Clinical Study Protocol

Distribution of Eosinophils in Asthma after Reslizumab (DEAR). A 7-week, Placebo-Controlled, Double-Blinded, Parallel-Group, Imaging Study Using Positron Emission Tomography/Computed Tomography (PET/CT) to Characterize the Effect of Intravenous Reslizumab on Airway Inflammation in Patients with Eosinophilic Asthma

Study Number C38072-AS-40105 (or CEP38072-AS-40105)

NCT02937168

Protocol Approval Date: 24 June 2016

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Phase 4

BLA number: 761033

Protocol Approval Date: 24 June 2016

Confidentiality Statement

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

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INVESTIGATOR AGREEMENT

Clinical Study Protocol

BLA number: 761033

Distribution of Eosinophils in Asthma after Reslizumab (DEAR). A 7-week, Placebo-Controlled, Double-Blinded, Parallel-Group, Imaging Study Using Positron Emission Tomography/Computed Tomography (PET/CT) to Characterize the Effect of Intravenous Reslizumab on Airway Inflammation in Patients with Eosinophilic Asthma

Principal Investigator: [redacted]

Title: [redacted]

Address of Investigational Center: [redacted]

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

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

Principal Investigator	**Signature**	**Date**

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	**Signature**	**Date**
[redacted] Teva Pharmaceuticals	[redacted]	23 June 2016

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Send by email to the local safety officer (LSO). 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 CEP38072-AS-40105

Title of Study: Distribution of Eosinophils in Asthma after Reslizumab (DEAR). A 7-week, Placebo-Controlled, Double-Blinded, Parallel-Group, Imaging Study Using Positron Emission Tomography/Computed Tomography (PET/CT) to Characterize the Effect of Intravenous Reslizumab on Airway Inflammation in Patients with Eosinophilic Asthma

Sponsor: Teva Global Medical Affairs

Biologic License Application (BLA) Number: 761033

Name of Active Ingredient: Reslizumab (CEP-38072)

Name of Investigational Product: Reslizumab (CEP-38072)

Phase of the Study: 4

Number of Investigational Centers Planned: 1 clinical center [redacted] and 1 radiology center [redacted]

Countries Planned: United States

Planned Study Period: Approximately 4th quarter 2016 to 4th quarter 2018

Number of Patients Planned: This study is exploratory in nature; therefore, no formal hypothesis testing is planned. Based on clinical and practical considerations, 5 healthy subjects and 10 eosinophilic asthma patients (5 patients treated with reslizumab, 5 patients treated with placebo) is considered adequate for:

- a validation of the ability of positron emission tomography (PET)/ computed tomography (CT) to differentiate patients with eosinophilic asthma from healthy controls (HCs)
- an evaluation of the effect of reslizumab versus placebo on inflammation of the lungs.

Study Population: Males and females, from the ages of 18 through 50 years. Five HCs and 10 patients with asthma and current blood eosinophil levels of at least 400/μL, using ≥440 mcg of fluticasone-equivalent and an allowed 2nd asthma controller (eg, long-acting β-agonist [LABA]) will be recruited.

Enrollment will include a minimum of 2 and a maximum of 3 female healthy control subjects and a minimum of 4 and a maximum of 6 female patients with eosinophilic asthma.

Primary Objective: There are 2 related primary objectives of this study:

- To establish that PET/CT imaging of the lung can reliably distinguish healthy, non-asthmatic volunteers and patients with severe asthma with an eosinophilic phenotype (initial validation).
- If the utility of PET/CT scanning is established as per objective 1: to show that reslizumab produces a reduction in signal intensity (reduction in lung inflammation) in patients with severe asthma with an eosinophilic phenotype.

Secondary Objectives: The secondary objectives of this study are:

- to demonstrate a correlation between the benefit observed on imaging (PET/CT) with:
  - reductions blood eosinophil counts
  - improvement in clinic visit lung function
  - reductions in fractional exhaled nitric oxide (FeNO)

- improvements in Asthma Quality of Life questionnaire (AQLQ) scores

Exploratory Objectives: The exploratory and other objectives of the study are:

- to demonstrate a correlation between changes in the lung PET/CT signal produced by reslizumab and serum biological markers of asthmatic inflammation
- to demonstrate a correlation between changes in the lung PET/CT signal produced by reslizumab and other lung function variables including forced vital capacity (FVC), peak expiratory flow rate (PEFR) and forced expiratory flow at the 25% point to the 75% point of forced vital capacity ($FEF_{25\%-75\%}$)
- to demonstrate that reslizumab produces greater reductions in inflammation of whole body lymph nodes and bone marrow than placebo as seen on PET/CT
- for those patients that can produce sputum, to demonstrate an association between changes in sputum eosinophil numbers produced by reslizumab and the lung PET/CT signal produced by reslizumab

