdrawn from the study. Myalgia 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.	This information was added and updated to provide details and update the organization of the section.

Original text with changes shown	New wording	Reason/Justification for change
Additional safety issues ***Malignancy*** As of ~~September 2014~~**February 2015**, there were ~~24~~**27** treatment-emergent adverse events reported by ~~21~~**24** patients related to malignancy for the entire clinical program. ~~The malignancies,~~**Malignancies** in ~~the~~ reslizumab~~-~~treated patients were of diverse ~~tissue origin (1~~**tissues (** colon, ~~1~~ anal, ~~3~~ melanoma,~~ 2~~ prostate,~~ 3~~ breast, ~~2~~ lung, ~~1~~ plasmacytoma, ~~1~~ lymphoma,~~ 1~~ lung metastasis of a previous resected colon cancer, ~~and 5~~**ovarian adenocarcinoma, borderline ovarian tumor, and** non-melanoma skin cancer cases ~~reported as nonserious events).~~ **).** In the placebo-controlled **asthma** studies **utilizing the 3.0-mg/kg dose**, ~~the~~ incidence of ~~the~~ overall malignancies was 6 ~~(0.58%)~~ 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~~**. All** malignancies in ~~the~~ reslizumab-treated patients were diagnosed within less than 6 months from first reslizumab dosing ~~with the exception of~~**, except for** the skin squamous cell carcinoma. In the **combined** placebo-controlled studies and ~~the~~ long-term, open-label, safety extension Study C38072/3085, ~~there were a total of 19 patients with~~ malignancies **were reported in** ~~19~~**21** patients**.**~~, including~~ **These included**~~, including~~ 5 **cases of** non-melanoma skin cancer. Most malignancies were diagnosed within less than ~~half a year~~**6 months** after starting reslizumab treatment, and in **5**~~4 of these~~ cases, there was a previous medical history of ~~malignancies~~ **malignancy**. ~~The~~ A thorough 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~~ **a causal relationship** between reslizumab and ~~malignancies~~ **cancer risk**.	**Additional safety issues** *Malignancy* As of February 2015, there were 24 treatment-emergent adverse events reported by 21 patients related to malignancy for the entire clinical program. 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 non-melanoma skin cancer cases). 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. 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.	This information was added and updated to provide details and update the organization of the section.

Original text with changes shown	New wording	Reason/Justification for change
Pregnancy 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~~**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 ~~were on~~**in patients receiving** reslizumab. All patients were withdrawn from the study. Two pregnancies ~~ended in~~**were terminated by** an elective abortion with no complications, and 5 ~~concluded with~~ **led to the birth of** full-term ~~live births of~~ infants with no malformations and no obstetric or perinatal complications. One male ~~baby~~**newborn** had a neonatal jaundice that was reported as an unrelated adverse event and was assessed as a physiological jaundice. ~~There was 1~~**One** pregnancy case ~~that~~ was lost to follow-up, and the outcome is unknown.	*Pregnancy* The safety of reslizumab in pregnant women or 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 a physiological jaundice. One pregnancy case was lost to follow-up, and the outcome is unknown.	This information was added and updated to provide details and update the organization of the section.
Immunogenicity ~~analysis showed anti~~ **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~~) were observed in 3.3% to 11.8% of patients.~~**).** In general, the ADA responses were low in titer and often transient and were not associated with an effect on reslizumab concentration ~~or~~**,** eosinophil count~~,~~ or ~~associated with~~ specific clinical manifestations~~,~~ **(**including hypersensitivity reactions~~. Myalgia, which was slightly higher in the reslizumab 3.0 mg/kg group (1%) than in the placebo group (0.5%), and anaphylaxis reactions are considered adverse drug reactions (ADRs).~~**).**	*Immunogenicity* 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). 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).	This information was added and updated to provide details and update the organization of the section.

Original text with changes shown	New wording	Reason/Justification for change
Section 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 ~~iv~~ has been generally well tolerated over the range of doses evaluated (ie, from 0.03 through 3 mg/kg). **Systemic severe reactions (including** ~~A~~**a**naphylaxis**)** and myalgia are considered as adverse drug reactions of iv reslizumab. **There are limited safety data regarding sc administration 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 as adverse drug reactions of iv reslizumab. There are limited safety data regarding sc administration of reslizumab.	This section was updated with information found in the current Investigator's Brochure.
Section 1.4.3. Overall Risk and Benefit Assessment for This Study:		
The majority of adverse events in reslizumab-treated patients ~~was~~ **were** mild to moderate in severity, ~~and~~ 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 ~~AE~~**adverse event** profile between patient**s** treated with reslizumab and patients treated with placebo with the exception of **the following ADRs: "systemic severe reactions (including anaphylaxis)" and "myalgia". Three**~~3~~ anaphylaxis reactions related to reslizumab infusions~~-~~that were reported during the BREATH asthma program; ~~N~~**n**one of the 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.~~ **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.** ~~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.~~	The majority of adverse events in reslizumab-treated patients were mild to moderate in severity, were considered to be unrelated to study drug treatment, as determined by the investigator, and as expected, were associated with underlying asthma disease. There were no significant differences in the adverse event profile between patient 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.	The overall risks were updated and ADRs were further defined by this change. Text on myalgia was moved to this section.

Original text with changes shown	New wording	Reason/Justification for change
Section 1.7: Population to be Studied and Justification (Other sections affected by this change: Clinical Study Protocol Synopsis, and Sections 3.1 and 4.1):		
The study will enroll male and female patients, 12 years of age and older, with asthma and elevated blood eosinophils who are inadequately controlled on at least ~~440 µg of inhaled fluticasone propionate or equivalent~~**a medium** total daily **ICS** dose and a second asthma controller.	The study will enroll male and female patients, 12 years of age and older, with asthma and elevated blood eosinophils who are inadequately controlled on at least a medium total daily ICS dose and a second asthma controller.	This change generalized the ICS requirements for subjects enrolled in the study.
Section 2: PURPOSE OF THE STUDY AND STUDY OBJECTIVES		
Section 2.3.2: Secondary Efficacy Endpoints (Other sections affected by this change: Clinical Study Protocol Synopsis and Section 9.5.2):		
~~•~~ change in total asthma symptom scores (day and night) from baseline~~/DoR~~ at week 52 • ~~change in~~ percentage of asthma control days from baseline/DoR ~~at~~**to** week 52	• change in total asthma symptom scores (day and night) from baseline at week 52 • percentage of asthma control days from baseline/DoR to week 52	These changes creates clarity for the endpoints.
[redacted]		
[redacted]	[redacted]	[redacted]
Section 2.3.4: Target Biomarker Endpoints (Other sections affected by this change: Clinical Study Protocol Synopsis and Section 9.5.5):		
The target biomarker endpoints are the blood eosinophil counts at baseline/DoR; weeks 2, 4, 8, 12, 16, ~~20,~~ 32, 52 or early withdrawal; and the follow-up visit (approximately week 60).	The target biomarker endpoints are the blood eosinophil counts at baseline/DoR; weeks 2, 4, 8, 12, 16, 32, 52 or early withdrawal; and the follow-up visit (approximately week 60).	Change made for consistency with Table 2 Study Procedures and Assessments.

Original text with changes shown	New wording	Reason/Justification for change
Section 2.3.6: Pharmacokinetic Endpoints (Other sections affected by this change: Clinical Study Protocol Synopsis, Sections 2.3.5 and 9.7.3):		
The PK endpoints are the serum reslizumab concentrations at baseline/DoR; weeks 1 (patients in US study centers only), 2, **and prior to study drug administration at weeks** 4, 8, 12, 16, 20, 32, 48, 52 or early withdrawal; and the follow-up visit (approximately week 60). An additional PK sample will be taken at long term follow-up (approximately week 76) **at the same time** for anti-drug antibody (ADA) **sample collection**~~assessment~~.	The PK endpoints are the serum reslizumab concentrations at baseline/DoR; weeks 1 (patients in US study centers only), 2, and prior to study drug administration at weeks 4, 8, 12, 16, 20, 32, 48, 52 or early withdrawal; and the follow-up visit (approximately week 60). An additional PK sample will be taken at long term follow-up (approximately week 76) at the same time for anti-drug antibody (ADA) sample collection.	This addition clarified that the sample collection was to be done prior to study drug administration at certain visits.
Section 3: STUDY DESIGN		
Section 3.1: General Design and Study Schema (Other sections affected by this change: Table 2, Footnote a, 3.16.1. Procedures for Screening and Start of Run-In Period [Visits 1 and 2])		
Patients will begin screening up to **approximately** 5 weeks **(±1 week) before** ~~prior to~~ DoR.	Patients will begin screening up to approximately 5 weeks (±1 week) before DoR.	Clarifies the duration of the screening period and allows flexibility for scheduling around holidays and weekends.
Section 3.1: General Design and Study Schema (Other sections affected by this change: Clinical Study Protocol Synopsis):		
Patients will return 8 weeks after the end of treatment visit (EOT visit) for follow-up hematology, PK, **and** immunogenicity, ~~biomarker, lung function~~, and safety assessments.	Patients will return 8 weeks after the end of treatment visit (EOT visit) for follow-up hematology, PK, and immunogenicity, and safety assessments.	Biomarker in this case refers to eosinophils which falls under hematology which is already listed. Lung function will not be assessed during the follow-up. The deletion makes this consistent with Table 2.
Section 3.1: General Design and Study Schema:		
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 their withdrawal from the study **(see Section 4.4)**~~drug~~.	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 their withdrawal from the study (see Section 4.4).	Section link added for clarity.
Section 3.1: General Design and Study Schema; Figure 1: Overall Study Schema:		
Figure 1: Reversibility ≥12%~~ and absolute change of ≥200 mL~~	**Figure 1:** Reversibility ≥12%	Deletions were made to improve clarity in the figure.
Figure 1: (**CBC,** PK, immunogenicity, ~~biomarker, AE,~~ and ~~FEV$_1$~~**safety assessment**)	**Figure 1:** (CBC, PK, immunogenicity, and safety assessment)	Assessments at the follow-up visit EOT + 8 weeks were clarified.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.1: General Design and Study Schema (Other sections affected by this change: Clinical Study Protocol Synopsis, and Sections 3.16.1 and 4.1):		
To be eligible to enroll in the study, a patient will have an ACQ-6 score of at least 1.5, airway FEV_1 reversibility of at least 12% ~~and an absolute change of at least 200 mL~~ to beta-agonist administration, blood eosinophil count of at least 300/µL, and a current fluticasone propionate dosage of at least 440 µg daily (or equivalent) with a second asthma controller and will have met all the inclusion and none of the exclusion criteria at screening.	To be eligible to enroll in the study, a patient will have an ACQ-6 score of at least 1.5, airway FEV_1 reversibility of at least 12% to beta-agonist administration, blood eosinophil count of at least 300/µL, and a current fluticasone propionate dosage of at least 440 µg daily (or equivalent) with a second asthma controller and will have met all the inclusion and none of the exclusion criteria at screening.	This deletion was made for severe asthma patients on high GINA step therapy (ie, ICS plus another controller (s) including OCS), it may be overly difficult to achieve both criteria.
[redacted]		
Section 3.9: Randomization and Blinding:		
The randomization list and treatment will be assigned to the relevant treatment groups through a qualified ~~service provider~~ **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 ~~service provider~~**CRO** under the oversight of Teva's Clinical Supply Chain.	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.	Change wording from "service provider" to "CRO."
Section 3.9: Randomization and Blinding (Other sections affected by this change: Clinical Study Protocol Synopsis):		
~~In addition, t~~**T**he sponsor's clinical 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 who will not be blinded to facilitate PK and ADA sample analysis. Eosinophils and monocytes will be redacted from the post-baseline differential cell count reports to avoid the possibility of unblinding patients.	The sponsor's clinical 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 who will not be blinded to facilitate PK and ADA sample analysis. Eosinophils and monocytes will be redacted from the post-baseline differential cell count reports to avoid the possibility of unblinding patients.	This addition clarified that the external vendor responsible for PK/PD analyses will not receive randomization codes.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.10.2: Blinding/Unblinding		
In order to complete the ~~bioanalysis of~~ **data analysis** for PK ~~within the demonstrated time window of stability of reslizumab in serum~~, **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~~ 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 **the responsible** Teva statistician, ~~service provider~~**CRO** statistician and randomization code generator. ~~Personnel responsible for bioanalysis and PK data analysis~~ **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 ~~(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).	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).	These edits clarify that randomization codes will be provided directly to the bioanalysis team. The paragraph addition also clarifies Teva's use of PK samples collected during the course of the study.
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.**	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.	This addition clarifies that individuals aware of treatment assignments will also not be involved with assessement of safety or efficacy data.
Section 3.13: (Other sections affected by this change: Clinical Study Protocol Synopsis, Table 2 [Footnote i], Section 3.16.1, and Section 7.3.1):		
The study's duration is approximately 65 weeks, including up to a 2-week **(±3 days)** screening period, a minimum 3-week run-in period, a 52-week treatment period, and a follow-up visit approximately 8 weeks after the end of treatment visit.	The study's duration is approximately 65 weeks, including up to a 2 week (±3 days) screening period, a minimum 3 week run in period, a 52 week treatment period, and a follow-up visit approximately 8 weeks after the end of treatment visit.	This change was made to allow scheduling flexibility for weekends and holidays.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.14 Stopping Rules and Discontinuation Criteria:		
Other than pregnancy, t~~T~~here are no formal rules for early withdrawal from this study.	Other than pregnancy, there are no formal rules for early withdrawal from this study.	This addition clarifies that pregnancy can lead to early withdrawal from the study.
Section 3.16: Study Procedures; Table 2: Study Procedures and Assessments:		
Addition of column for Late follow-up (visit number V19 and week W76)	Addition of column for Late follow-up and visit number V19 and week W76	Clarification added.
Additional day for pregnancy testing at V18	Additional day for pregnancy testing (V18)	Clarification added.
Additional days for providing/collecting asthma control diary and reinforcing diary and PEF compliance at V_{PK} and V4	Additional days for providing/collecting asthma control diary and reinforcing diary and PEF compliance at V_{PK} and V4	Clarification added.
[d] Beta-human chorionic gonadotropin serum pregnancy tests will be performed at screening (female patients who are not 2 years postmenopausal or surgically sterile only). Urine pregnancy tests will be performed at baseline/DoR, before study drug injection at each administration visit and at week 52, or early withdrawal, **and at follow-up V18**. Pregnancy tests are not required for female patients who are 2 years postmenopausal or surgically sterile.	[d] Beta-human chorionic gonadotropin serum pregnancy tests will be performed at screening (female patients who are not 2 years postmenopausal or surgically sterile only). Urine pregnancy tests will be performed at baseline/DoR, before study drug injection at each administration visit and at week 52, or early withdrawal, and at follow-up V18. Pregnancy tests are not required for female patients who are 2 years postmenopausal or surgically sterile.	Text was updated to be consistent with Table 2.
Serum chemistry tests**[f]** **[f] 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.**	Serum chemistry tests[f] [f] 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 f was added for Serum Chemistry Tests.

Original text with changes shown	New wording	Reason/Justification for change
~~h~~ ~~i~~ A failed reversibility test may be repeated once, within the 2-week **(±3 days)** screening period. Reversibility testing will be confirmed **before**~~prior to~~ entering the run-in period. **Documented historical reversibility within 12 months of signing the Informed Assent Form/Informed Consent Form is acceptable as per inclusion criterion f.**	[i] A failed reversibility test may be repeated once, within the 2-week (±3 days) screening period. Reversibility testing will be confirmed before entering the run-in period. Documented historical reversibility within 12 months of signing the Informed Assent Form/Informed Consent Form is acceptable as per inclusion criterion f.	Clarification added.
~~[i] An additional, late follow-up for PK testing will be performed 28 weeks (±2 weeks) after the last dose of study drug (~ week 76) for ADA assessment.~~	*The footnote was deleted.*	Clarification added.
Adverse event inquiry**[o]** **[o] 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).**	Adverse event inquiry[o] [o] 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).	Footnote o was added for Adverse Event Inquiry.
3.16.1. Procedures for Screening and Start of Run-In Period (Visits 1 and 2) Other sections affected by this change: Table 2 and Section 3.1):		
The screening visit (visit 1) will take place ~~not more than~~**approximately** 5 weeks **(±1 week)** ~~but not less than 3 weeks~~ before the baseline/DoR visit. The following procedures will be performed at visit 1:	The screening visit (visit 1) will take place approximately 5 weeks (±1 week) before the baseline/DoR visit. The following procedures will be performed at visit 1:	This change clarifies the duration of the screening period and allows flexibility for scheduling around holidays and weekends.
Section 3.16.1: Procedures for Screening and Start of Run-In Period (Visits 1 and 2) (Other sections affected by this change: Sections 3.16.2 and 3.16.3.1.2):		
Perform reversibility testing if long acting and short acting inhaled ~~beta-agonists~~ **bronchodilators** were held for the specified time; if not, the patient should be brought back on another day to complete.	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.	The wording "beta-agonists" was changed to "bronchodilators."

Original text with changes shown	New wording	Reason/Justification for change
Section 3.16.1: Procedures for Screening and Start of Run-In Period (Visits 1 and 2):		
Reversibility testing may be repeated once within the 2-week **(±3 days)** screening period. Airway reversibility will be demonstrated by measuring the change in FEV_1 before and after inhalation of ~~albuterol~~**SABA**; reversibility testing should **only** be attempted after withholding ~~long~~**short-acting bronchodilators (ie, inhaled short**-acting beta-~~agonist therapy for at least 12 hours and SABA therapy~~**adrenergic agonists and/or short-acting anticholinergics)** for at least 6 hours~~.~~ ~~Up~~ **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 ~~4 puffs of SABA therapy~~**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 metered dose inhaler**, as tolerated. **Post-bronchodilator spirometry should be completed a minimum of 15 minutes after dosing of SABA.**	Reversibility testing may be repeated once within the 2-week (±3 days) screening period. Airway reversibility will be demonstrated by measuring the change in FEV_1 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 metered dose inhaler, as tolerated. Post-bronchodilator spirometry should be completed a minimum of 15 minutes after dosing of SABA.	To make consistent with the text provided Table 2 Study Procedures and Assessments.
Section 3.16.3.1: Double-Blind Treatment Period:		
Study drug will be administered at approximately ~~0800 (±2 hours)~~**the same time in the morning** on the day**s** indicated in Table 2.	Study drug will be administered at approximately the same time in the morning on the days indicated in Table 2.	As this is an anti-inflammatory drug with a long half-life, the exact hour not critical.
Section 3.16.3.1.2: Other On-Treatment Visits (Visits 4 through 17 [EOT]):		
• Complete the ACQ-6 **(may be completed after study drug administration during the 1-hour observation period.)** • Complete the AQLQ +12 (weeks 4, 8, 12, 16, 32, and 52 or early withdrawal only) **(AQLQ+12 may be completed after study drug administration during the 1-hour observation period.)** • Complete the SGRQ (weeks 32 and 52) **(may be completed after study drug administration during the 1-hour observation period.)** • [redacted]	• Complete the ACQ-6 (may be completed after study drug administration during the 1-hour observation period.) • Complete the AQLQ +12 (weeks 4, 8, 12, 16, 32, and 52 or early withdrawal only) (AQLQ+12 may be completed after study drug administration during the 1-hour observation period.) • Complete the SGRQ (weeks 32 and 52) (may be completed after study drug administration during the 1-hour observation period.) • [redacted]	Clarification around timing of questionnaires was also added.

Original text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	
The following procedures/assessments will be performed during and after administration of study drug: • **Patients will be observed for 1 hour after study injection** • **Perform adverse event inquiry** – **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 7.1.6.** **Remind the patients that they will receive a post-injection symptom inquiry via the eDiary.**	The following procedures/assessments will be performed during and after administration of study drug: • Patients will be observed for 1 hour after study injection • Perform adverse event inquiry – 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 7.1.6. Remind the patients that they will receive a post-injection symptom inquiry via the eDiary.	These additions were added to clarify the procedures and assessments to be performed during and after administration of study drug, as well as 24 hours after administration of the study.
Section 3.16.4: eDiary Procedures After Study Drug Treatment (Other sections affected by this change: Sections 3.1):		
Patients who discontinue treatment prematurely must be encouraged to continue to attend the regular scheduled visits, and complete the prescribed safety and efficacy evaluations through the end-of-treatment/early withdrawal visit and the follow-up visit, if at all possible **(see Section 4.4).**	Patients who discontinue treatment prematurely must be encouraged to continue to attend the regular scheduled visits, and complete the prescribed safety and efficacy evaluations through the end-of-treatment/early withdrawal visit and the follow-up visit, if at all possible (see Section 4.4).	A cross-reference was added to improve clarity.
The following procedures/assessments will be performed at the follow-up visit (EOT +8 weeks ±14 days, end of study visit): • **Perform urine pregnancy test.**	The following procedures/assessments will be performed at the follow-up visit (EOT +8 weeks ±14 days, end of study visit): • Perform urine pregnancy test.	Edit made for consistency with Table 2.

Original text with changes shown	New wording	Reason/Justification for change
Section 4: SELECTION AND WITHDRAWAL OF PATIENTS		
Section 4.1: Patient Inclusion Criteria (Other sections affected by this change: Clinical Study Protocol Synopsis):		
g. The patient has required at least ~~4~~40 ~~µg of~~**a medium** total daily **ICS** dose **based on GINA 2015 clinical comparability table (Appendix A)** ~~inhaled fluticasone propionate or equivalent total daily dose~~for at least 3 months.	g. The patient has required at least a medium total daily ICS dose based on GINA 2015 clinical comparability table (Appendix A) for at least 3 months.	Clarification: intent is 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 (with an additional asthma controller as per inclusion h).
i. Females of childbearing potential (not surgically sterile 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 ~~4~~**5** months after ~~discontinuation of~~**last** study drug **dose**. **Contraception is further clarified in an administrative letter in Section 17.3.1.**	i. Females of childbearing potential (not surgically sterile 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. Contraception is further clarified in an administrative letter in Section 17.3.1.	Correction of time point after last dose of study drug with regards to use of contraception.
l. inadequate asthma control at baseline/DoR as evidenced by **1 of the 4 criteria below**:	l. inadequate asthma control at baseline/DoR as evidenced by 1 of the 4 criteria below:	This addition provides context to the text that follows.
Section 4.2: Patient Exclusion Criteria (Other sections affected by this change: Clinical Study Protocol Synopsis):		
e. The patient is a pregnant or lactating woman, or intends to become pregnant during the study **or within 5 months after the last dose of study drug**. Any woman becoming pregnant during the study will be withdrawn from the study.	e. The patient is a pregnant or lactating woman, or intends to become pregnant during the study or within 5 months after the last dose of study drug. Any woman becoming pregnant during the study will be withdrawn from the study.	This addition specified the period after the last dose of the study drug during which patient may not become pregnant.
Section 4.4: Criteria and Procedures for Discontinuation of Study Treatment and/or Study Withdrawal:		
~~Withdrawal~~ Criteria and Procedures **for Discontinuation of Study Treatment and/or Study Withdrawal**	Criteria and Procedures for Discontinuation of Study Treatment and/or Study Withdrawal	The title for the section was updated.
In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), ~~each patient is free to~~**patients may voluntarily discontinue study treatment (ie, refuse study treatment**	In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), patients may voluntarily discontinue study treatment (ie, refuse study	These edits clarified the procedures for discontinuation or withdrawal from the study.

Original text with changes shown	New wording	Reason/Justification for change
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. ~~In addition, a patient may be withdrawn from the study as described in Sections 3.10, 3.14, 3.16.3.1, 5.4, and 7.1.7.~~ ~~Should a patient decide to withdraw from the treatment period 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 given as to why the patient is withdrawing or being withdrawn from the study. The reason for and date of withdrawal from study drug treatment and the reason for and date of withdrawal from the study~~ 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.	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 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.	
Section 4.4.1: Discontinuation of Study Treatment		
4.4.1: Discontinuation of Study Treatment **If premature discontinuation of study treatment occurs for any reason the patient should continue attending remaining study**	**4.4.1: Discontinuation of Study Treatment** If premature discontinuation of study treatment occurs for any reason the	This section was inserted to clarify discontinuation of study treatment.

Original text with changes shown	New wording	Reason/Justification for change
visits while off study treatment. 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 ~~protocol-specified~~ evaluations should be performed ~~at~~**as specified in the protocol for** the early withdrawal visit (see Table 2). ~~Patients who~~ **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 52 (visit 17). The CAE event status and safety assessments at week 52 (visit 17) 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, CAE events, and survival status at week 52. A safety follow-up visit (visit 18) should be conducted 8 weeks after visit 17.**	patient should continue attending remaining study visits while off study treatment. The patient should not be considered withdrawn from the study due to interruption or discontinuation 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 2). 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 52 (visit 17). The CAE event status and safety assessments at week 52 (visit 17) 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, CAE events, and survival status at week 52. A safety follow-up visit (visit 18) should be conducted 8 weeks after visit 17.	
4.4.2: Complete Withdrawal from Study **If a patient decides to completely** withdraw from the study ~~will be asked to return to the clinical site for a follow-up visit 8 weeks ±14~~	**4.4.2: Complete Withdrawal from Study** If a patient decides to completely withdraw from the study (ie, refuses	

Original text with changes shown	New wording	Reason/Justification for change
~~days after the early~~**(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 4.4.1 (Discontinuation of Study Treatment) before** withdrawal~~ visit. All protocol-specified evaluations should be performed at the follow-up visit 8 weeks ±14 days after the early~~**. A complete final evaluation at the time of the patient's** withdrawal ~~visit (see Table 2). A subject~~**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, CAE events, and survival status at the end of the 52-week treatment period. A patient** should only be designated as lost to follow-up if the site is unable to establish contact with the ~~subject~~**patient** after 3- documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc). ~~If the final visit is conducted more than 28 (±7) days after the final dose of study drug, all safety evaluations will be performed, but efficacy evaluations will not be made (see Section 3.16.3.1).~~	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 4.4.1 (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, CAE events, and survival status at the end of the 52-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).	
Section 5: TREATMENT OF PATIENTS		
Section 5.1. Drugs Administered During the Study		

Original text with changes shown	New wording	Reason/Justification for change
Study drug will be administered as a single sc injection containing either placebo (1.0 mL) or 110 mg of reslizumab (1.0 mL). ~~In the CRF, injection sites will be labeled (eg, "A," "B," or "C").~~	Study drug will be administered as a single sc injection containing either placebo (1.0 mL) or 110 mg of reslizumab (1.0 mL).	Text was deleted to provide additional clarity.
Section 5.3: Prior and Concomitant Therapy or Medication:		
Indication, dosage, and start and end dates should be entered on the **appropriate** CRF.	Indication, dosage, and start and end dates should be entered on the appropriate CRF.	Clarification added.
Section 6: ASSESSMENT OF EFFICACY		
Section 6.2. Spirometry		
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 metered dose inhaler, as tolerated. Post-bronchodilator spirometry should be completed a minimum of 15 minutes after dosing of SABA.	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 metered dose inhaler, as tolerated. Post-bronchodilator spirometry should be completed a minimum of 15 minutes after dosing of SABA.	The doses of various beta-agonists for spirometry were clarified by this addition.
Spirometry will be done according to American Thoracic Society/European Respiratory Society **2005** procedural guidelines.	Spirometry will be done according to American Thoracic Society/European Respiratory Society 2005 procedural guidelines.	Year of guidance was specified for clarity.
Section 6.10: Asthma Rescue Medication Use		
6.10: ~~Short-Acting Beta-Agonist~~ **Asthma Rescue Medication Use** The number of times ~~SABA therapy~~ **asthma rescue medication** (number of inhalataions/puffs) is used ~~for rescue purposes~~ will be assessed by reviewing the asthma control diary.	**6.10: Asthma Rescue Medication Use** The number of times asthma rescue medication (number of inhalataions/puffs) is used will be assessed by reviewing the asthma control diary.	SABA therapy was changed to asthma rescue medication and the title of the section was also updated.