Study Endpoints:

This study is designed in 2 parts. Part 1 is a validation step which will include 2 measures, (1) the intrapatient reproducibility in the global lung glycolysis (GLG) measure, and (2) the signal window representing difference in the measure of GLG for individual patients with severe asthma with an eosinophilic phenotype and the mean GLG of the healthy controls group. The limit for step 1 above (reproducibility within patients) will be set at ≤10% of sequential GLG measures. The limit for step 2 above (the signal window) will be set at ≥5%. These limits have been provided by subject matter experts.

Primary Endpoint: The primary efficacy endpoint is the change from baseline to week 4 in GLG (ΔGLG).

The supportive primary efficacy endpoint is the change from baseline to week 4 in lung parenchyma (LP) standardized uptake value (SUV) mean.

Secondary Endpoints: The secondary efficacy endpoints are:

- the change from baseline to week 4 in blood eosinophil counts
- the change from baseline to week 4 in forced expiratory volume in 1 second (FEV_1)
- the change from baseline to week 4 in FeNO
- the change from baseline to week 4 in AQLQ

Exploratory Endpoints: The exploratory endpoints of this study are changes in:

- biological markers of inflammation and asthma (blood):
  - immunoglobulin E (IgE)
  - dipeptidyl peptidase 4 (DPP4)
  - 25-hydroxy vitamin D
  - eotaxin-1, -2, and -3
  - thymus and activation regulated chemokine (TARC)
  - monocyte chemoattractant protein-1 (MCP-1) and MCP-4
  - group 2 innate lymphoid cells (ILC2)

- lung function variables:
  - FVC
  - PEFR
  - $FEF_{25\%-75\%}$
- the global uptake of fludeoxyglucose (FDG) in the lymph nodes and bone marrow as measured by the PET/CT imaging parameters indicated for the primary efficacy variable
- sputum eosinophils for those patients that can produce sputum

Safety Endpoints: The safety endpoints are:

- occurrence of adverse events throughout the study
- vital signs (pulse, respiratory rate, and blood pressure) throughout the study
- clinical laboratory evaluations throughout the study
- physical examination findings throughout the study
- use of concomitant medication throughout the study

General Design and Methods: All subjects who participate in this study will consent at [redacted] prior to undergoing any study procedures. After consent is obtained, all participants will undergo all tests and procedures required for eligibility, including sputum and blood eosinophil level assessments. Patients with asthma (does not apply to HC subjects) must have a screening blood eosinophil count of ≥400 cells/μL to be included. A maximum of 3 blood eosinophil assessments will be conducted. If the 1st assessment yields a blood eosinophil level below 400 cells/μL patients with asthma may return for a 2nd assessment of blood eosinophil level after 7 days. A 3rd and final assessment will be performed 7 days after the 2nd assessment, if necessary (eg, if the blood eosinophil level remains <400 cells/μL at the 2nd assessment).

The patient must maintain their usual asthma controller regimen without change throughout the screening and study periods. A patient who experiences an asthma exacerbation during this time that requires additional medication, beyond increased short-acting β-agonist (SABA) use, will be considered to have failed screening and cannot undergo randomization. A patient may be rescreened for this reason 1 time only. If a patient experiences an asthma exacerbation requiring treatment with systemic steroids, they will only be allowed to be rescreened 6 weeks after completion of treatment. All patients that have to be rescreened must be stable on other asthma medications for 30 days prior to rescreening.

The DEAR study is designed in 2 parts. Part 1 is a validation of the PET/CT signal as a surrogate of lung inflammation. In this part, the sponsor wishes to determine (1) the intrapatient reproducibility in the GLG measure, and (2) the difference in the GLG measure between individual patients with severe asthma with an eosinophilic phenotype (1-by-1) and the entire HC group. Limits for both the reproducibility within patients and difference among the 2 groups have been provided by subject matter experts.

Part 2 will be a 7-week double-blind evaluation of patients with severe asthma with an eosinophilic phenotype that have been randomized to receive a single dose of either placebo or reslizumab at 3 mg/kg.

Part 1

Within 7 days (±3 days) of eligibility being confirmed, participants will have a PET/CT scan. Participants will return to the [redacted] 7 days (±3) after the first PET/CT scan (taken during visit 2) for a second PET/CT

scan. Healthy control subjects (n=5) may also have a second sputum induction and blood sample collection at [redacted] with 1 day of the 2nd PET/CT scan, if feasible (preferred but not required). Healthy subjects will be considered complete at this time. Only after all 5 HCs have completed the study will patients with asthma be screened.