Original text with changes shown	New wording	Reason/Justification for change
Section 7: ASSESSMENT OF SAFETY		
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." **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.**	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 7.1.5.3.1: Investigator Responsibility (Other sections affected by this change: Section 8.3):		
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.	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.	This text was added to clarify that a blood sample to measure serum reslizumab will be collected for patients experiencing certain types of adverse events.
cause of death (whether or not the death was related to study drug **as determined by the investigator**)	cause of death (whether or not the death was related to study drug as determined by the investigator)	Clarification added.
Section 7.1.6: 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~~, (possibly related to the study drug),~~ 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 7.1.5.1. 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 7.1.5.3).**	For 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 7.1.5.1. 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 7.1.5.3).	This addition clarified where all anaphylaxis events were to be recorded.
Section 7.1.7 Specific Adverse Event Case Report Form Capturing		
Section 7.1.7.1 Anaphylaxis/Hypersensitivity Reactions Case Report Form		
~~Hypersensitivity reactions will be monitored~~	Information about all suspected	Section 7.1.7 and its

Original text with changes shown	New wording	Reason/Justification for change
~~using the diagnostic createria for~~ **Information about all suspected** anaphylaxis ~~as outlined by~~ **events will be recorded on the Suspected Anaphylaxis/Hypersensitivity Reactions CRF, which is based on** 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.**	anaphylaxis events will be recorded on the Suspected Anaphylaxis/Hypersensitivity Reactions CRF, which is based on the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis (Sampson et al, 2006; Appendix H). The anaphylaxis 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.	2 subsections were added to describe the capturing of specific adverse events on the CRF.
Section 7.1.7.2: Creatine Phosphokinase/Muscular Adverse Events Case Report Form:		
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 ≥3.1× 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").	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 ≥3.1× 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").	This section was added to address the reporting of muscular adverse events.
Section 7.1.9: Overdose of Study Drug:		
Medication errors will be captured as protocol violations or deviations depending on the error.	Medication errors will be captured as protocol violations or deviations depending on the error.	This text clarified how medication errors would be captured.
Section 7.3.3.1: Urinalysis:		
Urinalysis will **be performed at screening and will** include testing for the following:	Urinalysis will be performed at screening and will include testing for the following:	Text was added that urinalysis was to be collected for an elevated CPK level.
Section 7.3.4.1: Human Chorionic Gonadotropin Tests:		

Original text with changes shown	New wording	Reason/Justification for change
Human chorionic gonadotropin serum tests will be performed for all females of childbearing potential at screening (visit 1). ~~Human chorionic gonadotropin urine~~**Urine pregnancy** tests will be performed ~~for all females of childbearing potential~~**at baseline/DoR**, before study drug injection at each administration visit and at week 52**,** or early withdrawal**, and at follow-up V18**. Any patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.	Human chorionic gonadotropin serum tests will be performed for all females of childbearing potential at screening (visit 1). Urine pregnancy tests will be performed at baseline/DoR, before study drug injection at each administration visit and at week 52, or early withdrawal, and at follow-up V18. Any patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.	These edits clarified the visits at which pregnancy tests would be performed.
Section 9: STATISTICS		
Section 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. ~~In this analysis set, treatment will be assigned based upon the treatment Patients actually received, regardless of the treatment to which they were randomized.~~	The Per-Protocol (PP) Analysis Set is a subset of the ITT Analysis Set including only Patients without major protocol violations.	These deletions add clarity to the definition of the per-protocol analysis set.
Section 9.5.6: Planned Method of Analysis:		
The baseline for diary variables will be the average of the run-in values over the 7 days preceding baseline/DoR. The baseline for clinic visit variables will be the **last observed**~~predose, pre bronchodilator baseline/DoR~~ value **before the first dose of study drug.** The baseline for eosinophils levels analysis will be screening value.	The baseline for diary variables will be the average of the run-in values over the 7 days preceding baseline/DoR. The baseline for clinic visit variables will be the last observed value before the first dose of study drug. The baseline for eosinophils levels analysis will be screening value.	Clarification of baseline values
Section 9.5.6.1: Primary Efficacy Analysis:		
[redacted]		
Section 9.5.6.1: Primary Efficacy Analysis (Other sections affected by this change: Clinical Study Protocol Synopsis):		
The primary analysis of frequency of CAEs will use the NB regression model. The primary NB model will include the treatment group**,**~~and~~ randomization stratification factors, **and number of exacerbations in the previous year** as model factors and an offset variable.	The primary analysis of frequency of CAEs will use the NB regression model. The primary NB model will include the treatment group, randomization stratification factors, and number of exacerbations in the previous year as model factors and an offset variable.	This change clarified that the number of exacerbations in the previous year will also be included in the NB regression model.
Section 9.5.6.2: Secondary Efficacy Analysis (Other sections affected by this change: Clinical Study Protocol Synopsis):		

Original text with changes shown	New wording	Reason/Justification for change
Analysis of percentage of asthma control days will use an analysis of ~~co~~variance (AN~~C~~OVA) model with treatment group and stratification factors. ~~Additional covariates or factors may be added to the model. These will be detailed in the Statistical Analysis Plan.~~ **Additional covariates or factors may be added to the statistical models. These will be detailed in the Statistical Analysis Plan.**	Analysis of percentage of asthma control days will use an analysis of variance (ANOVA) model with treatment group and stratification factors. Additional covariates or factors may be added to the statistical models. These will be detailed in the Statistical Analysis Plan.	Updated based on statistical analysis plan and moved last 2 sentences from first paragraph to fourth paragraph for clarity.
Section 9.7.2: Safety Analysis:		
Summaries will be presented for all adverse events that started after first study dosing (overall and by severity), adverse events determined by the investigator to be related to study treatment (ie, reasonable possibility; see Section 7.1.4) (defined as related or with missing relationship) (overall and by severity), serious adverse events, adverse events causing ~~withdrawal from the study~~**discontinuation from study treatment**, adverse events with onset ~~date after end of treatment 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. In addition, summaries of adverse events will be presented separately for patients with ADA positive status and patients with ADA negative status. Patient listings of adverse events, serious adverse events, and adverse events leading to ~~withdrawal~~ **discontinuation** will be presented.	Summaries will be presented for all adverse events that started after first study dosing (overall and by severity), adverse events determined by the investigator to be related to study treatment (ie, reasonable possibility; see Section 7.1.4) (defined as related or with missing relationship) (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. In addition, summaries of adverse events will be presented separately for patients with ADA positive status and patients with ADA negative status. Patient listings of adverse events, serious adverse events, and adverse events leading to discontinuation will be presented.	Adverse events causing discontinuation were further clarified by these additions.
Section 9.10: Immunogenicity Analysis (Other sections affected by this change: Clinical Study Protocol Synopsis):		
Anti-reslizumab antibody ~~data~~**information** will be **described for subjects who test positive**~~listed at a patient level~~. Samples from placebo-treated patients will not be analyzed.	Anti-reslizumab antibody information will be described for subjects who test positive. Samples from placebo-treated patients will not be analyzed.	Clarification added.
Section 11: QUALITY CONTROL AND QUALITY ASSUARANCE		
Section 11.1.2: Protocol Violations:		

Original text with changes shown	New wording	Reason/Justification for change
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.	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.	Clarification added.
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.	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.	Clarification added.

Original text with changes shown	New wording	Reason/Justification for change
Section 12: ETHICS		
Section 12.1: Informed Consent/Assent:		
For patients 18 **years** of age or 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.	For patients 18 years of age or 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.	Missing "years" added.
Appendices A, B, C, D, and E:		
(Sample provided in this appendix is for reference only.)	(Sample provided in this appendix is for reference only.)	Clarification added.

17.4. Amendment 01 Dated 04 May 2015

The revisions listed below have been made to the protocol Study C38072-AS-30025 and are not considered substantial by the Teva Authorized Representative.

Table 6: Changes to the Protocol

Original Text with changes shown	New wording	Reason/Justification for change
Title Page:		
Sponsor ~~(and Monitor)~~ Teva Branded Pharmaceutical Products R&D, Inc. 41 Moores Road Frazer, Pennsylvania 19355 United States	Sponsor Teva Branded Pharmaceutical Products R&D, Inc. 41 Moores Road Frazer, Pennsylvania 19355 United States Monitor [redacted]	This change was to clarify that Teva Branded Pharmaceutical Products R&D, Inc was incorrectly identified as a Monitor
Title Page: Sponsor's Safety Representative		
[redacted] ~~Teva Branded Pharmaceutical Products R&D, Inc.~~ [redacted] [redacted] Teva Pharmaceutical [redacted]	[redacted] Teva Pharmaceuticals [redacted]	Sponsor's Safety Representative changed

Original Text with changes shown	New wording	Reason/Justification for change
CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS:		
Central Spirometry, e-diary and ECG [redacted] Spirometry and e-diary: [redacted] ECG: [redacted]	**Central Spirometry, e-diary and ECG** [redacted] Spirometry and e-diary: [redacted] ECG: [redacted]	Change in vendor for Spirometry and ECG measurements
5.5 TOTAL BLOOD VOLUME:		
The estimated total blood volume withdrawn over the entire study (including screening) is approximately ~~77~~ 115 mL per patient.	The estimated total blood volume withdrawn over the entire study (including screening) is approximately 115 mL per patient.	An internal review identified that the estimated total blood volume was incorrect
Appendix A		
~~AQLQ Questionaire~~ replaced by AQLQ +12 Questionnaire	AQLQ +12 Questionaire	AQLQ +12 Questionaire is appropriate for patients in Study

17.5. Clarification Letters

17.5.1. Administrative Letter Dated 22 July 2015

Teva Branded Pharmaceutical Products R&D, Inc.
Study C38072-AS-30025

Branded Pharmaceutical Products R&D

22 July 2015

RE: Administrative Letter to Protocol Number: C38072-AS-30025 | EudraCT Number: 2015-000865-29

A 52-Week Double-Blind, Placebo-Controlled, Parallel-Group Efficacy and Safety Study of Reslizumab 110 mg Fixed, Subcutaneous Dosing in Patients with Uncontrolled Asthma and Elevated Blood Eosinophils
Clinical Study Protocol With Amendment 1 – Protocol Approval Date: 04 May 2015

Contraception Use

The purpose of this administrative letter is address minor differences in the wording of inclusion criterion (i.) between the clinical protocol synopsis and full protocol; please refer to reference text below:

Page 10 < CLINICAL STUDY PROTOCOL SYNOPSIS – Inclusion Criteria >

Females of childbearing potential (not surgically sterile 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, steroidal contraceptive (oral, implanted, transdermal, or injected), barrier method with spermicide, abstinence, and partner vasectomy.

Page 57 < 4.1. Patient Inclusion Criteria >

Females of childbearing potential (not surgically sterile 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 4 months after discontinuation of study drug. Acceptable methods of contraception include intrauterine device (IUD), steroidal contraceptive (oral, implanted, transdermal, or injected), barrier method with spermicide, abstinence, and partner vasectomy.

The intent of the aforementioned inclusion criteria is the same. The last dose of study drug is given 1 month prior to end of treatment. Patients should use contraception for 5 months after last study drug dose, which is consistent with using contraception for 4 months after the treatment period ends.

This letter is an addendum to Protocol C38072-AS-30025 and is not considered a substantial amendment. An update will be made in an amendment to the protocol at the next opportunity. If you have any questions, please contact the study personnel designated for protocol issues on the Clinical Study Personnel Contact Information page of the protocol. *Please ensure that a copy of this letter is maintained with the protocol.*

Sincerely,

[redacted]

17.5.2. Addendum Letter Dated 22 April 2015

22 April 2015

RE: Addendum to Protocol Number: C38072-AS-30025; EudraCT Number: 2015-000865-29

A 52-Week Double-Blind, Placebo-Controlled, Parallel-Group Efficacy and Safety Study of Reslizumab 110 mg Fixed, Subcutaneous Dosing in Patients with Uncontrolled Asthma and Elevated Blood Eosinophils (Protocol Approval Date: 26 March 2015)

Total Blood Volume

The purpose of this letter is to notify investigative sites, participating in the above-mentioned study, of a revision related to the estimated total blood volume taken over the entire study.

Following an internal review, it has been determined that the estimated total blood volume withdrawn over the entire study (including screening) is approximately 115 mL per patient and not 77 mL and therefore the following revision to the protocol text is applicable:

Per Section 5.5 Total Blood Volume:

Present:

The estimated total blood volume withdrawn over the entire study (including screening) is approximately 77 mL per patient. To further reduce the volume of blood withdrawn, pediatric tubes will be used when possible.

Proposed:

*The estimated total blood volume withdrawn over the entire study (including screening) is approximately **115 mL** per patient. To further reduce the volume of blood withdrawn, pediatric tubes will be used when possible.*

This letter is an addendum to Protocol C38072-AS-30025 and updated information will be made in an amendment to the protocol at the next opportunity.

If you have any questions, please contact the study personnel designated for protocol issues on the Clinical Study Personnel Contact Information page of the protocol.

A copy of this letter shall be maintained with the protocol approved on 26 March 2015.

Sincerely,

[redacted]

17.5.3. Administrative Letter Dated 14 April 2015

Teva Branded Pharmaceutical Products R&D, Inc.
Study C38072-AS-30025

Date: 14 April 2015

RE: Administrative Letter to Protocol Number: C38072-AS-30025; EudraCT Number: 2015-000865-29

A 52-Week Double-Blind, Placebo-Controlled, Parallel-Group Efficacy and Safety Study of Reslizumab 110 mg Fixed, Subcutaneous Dosing in Patients with Uncontrolled Asthma and Elevated Blood Eosinophils (Protocol Approval Date: 26 March 2015)

Change in Central Spirometry and ECG Vendor

The purpose of this administrative letter is to notify investigative sites, participating in the above-mentioned study, of the change in information for the Central Spirometry and ECG vendor listed on page 4 of the 26 March 2015 protocol under Clinical Laboratory and Other Departments and Institutions. [redacted] will replace [redacted] as the vendor providing these central services:

[redacted]

Spirometry:	ECG:
[redacted]	[redacted]

This administrative letter will be an addendum to Protocol C38072-AS-30025 and is not considered a substantial amendment. If you have any questions, please contact the study personnel designated for protocol issues on the Clinical Study Personnel Contact Information page of the protocol.

Sincerely,

[redacted]

17.5.4. Administrative Letter Dated 26 February 2016

Branded Pharmaceutical Products R&D

Teva Branded Pharmaceutical Products R&D, Inc.
Study C38072-AS-30025

26 February 2016

RE: Administrative Letter to Study Number: C38072-AS-30025;
IND number: 101,399; EudraCT Number: 2015-000865-29

A 52-Week Double-Blind, Placebo-Controlled, Parallel-Group Efficacy and Safety Study of Reslizumab 110 mg Fixed, Subcutaneous Dosing in Patients with Uncontrolled Asthma and Elevated Blood Eosinophils (Protocol Approval Date: 25 January 2016)

Change in Sponsor's Medical Expert

The purpose of this administrative letter is to notify investigative sites, participating in the above-mentioned study, of the change in the Sponsor's Medical Expert listed on page 1 of the C38072-AS-30025 protocol. [redacted] has replaced [redacted] as the Sponsor's Medical Expert for the above mentioned study.

Sponsor's Medical Expert

[redacted]

This administrative letter will be an addendum to Protocol Am 02 C38072-AS-30025, Canada Am 02 Study C38072-AS-30025 and Japan Am 03 Study C38072-AS-30025. It is not considered a substantial amendment; these above mentioned changes will be made to the protocols during the next amendment. If you have any questions, please contact the study personnel designated for protocol issues on the Clinical Study Personnel Contact Information page of the protocol.

[redacted]
Teva Branded Pharmaceutical Products R&D, Inc.

Teva Pharmaceuticals
41 Moores Road | Frazer, PA 19355 | [redacted] | www.tevapharm-na.com

17.5.5. Administrative Letter Dated 08 March 2016

Branded Pharmaceutical Products R&D

Teva Branded Pharmaceutical Products R&D, Inc.
Study C38072-AS-30025

8 March 2016

RE: Administrative Letter to Study Number: C38072-AS-30025;
IND number: 101,399; EudraCT Number: 2015-000865-29

A 52-Week Double-Blind, Placebo-Controlled, Parallel-Group Efficacy and Safety Study of Reslizumab 110 mg Fixed, Subcutaneous Dosing in Patients with Uncontrolled Asthma and Elevated Blood Eosinophils (Protocol Approval Date: 25 January 2016)

Medical Monitors for North America and Latin America:

The purpose of this administrative letter is to notify investigative sites, participating in the above-mentioned study, that there is an error with the list of Medical Monitors on page 7 of Protocol Am 02 C38072-AS-30025. The correct Medical Monitors are [redacted] for the North America region and [redacted] for the Latin America region. [redacted] and [redacted] have been with the program from the start. [redacted] remains the Oversight Lead Medical Monitor for the entire study. [redacted] is no longer supporting the above mentioned study.

The corrected Medical Monitor contact information is:

For North America:

[redacted]

For Latin America:

[redacted]

This administrative letter will be an addendum to Protocol Am 02 C38072-AS-30025, Canada Am 02 Study C38072-AS-30025 and Japan Am 03 Study C38072-AS-30025. It is not considered a substantial amendment; these above mentioned changes will be made to the protocols during the next amendment. If you have any questions, please contact the study personnel designated for protocol issues on the Clinical Study Personnel Contact Information page of the protocol.

Sincerely,

[redacted]

Teva Branded Pharmaceutical Products R&D, Inc.

Teva Pharmaceuticals
41 Moores Road | Frazer, PA 19355 | [redacted] www.tevapharm-na.com

17.5.6. Administrative Letter Dated 21 March 2016

Branded Pharmaceutical Products R&D

Teva Branded Pharmaceutical Products R&D, Inc.
Study C38072-AS-30025

21 March 2016

RE: Administrative Letter to Study Number: C38072-AS-30025; IND number: 101,399;
EudraCT Number: 2015-000865-29

A 52-Week Double-Blind, Placebo-Controlled, Parallel-Group Efficacy and Safety Study of Reslizumab 110 mg Fixed, Subcutaneous Dosing in Patients with Uncontrolled Asthma and Elevated Blood Eosinophils (Protocol Approval Date: 25 January 2016)

Eosinophil count

The purpose of this administrative letter is to reiterate the eosinophil count required during the screening period (prior to visit 2).

There is no change to inclusion criterion e:

e. The patient has a blood eosinophil level of at least 300/μL during the screening period (ie, before visit 2). (A maximum of 30% of the patients with blood eosinophil levels of 300/μL to <400/μL will be enrolled. When this 30% threshold has been reached, only patients with blood eosinophil levels of ≥400/μL will then be enrolled.)

However, for clarity, the wording in Section 3.16.1 is modified as below. There are no inclusion criteria based on an eosinophil count obtained prior to Study participation.

3.16.1. Procedures for Screening and Start of Run-In Period (Visits 1 and 2)

- Perform clinical laboratory tests (chemistry, hematology, urinalysis). Only those patients with an eosinophil count of 300 eosinophils/μL or greater at screening will be eligible to continue in the study~~; patients with historic eosinophil counts of 400 eosinophils/μL or greater will not be eligible~~. Eosinophil testing may be repeated once during the 2-week (±3 days) screening period.

This administrative letter is an addendum to Protocol Am 02 Study C38072-AS-30025, Canada Am 02 Study C38072-AS-30025, and Japan Am 03 Study C38072-AS-30025. It is not considered a substantial amendment; the above mentioned change will be made to the protocols during the next amendment. If there are any questions, please contact the study personnel designated for protocol issues on the Clinical Study Personnel Contact Information page of the protocol.

Sincerely,

[redacted]

Teva Branded Pharmaceutical Products R&D, Inc.

Teva Pharmaceuticals
41 Moores Road | Frazer, PA 19355 | [redacted] | www.tevapharm-na.com

APPENDIX A. GLOBAL INITIATIVE FOR ASTHMA ICS CLINICAL COMPARABILITY TABLE

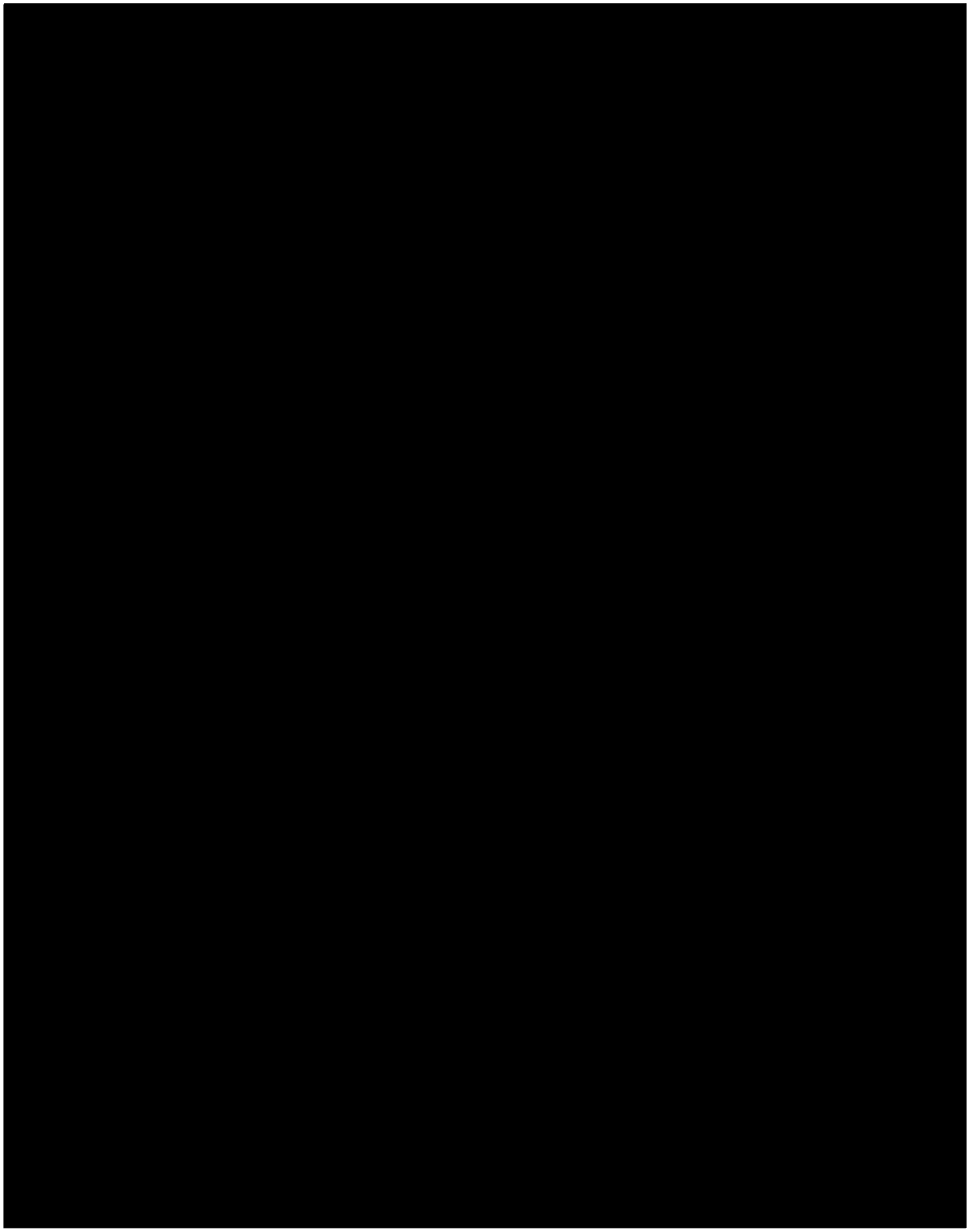
Table 7: Medium or Higher Daily Doses of Inhaled Corticosteroids in Patients 12 Years and Older

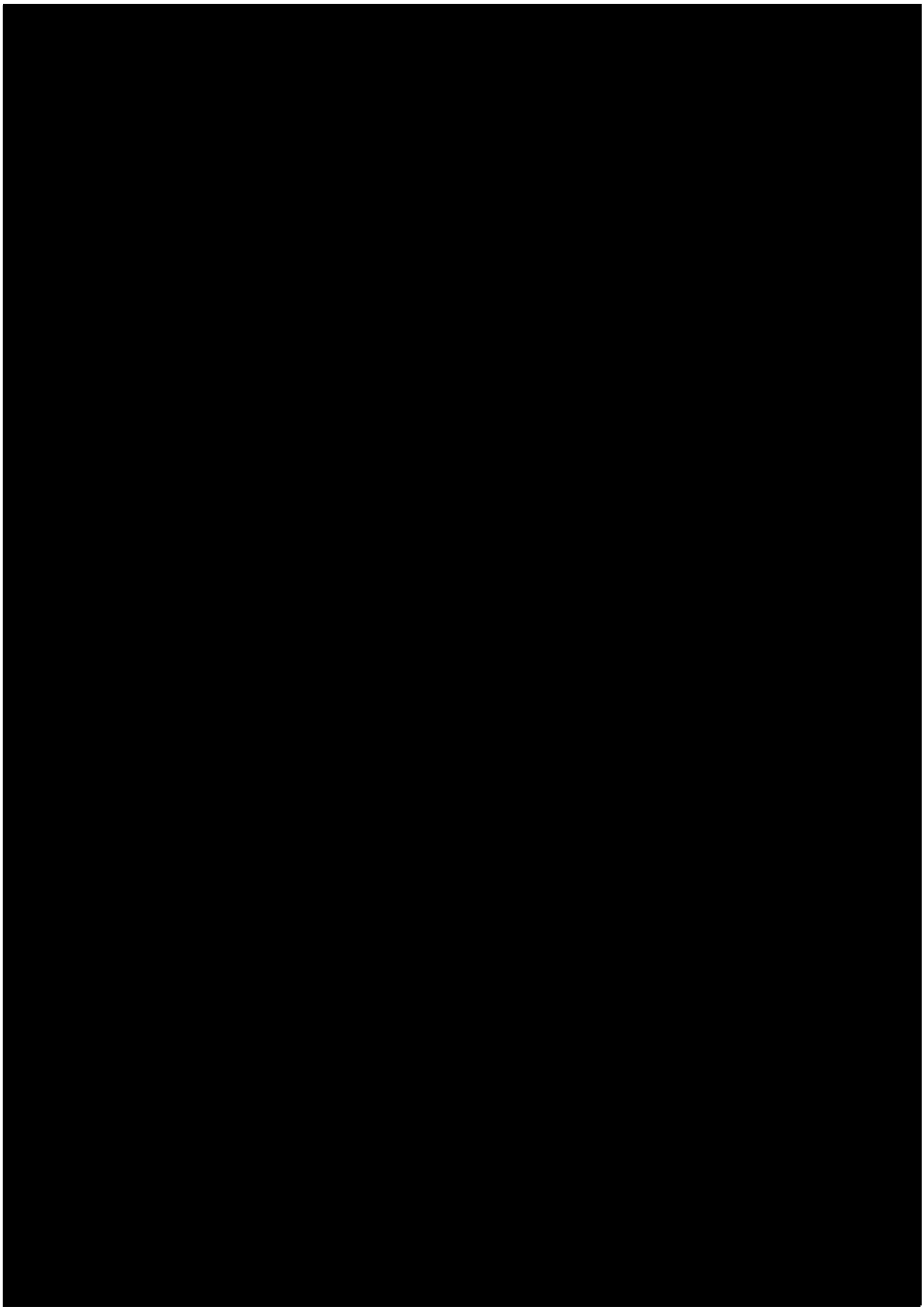
Drug	Daily Dose (µg)	
	Medium	**High**
Beclomethasone dipropionate (CFC)[a]	>500	>1000
Beclomethasone dipropionate (HFA)	>200	>400
Budesonide (DPI)	>400	>800
Ciclesonide (HFA)	>160	>320
Fluticasone fuorate (DPI)	N/A	≥200
Fluticasone propionate (DPI)	>250	>500
Fluticasone propionate (HFA)	>250	>500
Mometasone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