If the relative difference in GLG (based on the average of the 2 measurements) between healthy and asthma patients will be ≥5%, then the asthma patients will be randomized.

A 10% variability (measured as relative difference between first measurement and second measurement) between PET/CT scans as measured by GLG within each group will be considered as the maximum allowed variability. The part 1 criteria have been set at these levels to observe a difference between the healthy subjects and patients with asthma and to ensure intra-group reproducibility; the criteria are based on the investigators' prior experience. If these exploratory criteria are not met (eg, 8 or more patients do not meet the criteria to enter Part 2 [inclusion criteria k and l]), then the study will be reevaluated.

Part 2

If eligible (eg, if inter- and intra-group GLG variability criteria are met), patients will be randomized. This may occur at any time after confirmation of eligibility and up to the time of dosing. Patients will return to [redacted] for baseline clinical, serological, and biochemical measures according to standard procedures. Once these are completed, patients will receive either placebo or reslizumab and will receive the infusion at [redacted]. Any new serious adverse events, reslizumab-related adverse events, and new concomitant medications will be reported.

All planned PET/CT scans (weeks 2, 4, and 6) should be scheduled at the time of randomization. Within 2 weeks (±3 days) of the infusion, patients will return to [redacted] for clinical tests and procedures. Within 3 days of this visit, patients will undergo a PET/CT scan at the [redacted]. Patients repeat the clinical tests and procedures at weeks 4 and 6 post-infusion. Each visit at [redacted] will be followed by a PET/CT scan at the [redacted] as described above.

Method of Randomization and Blinding: After the 2 baseline PET/CT scans and successful completion of all requirements (Part 1), patients will be randomly assigned 1:1 in a double-blind fashion to receive either placebo or intravenous (iv) 3.0 mg/kg reslizumab.

In order to maintain the blind, each patient will be assigned a unique identifier number and all reference to the patient will be by using this identifier.

Study Drug Dose, Mode of Administration, and Administration Rate:

Investigational Product: Reslizumab will be provided as a sterile solution for infusion presented as 100 mg (10 mL) per vial, formulated at 10 mg/mL in 20 mM sodium acetate, 7% sucrose, pH 5.5 buffer. Reslizumab will be administered by iv infusion, over 20 to 50 minutes, at the baseline visit.

Reference Treatment:

Placebo: Placebo will be provided as a sterile solution of 20 mM sodium acetate, 7% sucrose, pH 5.5 buffer. Matching placebo will be administered by iv infusion at the baseline visit.

Comparator: None

Other: Fludeoxyglucose F 18 (FDG) injection will be provided as a ready to use isotonic, sterile, pyrogen free, clear, colorless citrate buffered solution. Each mL will contain between 0.740 to 7.40 gigabecquerel (20.0 to 200 millicurie [mCi]) of 2-deoxy-2-[^{18}F]fluoro-D glucose at the end of synthesis (EOS), 4.5 mg of sodium chloride and 7.2 mg of citrate ions. The pH of the solution will be between 5.5 and 7.5. The solution will be

packaged in a multiple-dose glass vial and will not contain any preservative. Fludeoxyglucose F 18 will be administered by iv infusion.

Duration of Patient Participation: This study will consist of Part 1, a 21-day PET/CT screening period, and Part 2 (only patients with asthma), a 6-week double blind treatment/assessment period followed by a 7-day follow up period.

Inclusion Criteria: Healthy subjects and patients may be enrolled in this study only if they meet all of the following criteria

a. Male or female, 18 through 50 years of age.

b. Females that are either surgically sterile, are 2 years postmenopausal, or have a negative pregnancy test beta-human chorionic gonadotropin (β-HCG) at screening (serum) and all PET/CT imaging visits (urine).

c. Females of childbearing potential (not surgically sterile or 2 years postmenopausal), have to use a medically accepted method of contraception and have to agree to continue to use of this method for the duration of the study and for 5 months after study drug administratin. Acceptable methods of contraception include barrier method with spermicide, abstinence, intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted, and injected). Note: partner sterility alone is not acceptable for inclusion in the study.

d. Subjects and patients with less that 10-pack year history of smoking.