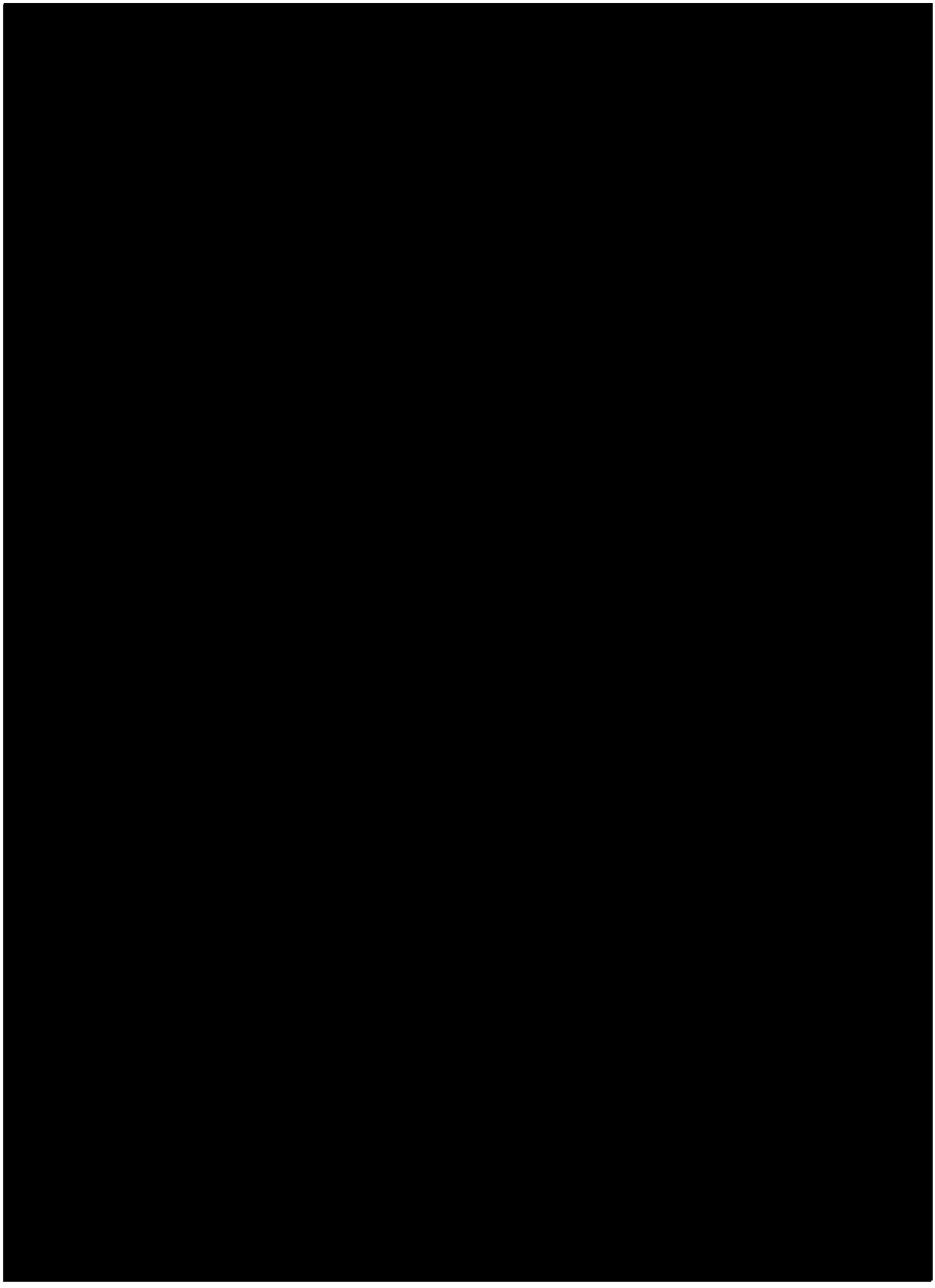
Source: Adapted from Box 8 in GINA 2016 Update (www.ginasthma.org).
[a] Beclometasone dipropionate CFC is included for comparison with older literature.
CFC = chlorofluorocarbon propellant; DPI = dry powder inhaler; HFA = hydrofluoroalkane propellant; N/A = not applicable.

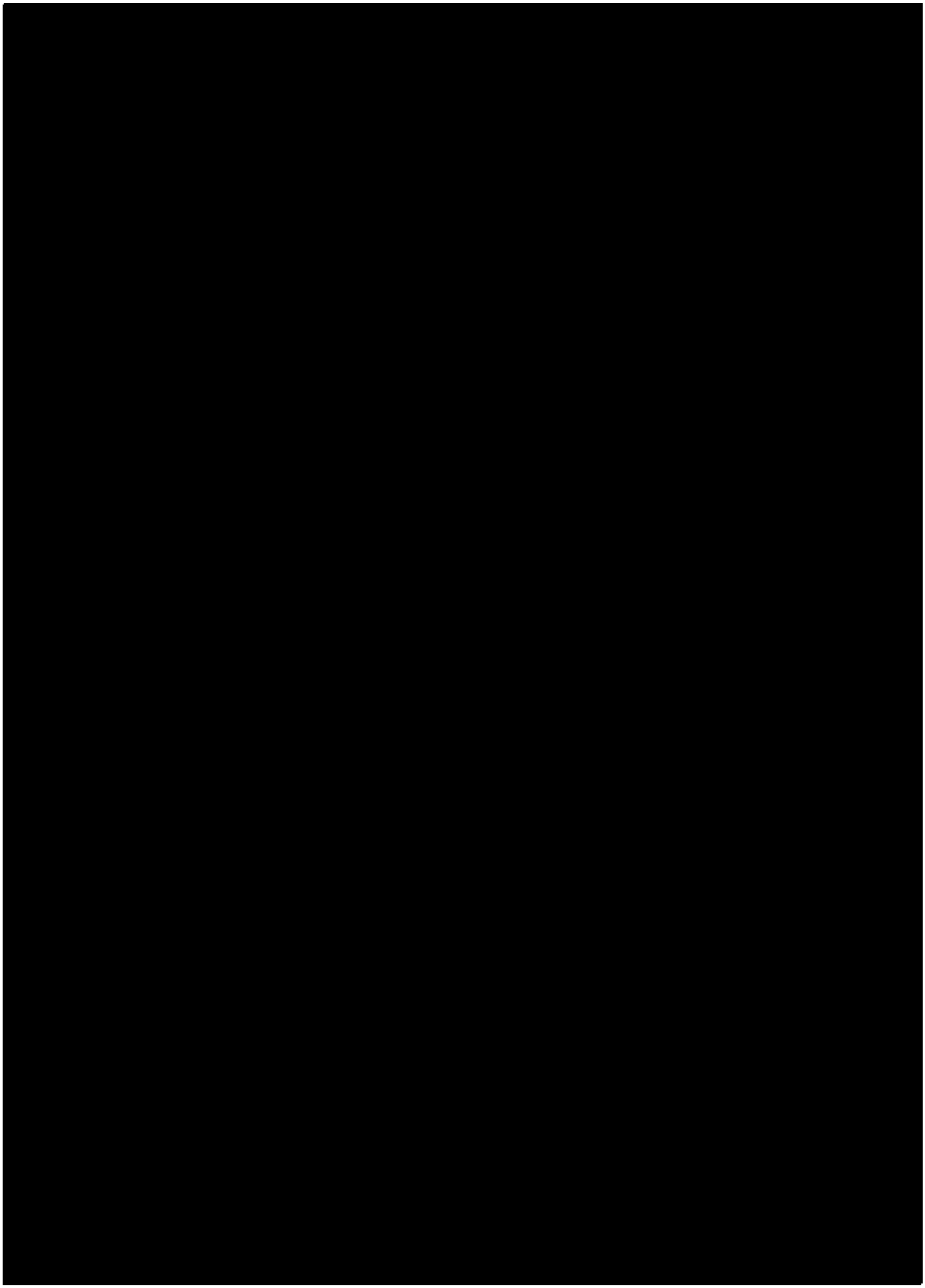
APPENDIX B. ASTHMA QUALITY OF LIFE QUESTIONNAIRE + 12

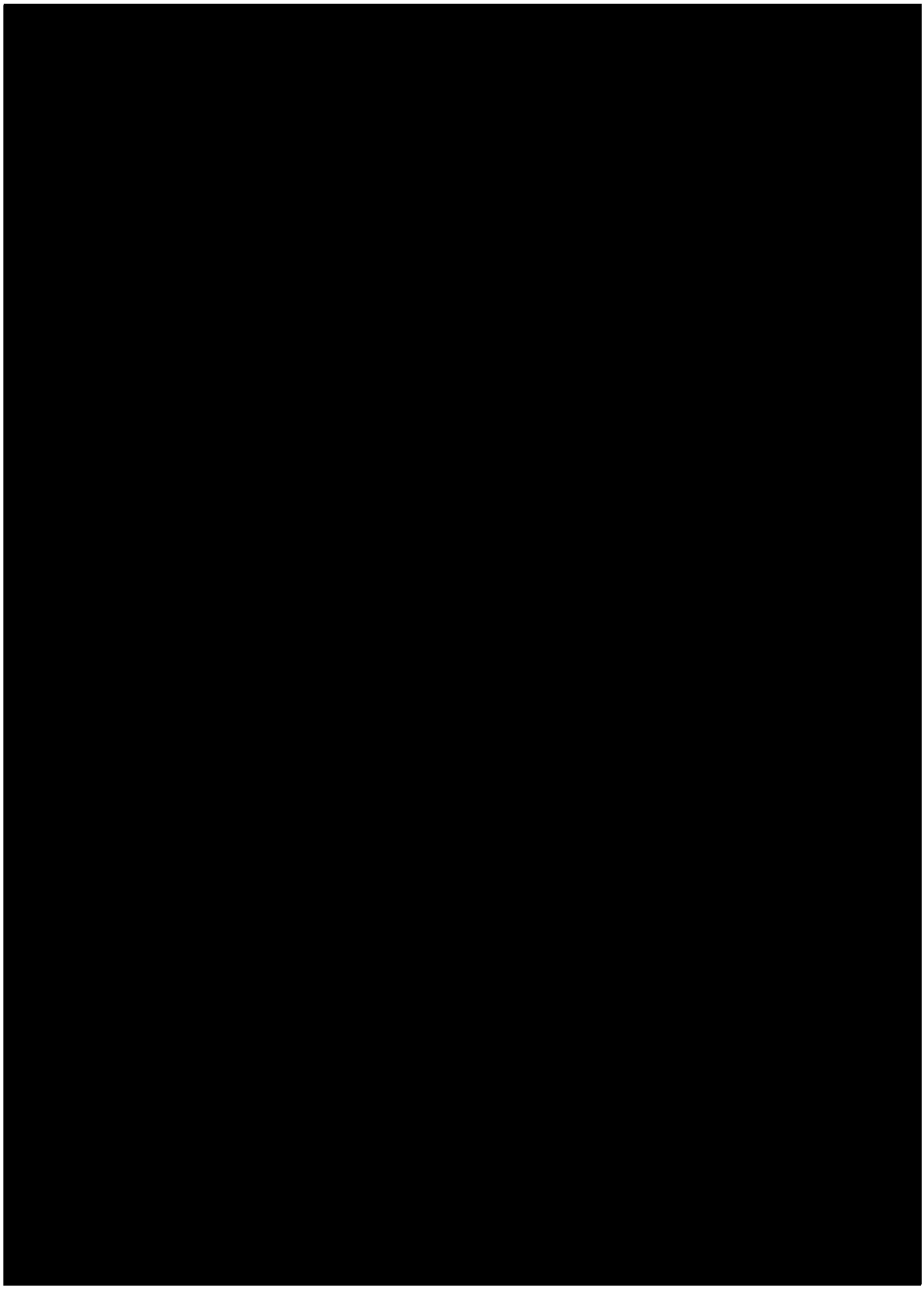
(Sample provided in this appendix is for reference only.)