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

e. Male or female, 18 through 50 years of age, with a previous diagnosis of asthma.

f. Patients taking inhaled fluticasone at a dosage of at least 440 mcg daily, or equivalent.

g. The patient's baseline asthma therapy regimen (including, but not limited to, inhaled corticosteroids, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, or cromolyn) must be stable for 30 days prior to screening and judged by their treating physician to be able to continue without dosage changes throughout the study.

h. Patients with a blood eosinophil level of at least 400/μL at screening. Patients with a blood eosinophil level below 400/μL will be given 2 additional screening opportunities to determine blood eosinophil levels.

i. Patients with airway reversibility of at least 12% to β-agonist administration.

j. Patients with an Asthma Control Questionnaire (ACQ) score of at least 1.5 at either screening or baseline visits.

Patients may be included in Part 2 of the study only if they also meet the following, additional criteria:

k. the intrapatient reproducibility, taken as sequential GLG measures on visits 2 and 3, differs by only ≤10%

l. the intragroup variability (signal window), taken as a difference in the 2 subcriteria (below) to be ≥5%:

- the mean GLG of healthy controls determined by taking the mean of the average GLG for visits 2 and 3 for each HC.
- the mean GLG of each single patient with severe asthma with an eosinophilic phenotype, taken as sequential GLG measures on visits 2 and 3.

Exclusion Criteria: Healthy subjects and patients will be excluded from participating in this study if they meet any of the following criteria:

a. Patients requiring treatment with oral, intramuscular, or iv corticosteroids within 6 weeks of the Part 1 baseline visit.

b. Patients with any other confounding underlying lung disorder including but not limited to: bronchiectasis, chronic obstructive pulmonary disorder, smoking ≥10 pack year history, pulmonary fibrosis, emphysema, cystic fibrosis, and lung cancer.

c. Patients with a blood glucose level at screening or baseline greater than or equal to 150 mg/dL.

d. Patients diagnosed with diabetes mellitus.

e. Patients with pulmonary conditions and blood eosinophilia other than eosinophilic asthma including, but not limited to: Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis and hypereosinophilic syndrome.

f. Patients with clinically meaningful comorbidity that can interfere with the study schedule or procedures, or compromise the patient's safety.

g. Patients that are current smokers (ie, have smoked within the last 12 months prior to screening).

h. Patients using systemic immunosuppressive, immunomodulating, or other biologic agents (including, but not limited to, anti-IgE monoclonal antibody [mAb], methotrexate, cyclosporin, interferon-α, or anti–tumor necrosis factor mAb) within 6 months prior to screening.

i. Patients who have previously received an anti-human interleukin-5 (anti-hIL-5) mAb (eg, reslizumab, mepolizumab [Nucala®]) or anti IL-5 receptor mAb (eg, benralizumab).

j. Patients who had concurrent infection or disease that may preclude assessment of active asthma.

k. Patients with a history of concurrent immunodeficiency (human immunodeficiency virus or acquired immunodeficiency syndrome or congenital immunodeficiency).

l. Patients that had an active parasitic infection within 6 months prior to screening.

m. Patients with a history of exposure to water-borne parasites within 6 weeks prior to screening or during the screening period or a history of diarrheal illness of undetermined etiology within 3 months prior to screening or during the screening period.

n. Any patient who had an infection requiring the following:

   – an admission to the hospital for at least 24 hours within 4 weeks prior to screening or during the screening period

   – treatment with iv antibiotics within 4 weeks prior to screening or during the screening period

   – treatment with oral antibiotics within 4 weeks prior to screening or during the screening period

o. Patients with any disorder that may interfere with drug absorption, distribution, metabolism, or excretion (including gastrointestinal surgery).

p. Female subjects who are pregnant or breast-feeding or considering becoming pregnant during the study or within 5 months after reslizumab dosing.

q. Known hypersensitivity to study drug or to FDG/contrast agents

r. Treatment with metformin.

s. Compromised renal function

Measures and Time Points:

A ≤10% variability between PET/CT scans as measured by global lung glycolysis (GLG) within each group will be considered as the maximum allowed variability.

A ≥5% difference in GLG (ΔGLG) between HC subjects and patients with eosinophilic asthma will be selected as minimal difference that validates the ability PET/CT to differentiate these 2 populations. If a 5% difference cannot be achieved, the study will be evaluated as patients with asthma complete Part 1 and are considered for eligibility to enter Part 2.

Primary Efficacy Measure and Time Points: GLG will be measured at 2 baseline visits and at weeks 2, 4, and 6 (all ±3 days) post randomization..

Secondary Efficacy Measures and Time Points: The secondary efficacy measures and time points for this study are as follows:

- blood eosinophil counts from baseline to weeks 2, 4, and 6 (all ±3 days)
- FEV_1 from baseline to weeks 2, 4, and 6 (all ±3 days)
- FeNO measurements from baseline to weeks 2, 4, and 6 (all ±3 days)
- AQLQ scores from baseline to weeks 2, 4, and 6 (all ±3 days)

Exploratory Efficacy Measures and Time Points: The exploratory efficacy measures and time points are:

- biological markers of inflammation and asthma:
  - IgE
  - DPP4
  - 25-hydroxy vitamin D
  - eotaxin-1, -2, and -3
  - TARC
  - MCP-1 and MCP-4
  - ILC2
- lung function variables:
  - FVC
  - PEFR
  - $FEF_{25\%-75\%}$
- the global uptake of FDG in the lymph nodes and bone marrow as measured by the PET/CT imaging parameters indicated for the primary efficacy variable
- for those patients that can produce sputum, to demonstrate a correlation between reductions in inflammation by reslizumab with a reduction in sputum eosinophils

All variables will be measured at 2 baseline visits and at weeks 2, 4, and 6 post-randomization.

Safety Measures and Time Points: The safety measures and timepoints are:

- occurrence of adverse events throughout the study
- vital signs (pulse, respiratory rate, and blood pressure) throughout the study
- clinical laboratory evaluations throughout the study
- physical examination findings throughout the study
- use of concomitant medication throughout the study

Patient safety will be assessed by standard asthma management and physician practice. If a patient experiences an asthma exacerbation during Part 1, they will be treated with oral corticosteroids (OCS) for a period of 2 weeks, followed by a 6-week period without OCS to ensure asthma control. Stable patients will then re-enter the study at the time point of the exacerbation.

Immunogenicity Measures and Time Points: Blood samples for assessment of anti-drug antibodies (ADA) will be collected at baseline (pre-study drug administration) and at weeks 2 and 6.

Allowed and Prohibited Medications before and during the Study: Patients currently taking, or who have previously taken, anti-IL-5/anti-IL-5 receptor medications may not participate in this study. Oral corticosteroids must have been stopped 6 weeks prior to screening. Immunosuppressive agents and biological drugs, including anti-IgE medications, must have been stopped at least 6 months prior to screening. Asthma therapies, including inhaled corticosteroids (with a LABA or long-acting muscarinic antagonist), leukotriene antagonists, 5-lipoxygenase inhibitors, and/or cromolyn must be stable for 30 days prior to screening and must remain stable throughout the study.

Statistical Considerations:

Sample Size Rationale: This study is exploratory in nature; therefore, no formal hypothesis testing is planned. Based on clinical and practical considerations, 5 healthy subjects and 10 eosinophilic asthma patients (5 patients treated with reslizumab, 5 patients treated with placebo) is considered adequate for:

- a validation of the ability of PET/CT to differentiate patients with eosinophilic asthma from HCs
- an evaluation of the effect of reslizumab versus placebo on inflammation of the lungs.

The below are only for Part 2:

Analysis of Primary Endpoint: The primary efficacy endpoint is the change from baseline to week 4 in GLG (ΔGLG).

The supportive primary efficacy endpoint is the change from baseline to week 4 in LP SUVmean.

All imaging variables will be measured at 2 baseline visits and at weeks 2, 4, and 6 post randomization.

Change in GLG from baseline to each of the postbaseline visits will be summarized using descriptive statistics (number [n], mean, standard deviation, median, minimum, and maximum) by treatment group. The difference in means between reslizumab and placebo will be summarized and reported. The same methods will be used to analyze the supportive-to-primary endpoint.

Analysis of Secondary Endpoints: The secondary efficacy endpoints are:

- Change from baseline to weeks 2, 4, and 6 in blood eosinophil count
- Change from baseline to weeks 2, 4, and 6 in FEV_1

- Change from baseline to weeks 2, 4, and 6 in FeNO measurements
- Change from baseline to weeks 2, 4, and 6 in AQLQ scores

The same methods as described for the primary efficacy analysis will be used to analyze the secondary endpoints.

In addition, correlation between each of the secondary endpoints and change from baseline to week 4 in GLG will be calculated. Spearman's Rho correlation will be used for this analysis. No inferential statistics will be used for secondary endpoints and analyses. Additional details about secondary endpoints analyses may be detailed in the statistical analysis plan.

Multiple Comparisons and Multiplicity: No multiple comparisons will be made.

Analysis of Exploratory Endpoints: Analysis of the exploratory endpoints will be detailed in the statistical analysis plan (to be finalized and signed before unblinding).