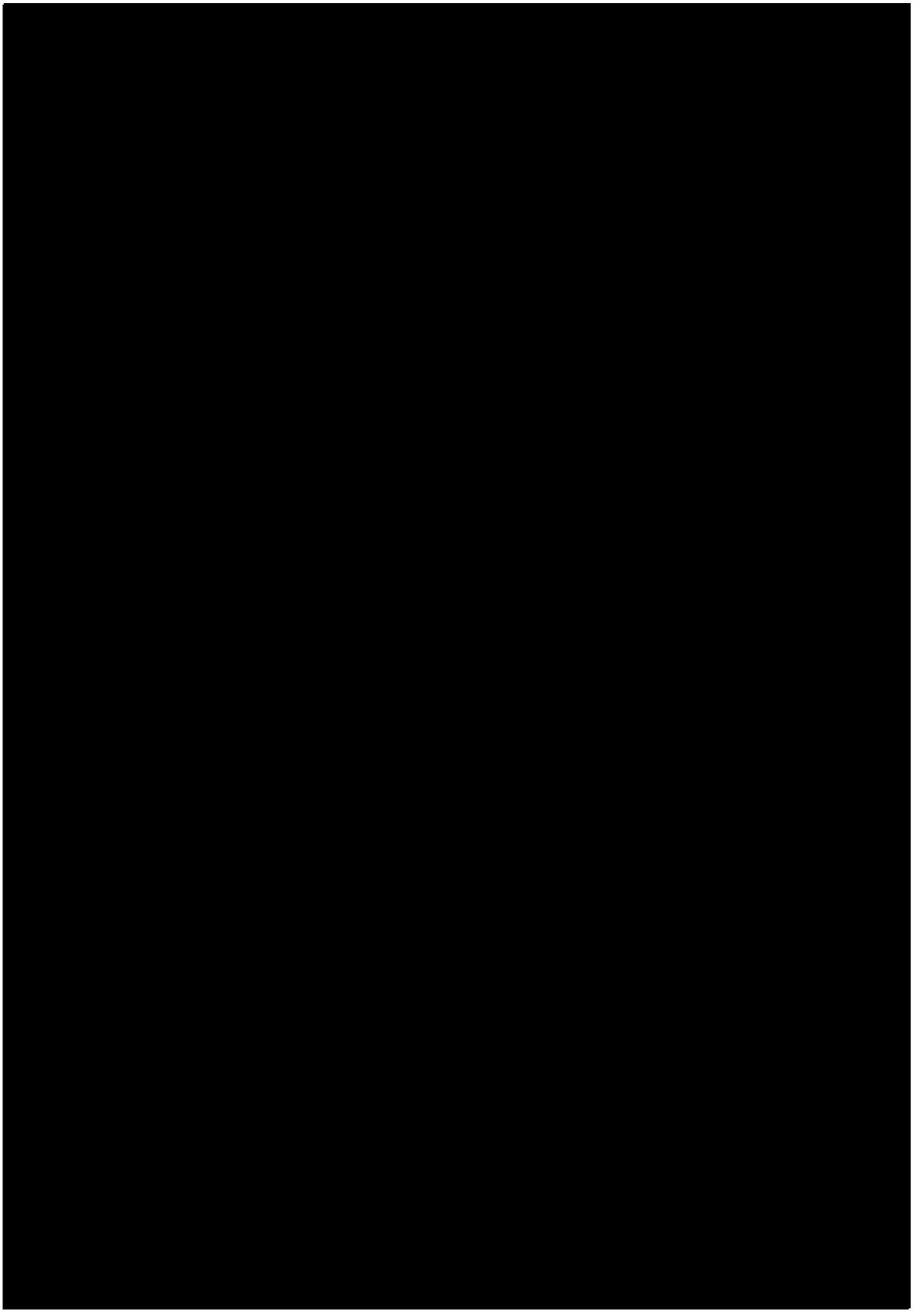






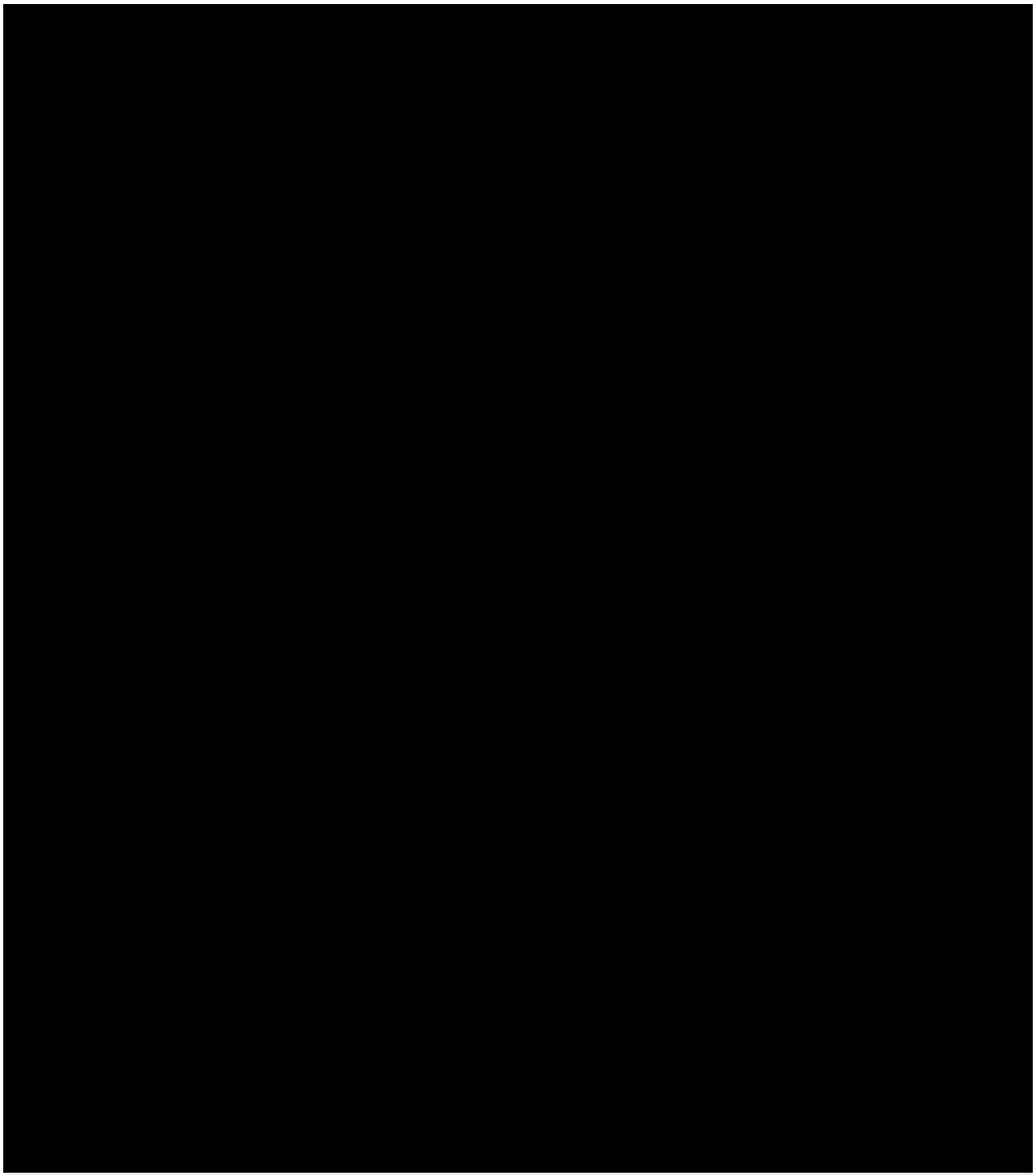




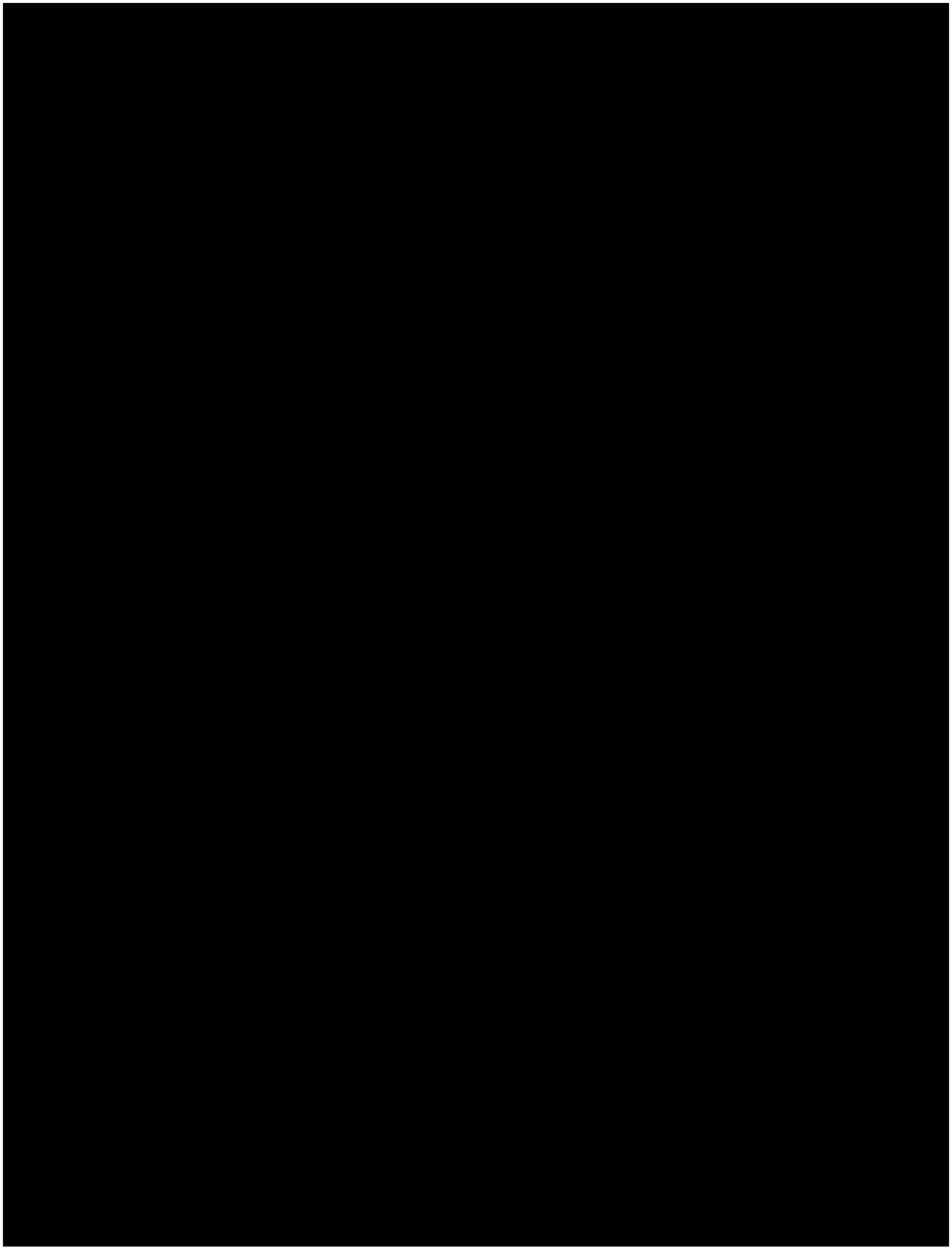


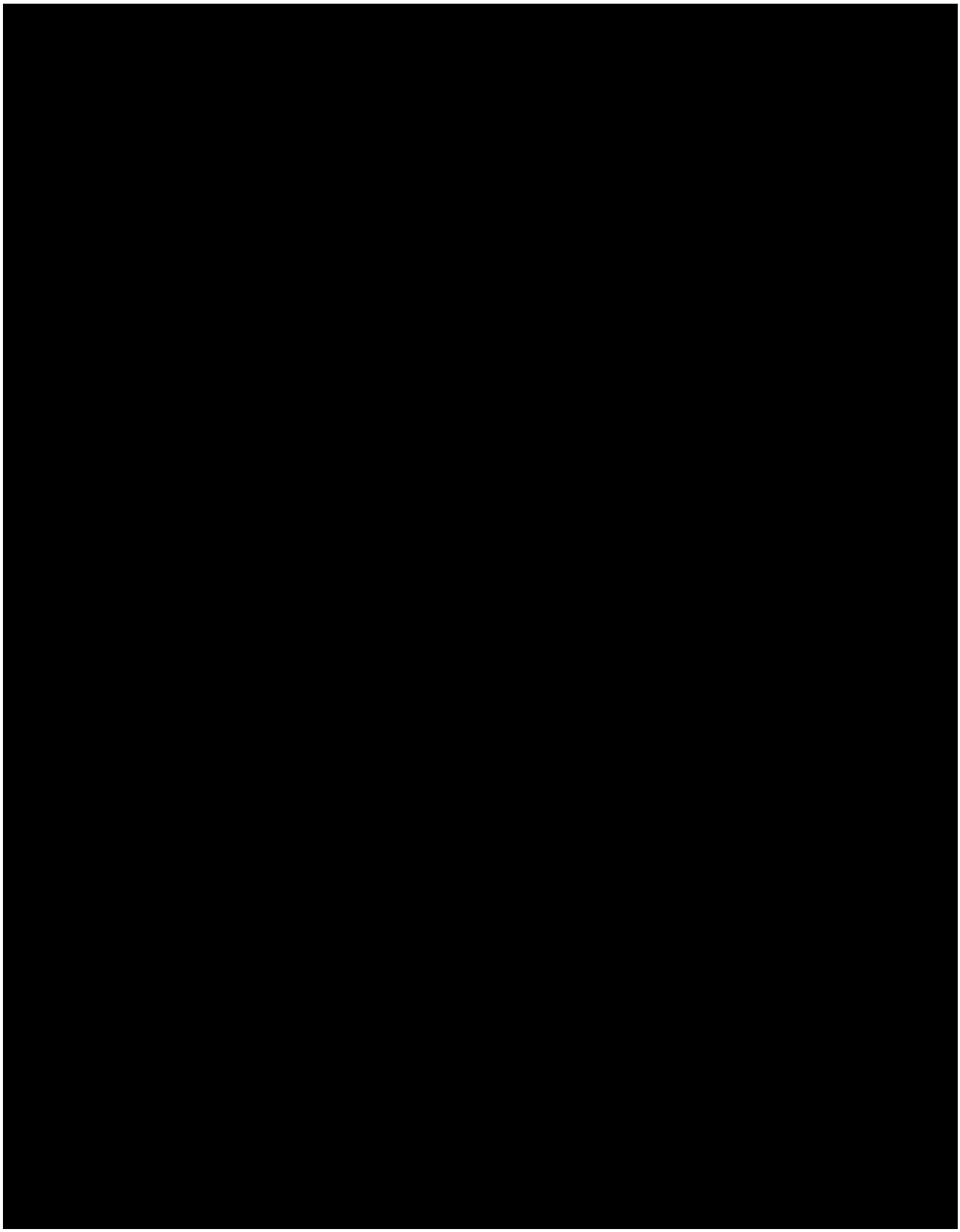
APPENDIX C. ASTHMA CONTROL QUESTIONNAIRE

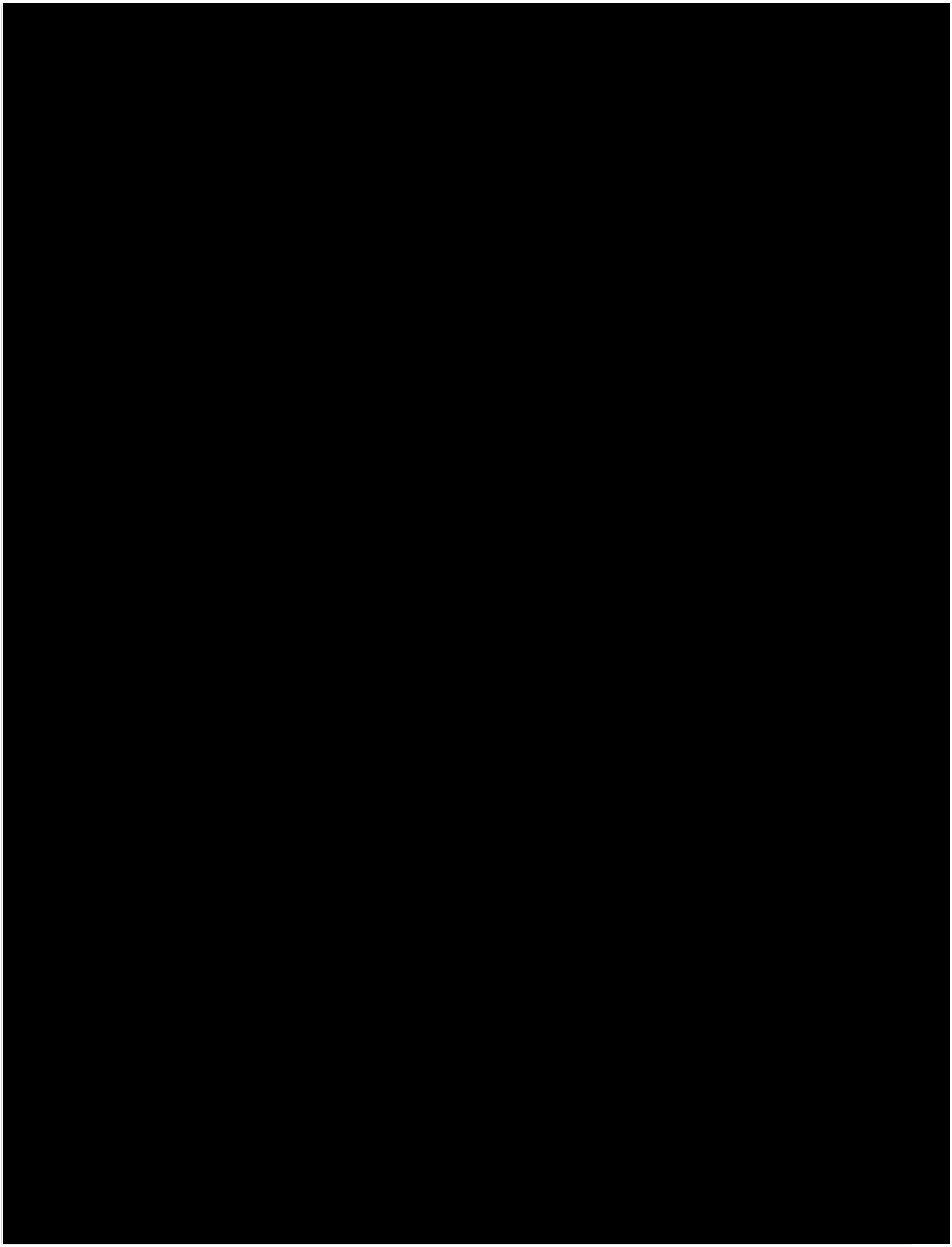
(Sample provided in this appendix is for reference only.)