Safety Analyses: The safety analysis set will include all patients who received at least 1 dose of reslizumab/placebo in this study. Safety will be summarized using descriptive statistics.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table of Abbreviations

Abbreviation	Term
ACQ	Asthma Control Questionnaire
ADA	anti-drug antibodies
ADR	adverse drug reaction
anit-hIL-5	anti-human interleukin-5
AQLQ	Asthma Quality of Life Questionnaire
ASUI	Asthma Symptom Utility Index
BAL	bronchoalveolar lavage
BP	blood pressure
CDMS	clinical data management system
CFR	Code of Federal Regulations (US)
CPK	creatine phosphokinase
CPP	clinical project physician
CRC	Clinical Research Center
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DPP4	dipeptidyl peptidase 4
ECG	electrocardiogram
EOS	end of synthesis
EU	European Union
FDA	United States Food and Drug Administration
FDG	fludeoxyglucose
$FEF_{25\%-75\%}$	forced expiratory flow at the 25% point to the 75% point of forced vital capacity
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice

Abbreviation	Term
GLG	global lung glycolysis
ΔGLG	change from baseline in global lung glycolysis
HC	healthy control
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroids
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IL-5	Interleukin-5
ILC	innate lymphoid cell
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
iv	intravenous
LABA	long-acting β-agonist
LP	lung parenchyma
LSO	local safety officer
LV	lung volume
mAb	monoclonal antibody
mCi	millicurie
MCP	monocyte chemoattractant protein
mrem	millirem
n	number
OCS	oral corticosteroids
PEFR	peak expiratory flow rate
PET	positron emission tomography
PI	Prescribing Information
PK	pharmacokinetic
RR	respiratory rate
RSI	reference safety information
ROI	region of interest
SABA	short-acting β-agonist
sc	subcutaneous

Abbreviation	Term
SOP	Standard Operating Procedure
sLG	sectional lung glycolysis
sLV	sectional lung volume
SpO_2	blood oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
SUV	standardized uptake value
sSUV	sectional mean standardized uptake value
TARC	thymus and activation regulated chemokine
ULN	upper limit of normal
US(A)	United States (of America)
VDBP	vitamin D-binding protein

1. BACKGROUND INFORMATION

1.1. Introduction

1.1.1. Asthma

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] 2015) 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 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 [Nucala®], reslizumab, and benralizumab) work by reducing eosinophil counts in the circulation and in the airway and have been shown to reduce asthma exacerbations, improve Asthma Control Questionnaire [ACQ] scores, and/or improve 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).

1.1.2. Molecular Imaging in Asthma

Molecular imaging has been broadly defined as the use of imaging methods that ‘‘directly or indirectly monitor and record the spatiotemporal distribution of molecular or cellular processes for biochemical, biologic, diagnostic, or therapeutic applications’’ (Thakur and Lentle 2008).

This study proposes the use of positron emission tomography/computed tomography (PET/CT) to investigate the inflammatory response in patients with eosinophilic asthma after anti-IL5 therapy.

Molecular imaging with PET/CT requires coupling a positron emitting radioisotope with a short half-life, such as ^{18}F, ^{11}C, or ^{15}O, to a molecule that functions within a known metabolic

pathway. The most commonly used molecule in PET/CT imaging is ^{18}F-fluorodeoxyglucose (18F-FDG), a radiolabeled glucose analog. When injected intravenously, FDG is transported into metabolically active cells and phosphorylated by the enzyme hexokinase in the same manner as glucose. However, the FDG-6-phosphate is not metabolized further and becomes trapped intracellularly, resulting in an increase in signal from the metabolically active cells.

FDG-PET/CT is most commonly used in oncologic imaging because of its ability to depict the increased glucose metabolism present in most malignant neoplasms. However, FDG-PET/CT has also shown promise as an imaging biomarker of lung inflammation. The accumulated evidence suggests that primed and activated neutrophils are the primary (although perhaps not the only) source of increased FDG signal in the lung (Chen and Schuster 2006). In animal models increased FDG uptake has been demonstrated in acute lung injury (Chen and Schuster 2004, Musch et al 2007) and after inhalation of cigarette smoke (Schroeder et al 2007). In human subjects increases in FDG uptake have been found in several conditions characterized by inflammation, such as respiratory tract infections, including pneumonia (Jones et al 1997), cystic fibrosis (Chen et al 2006), sarcoidosis (Brudin et al 1994, Xiu et al 2005), and chronic obstructive pulmonary disease (Jones et al 2003).

The ability to quantify a component of the inflammatory response with FDG-PET/CT suggests that it might also be useful for learning more about the pathogenesis of asthma, phenotypic differences, and responses to anti-inflammatory therapies.

1.2. Name and Description of Investigational Product

Reslizumab (CEP-38072) is a humanized anti-human interleukin-5 (anti-hIL-5) monoclonal antibody (mAb) of the immunoglobulin G4/κ isotype being developed for administration by the intravenous (iv) and subcutaneous routes. CINQAIR® (reslizumab iv 3 mg/kg) was recently approved by the United States Food and Drug Administration (FDA) for the add-on maintenance treatment of patients with severe asthma aged 18 years and older with an eosinophilic phenotype.

A more detailed description of the product is given in Section 3.9.

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 originally suggested by studies in the IL-5 gene knockout mouse (Foster et al 1996). When sensitized and challenged with antigen, mice lacking the IL-5 gene failed to develop airway eosinophilia, accumulate lung damage, or demonstrated any increased airway hyper-responsiveness. Otherwise, IL-5 gene knockout mice developed normally and had normal antibody and cytotoxic T-cell responses.

In vitro, reslizumab bound with high affinity to IL-5 from several species (mouse, rat, and monkey); in vivo, reslizumab showed biological activity in all species mentioned above plus guinea pig and rabbit. 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.

Further details may be found in the current United States (US) Prescribing Information (PI) for CINQAIR (reslizumab) (CINQAIR 2016).

1.3.2. Clinical Studies

1.3.2.1. Clinical Pharmacology Studies

The pharmacokinetics (PK), pharmacodynamics, 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 of 24 days. The volume of distribution for reslizumab is low (approximately 4 to 6 L), suggesting minimal distribution of reslizumab into extravascular tissues.

Further details may be found in the current PI (CINQAIR 2016).

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 dose of reslizumab in 14 clinical studies.

The Phase 3 BREATH program in adult and adolescent asthma evaluated the safety and efficacy of reslizumab administered iv every 4 weeks at 3 mg/kg (16-week Studies C38072/3081 and C38072/3084, 52-week Studies C38072/3082 and C38072/3083, and open label safety extension Study C38072/3085) and 0.3 mg/kg (Study C38072/3081 only). A significant reduction in the annual rate of asthma exacerbations, and significant improvements in lung function, asthma related quality of life, and patient reported measures of asthma control (ACQ and Asthma Symptom Utility Index [ASUI]) were observed for patients with eosinophilic asthma defined by a screening blood eosinophil count of ≥400/μL (Studies C38072/3081, C38072/3082, and C38072/3083). In asthma patients without elevated blood eosinophils (Study C38072/3084), reslizumab produced non-significant improvements in lung function and other measures of efficacy. In contrast, patients with blood eosinophil levels ≥400/μL in this study demonstrated

significant improvements in lung function and other measures of efficacy following treatment with reslizumab.

The safety of reslizumab was evaluated in adults and in children in clinical studies. 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. The safety profile of reslizumab, 3 mg/kg iv, in patients with asthma is reflected in the US PI (CINQAIR 2016).

The following summary relates to integrated adverse events data of the 5 asthma placebo-controlled completed studies (ie, Studies Res-5-0010, C38072/3081, C38072/3082, C38072/3083, and C30872/3084) that include the 3 mg/kg iv dose and every 4 weeks dosing regimen (up to 52 weeks). Serious adverse events and deaths from the open-label Study C38072/3085 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).

The incidence of all common adverse events (>2%) was the same or higher in the placebo group compared to the reslizumab group with the exception of oropharyngeal pain, which was slightly higher in the 3.0 mg/kg reslizumab-treated patients (2.6%) than in the placebo-treated patients (2.2%).

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. Three serious adverse events of anaphylaxis events were assessed as related to reslizumab treatment.

Deaths

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

Laboratory Findings

Overall, laboratory test values were similar in patients treated with reslizumab and placebo, with the exception of creatine phosphokinase (CPK) elevation and the expected pharmacological effect of decreasing blood eosinophil counts. There were no clinically meaningful differences or potentially clinically important trends in vital signs, electrocardiogram (ECG) intervals, or overall ECG assessments.

Adverse Drug Reactions

Anaphylaxis

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/immunotherapy, and not to reslizumab. In the Phase 3 BREATH program, 3 infusion-related reactions, reported as anaphylaxis, occurred during or shortly after reslizumab infusion and were characterized variously by dyspnea, decreased oxygen saturation,wheezing, vomiting, and skin and mucosal involvement, including urtcaria. The 3 events were treated at the study site, and patients were withdrawn from the study.