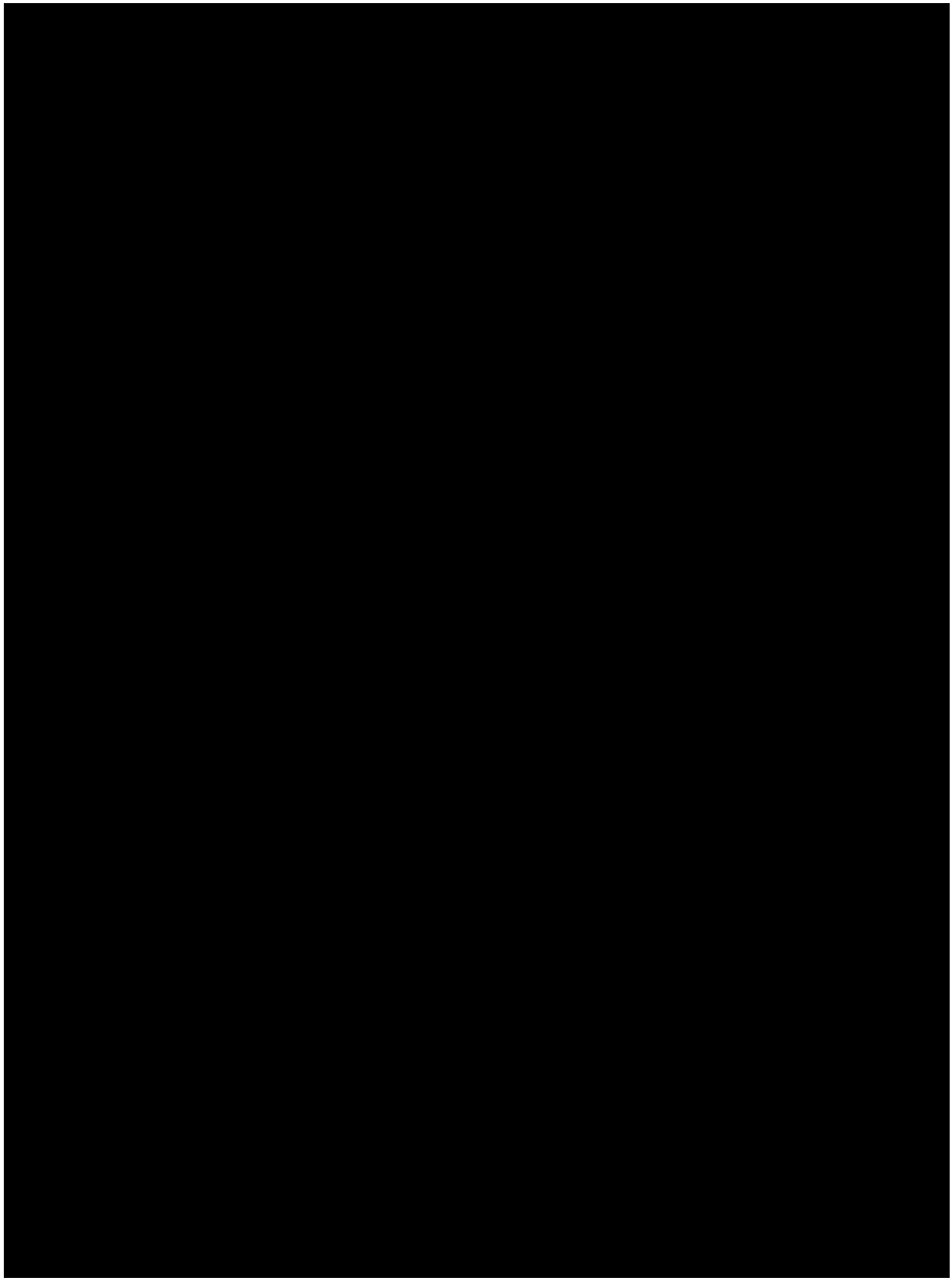


SOURCE: Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902-7.



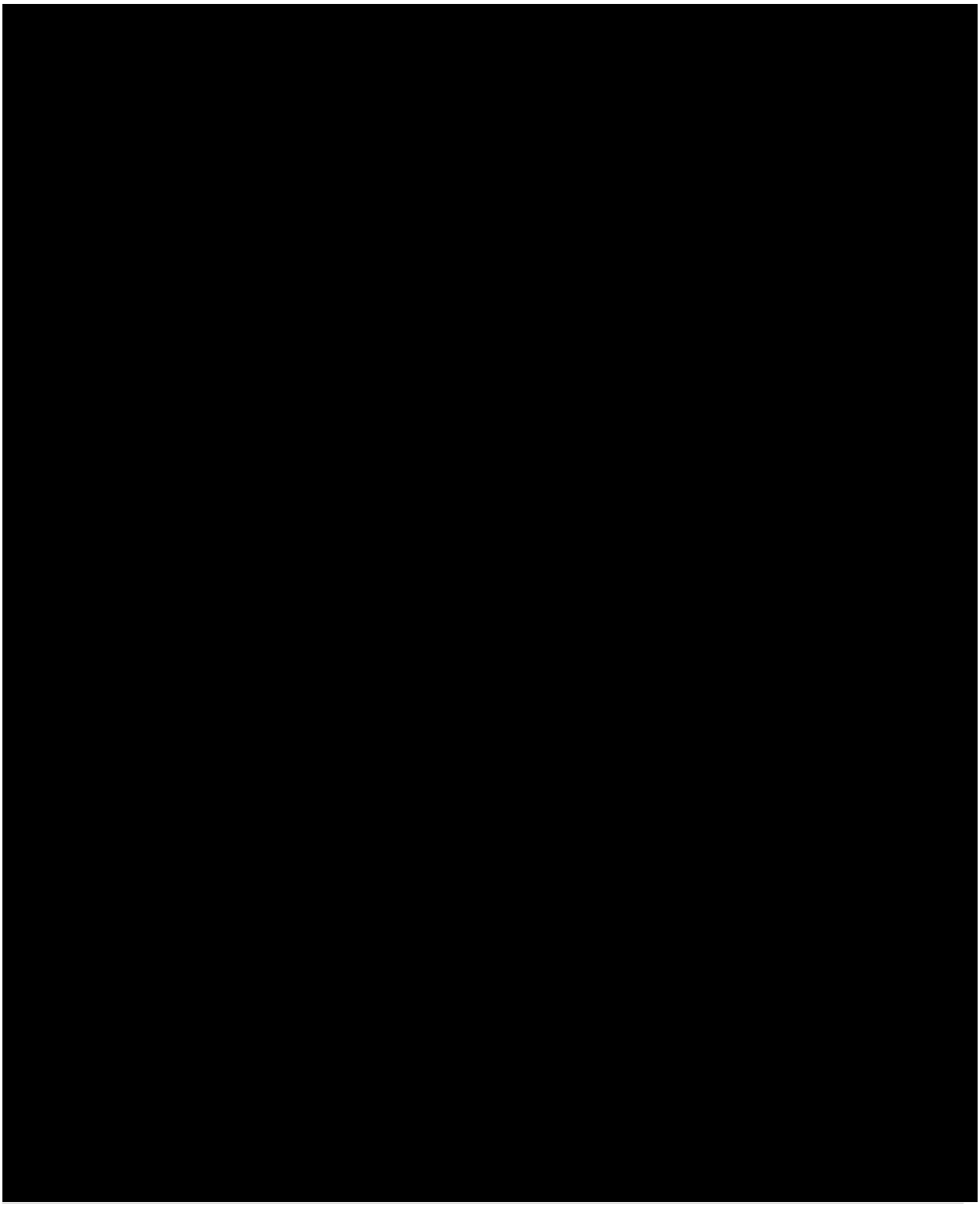


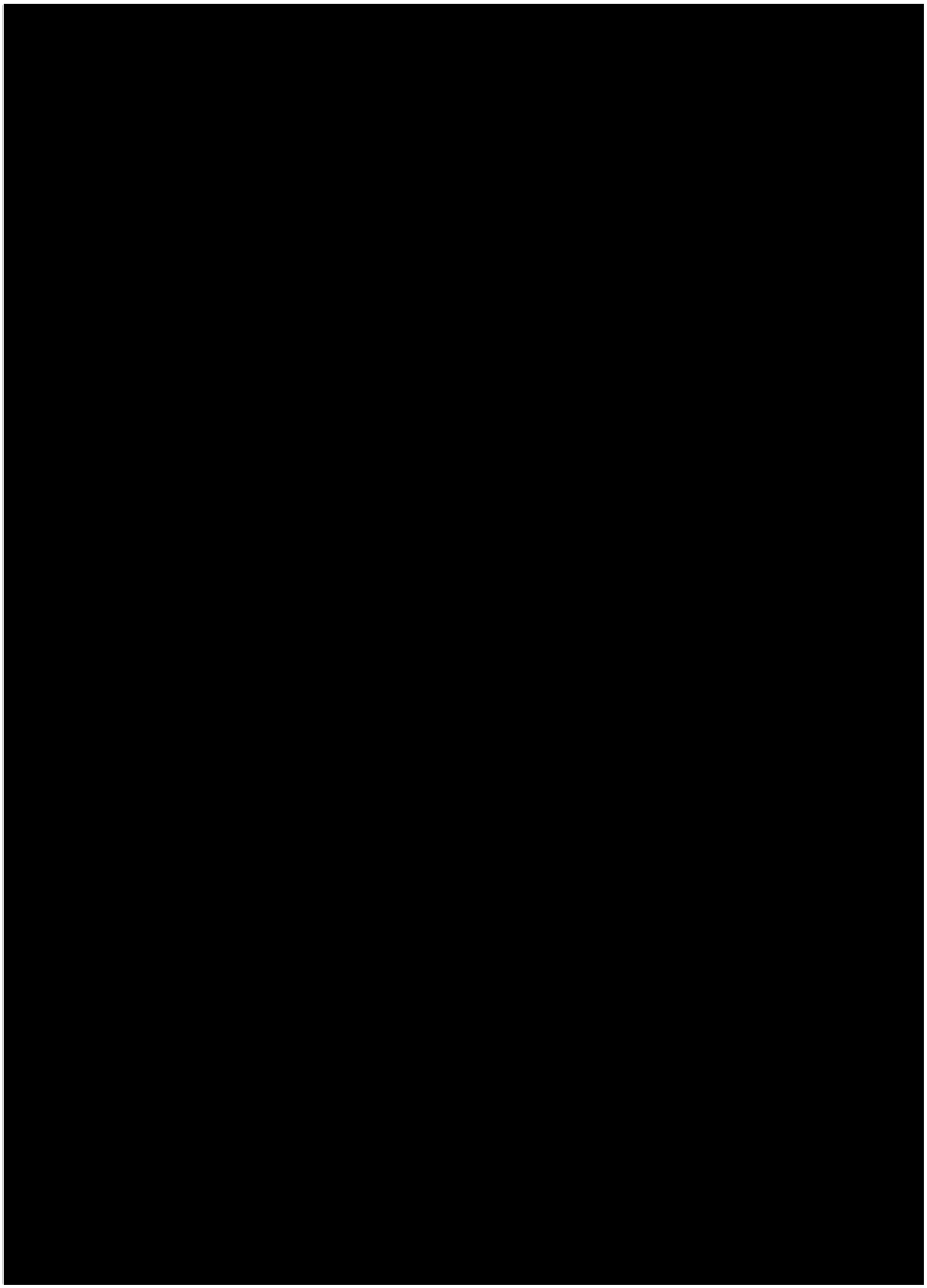


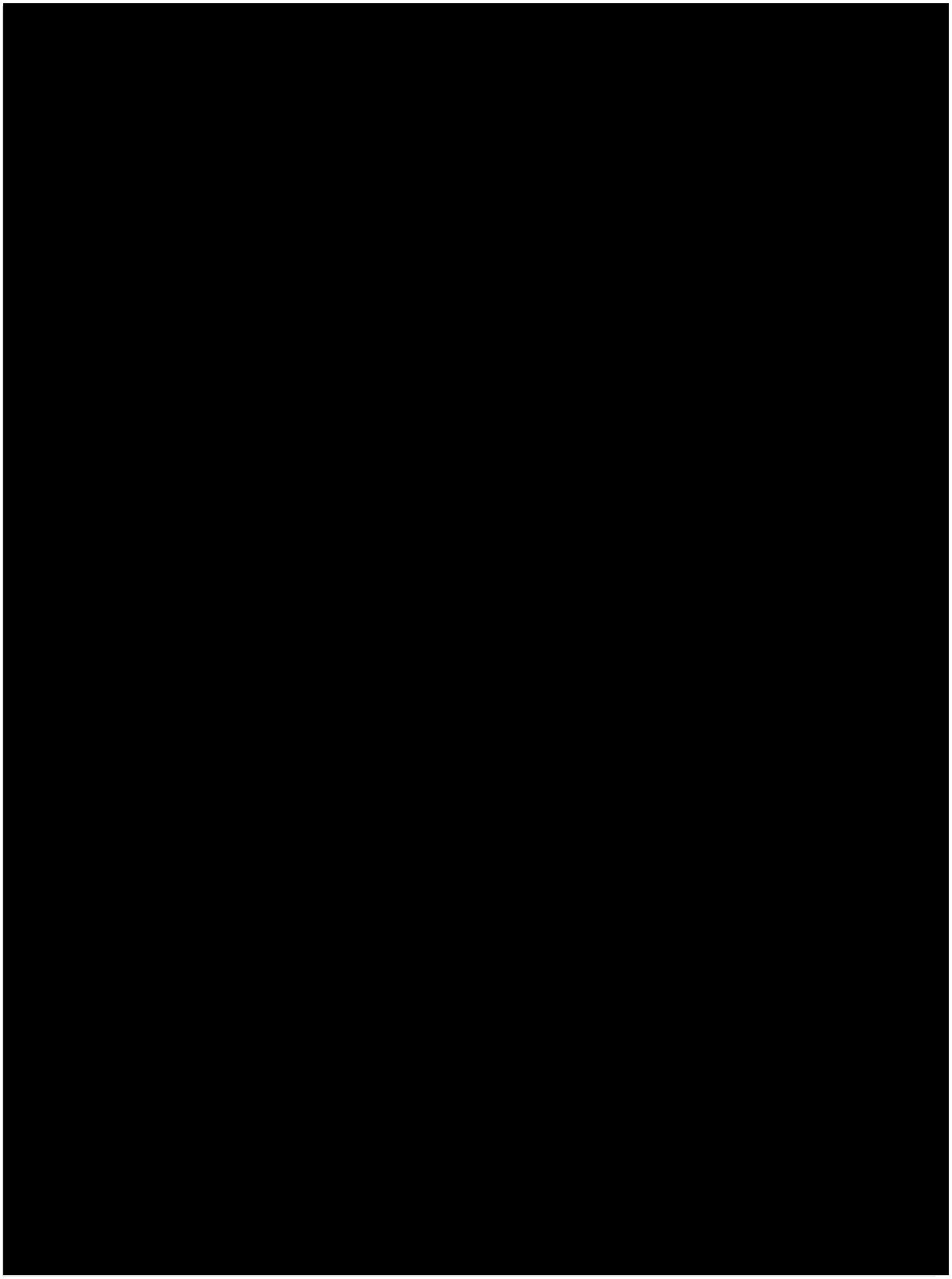


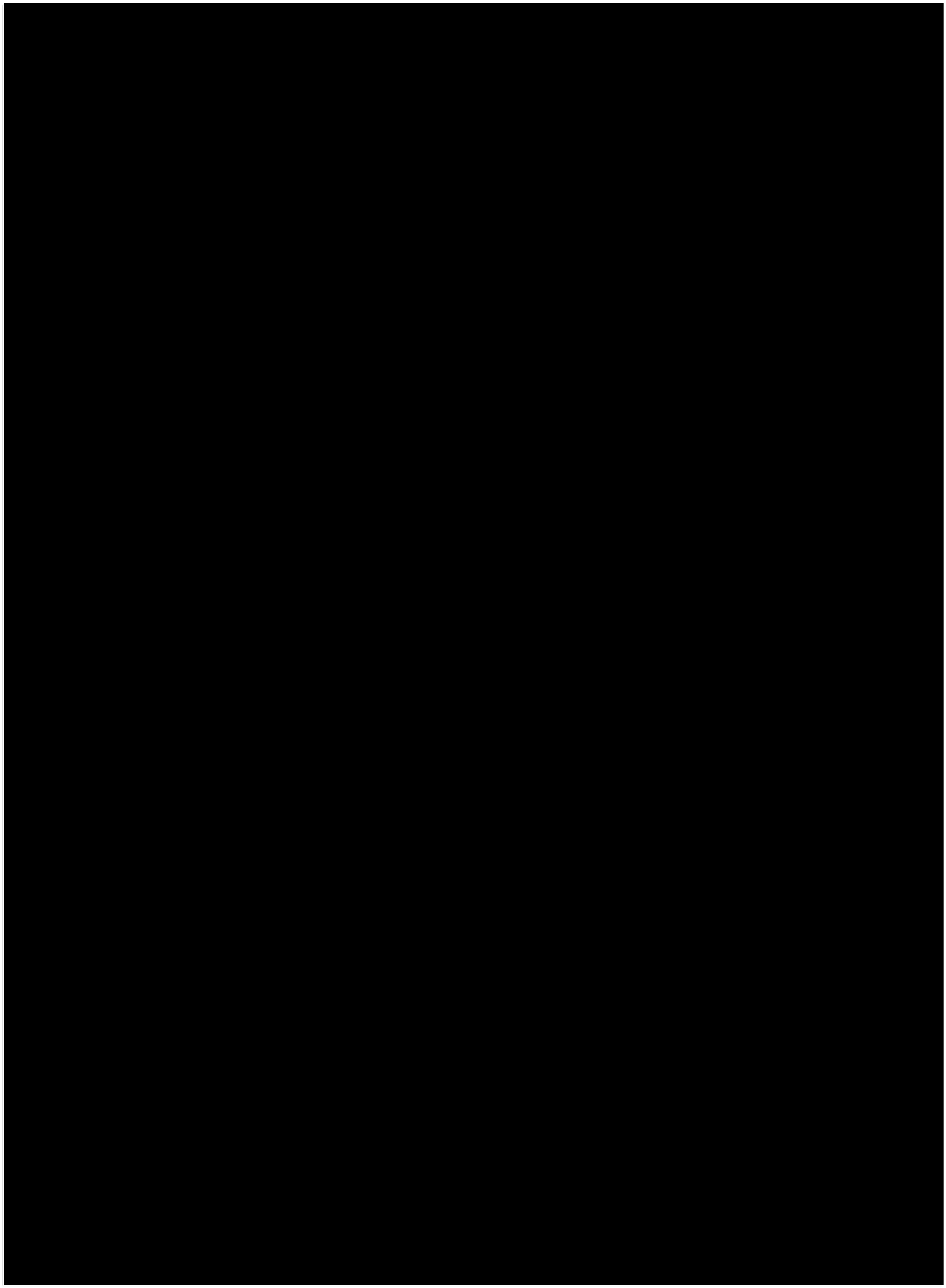
APPENDIX F. ST. GEORGE'S RESPIRATORY QUESTIONNAIRE

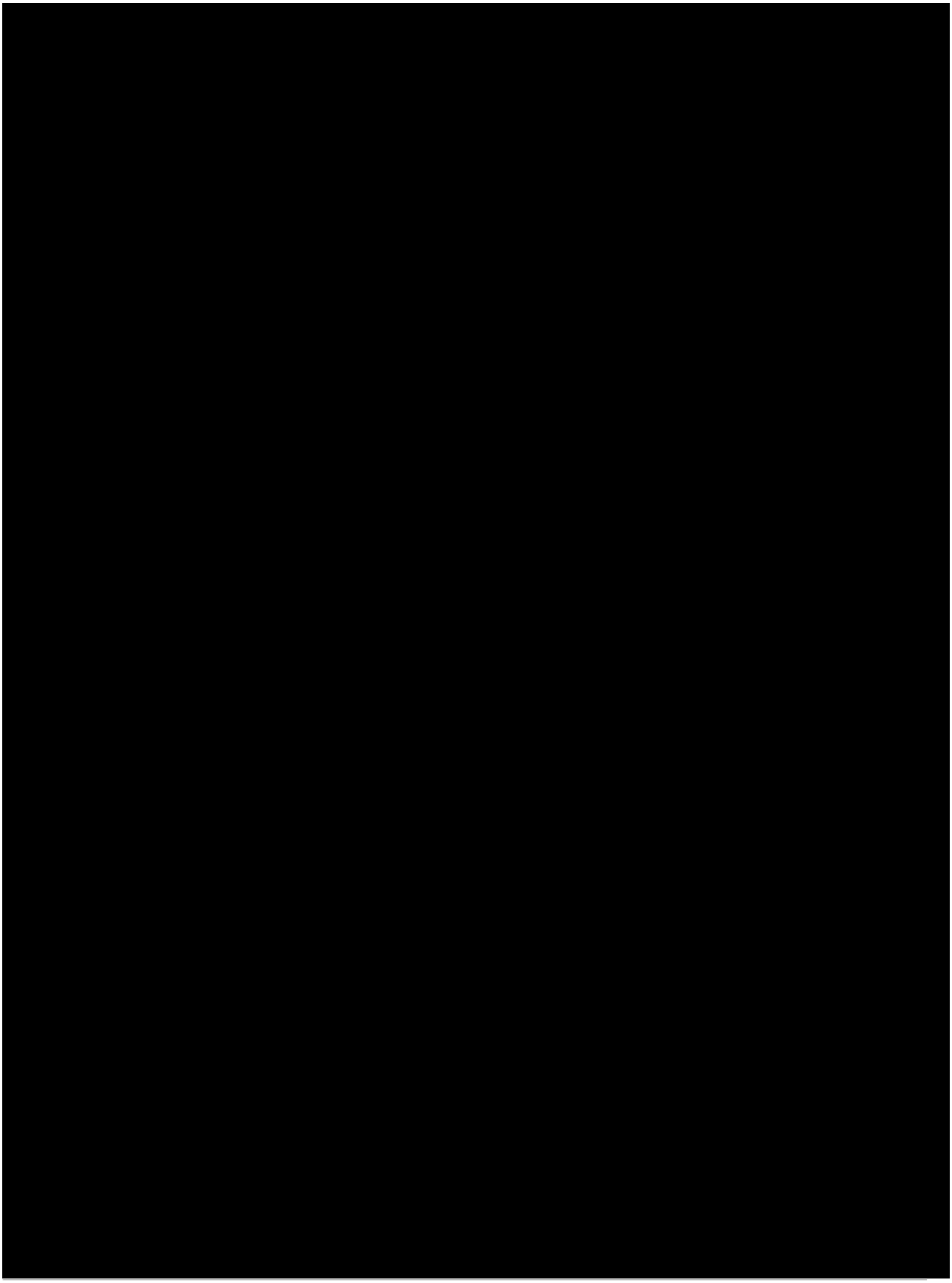
(Sample provided in this appendix is for reference only.)

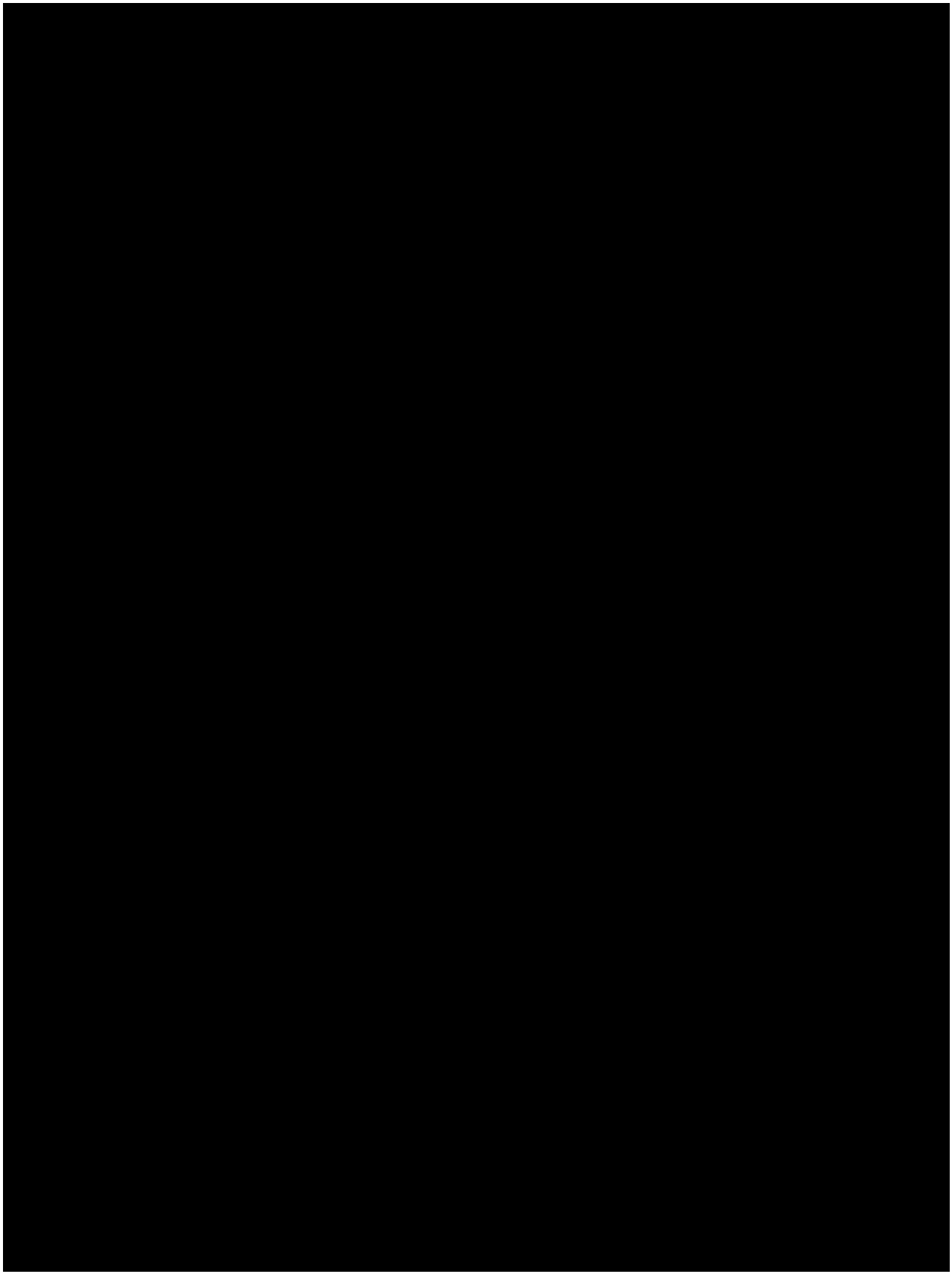












APPENDIX G. ASTHMA CONTROL DIARY

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 one short period during the day

2 = Symptoms for two 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 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 Apr;47(4):373-80; PMID: 16546624]. Journal of Allergy & Clinical Immunology. 2006 Feb;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, dissemintaed 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 from 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.