Oropharyngeal pain

Adverse reactions that occurred at greater than or equal to 2% incidence and more commonly than in the placebo group included 1 event: oropharyngeal pain (2.6% versus 2.2%).

CPK elevations and muscle-related adverse reactions

Elevated baseline CPK was more frequent in patients randomized to reslizumab (14%) versus placebo (9%). Transient CPK elevations in patients with normal baseline CPK values were observed more frequently with reslizumab (20%) versus placebo (18%) during routine laboratory assessments. CPK elevations >10x the upper limit of normal (ULN), regardless of baseline CPK value, were 0.8% in the CINQAIR group compared to 0.4% in the placebo group. CPK elevations >10xULN were asymptomatic and did not lead to treatment discontinuation.

Myalgia was reported in 1% (10/1028) of patients in the reslizumab 3 mg/kg group compared to 0.5% (4/730) of patients in the placebo group. On the day of infusion, musculoskeletal adverse reactions were reported in 2.2% and 1.5% of patients treated with reslizumab 3 mg/kg and placebo, respectively. These reactions included (but were not limited to) musculoskeletal chest pain, neck pain, muscle spasms, extremity pain, muscle fatigue, and musculoskeletal pain.

Malignancy

The impact of lowering eosinophils with an anti-IL-5 active substance, such as reslizumab on the development of malignancies is not known. In placebo-controlled iv clinical studies, 6 out of 1028 patients (0.6%) receiving 3 mg/kg reslizumab had at least 1 malignant neoplasm reported compared to 2 out of 730 patients (0.3%) in the placebo group. The observed malignancies in reslizumab treated patients were diverse in nature and without clustering of any particular tissue type. The majority of malignancies were diagnosed within less than 6 months of exposure to reslizumab.

Additional Safety Issues

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 May 2015, there have been 12 pregnancies during the entire clinical development of reslizumab, 4 of which occurred during the screening period of the study and 8 in patients receiving reslizumab. All patients were withdrawn from the study. Two of the 8 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 pregnancy outcome is unknown.

Immunogenicity

Anti-drug antibody (ADA) responses were observed in 5% 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). Neutralizing antibodies and product-specific IgE antibodies were not evaluated.

Further details may be found in the current PI (CINQAIR 2016).

1.4. Known and Potential Benefits and Risks to Patients

1.4.1. Benefits and Risks of Reslizumab

Information regarding the risks and benefits of reslizumab to human patients may be found in the current PI (CINQAIR 2016).

1.4.1.1. Benefits of Reslizumab

As described in Section 1.3.2, results from clinical studies indicate improved asthma control and forced expiratory volume in 1 second (FEV_1).

1.4.1.2. 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). Severe systemic reactions (including anaphylaxis), myalgia, elevated CPK, malignancy and oropharyngeal pain are considered as ADRs of iv reslizumab.

Additional information regarding the risks and benefits of reslizumab to human patients may be found in the current PI (CINQAIR 2016).

1.4.2. Risks of Computerized Tomography/Positron Emission Tomography Scans

1.4.2.1. Risks of Fludeoxyglucose F 18 Injection

Use in patients with diabetes mellitus or hyperglycemia has not been well studied. It is recommended that patients be normoglycemic when undergoing positron emission tomography (PET) imaging with Fludeoxyglucose (FDG) F 18 injection.

Additional information regarding the risks and benefits of FDG to human patients may be found in the current PI (FDG 2014).

1.4.2.2. Risks of Computerized Tomography/Positron Emission Tomography Scans

Potential risks from the study assessment procedures are low; FDG-PET/ computed tomography (CT) scans are associated with:

1. small radiation dose from the radiolabeled glucose and low dose CT

2. incidental findings that will be communicated to the participants themselves and to their primary health care providers
3. allergic reactions to the glucose tracer, which are rare and have not been reported within the past decade.

To minimize radiation-absorbed dose to the bladder, adequate hydration should be encouraged to permit frequent voiding during the first few hours after intravenous administration of FDG injection. This may be achieved by having patients drink at least an 8 oz glass of water prior to drug administration. To help protect themselves and others in their environment, patients should take the following precautions for 12 hours after injection: whenever possible, a toilet should be used and should be flushed several times after each use and hands should be washed thoroughly after each voiding or fecal elimination. If blood, urine or feces soil clothing, the clothing should be washed separately.

The exposure to radiation from this study is not significant and is within the acceptable range for research studies involving the use of radiotracers as outlined by the regulatory agencies. The radiation dose from FDG and the PET/CT scan is not necessary for medical care and will occur only as a result of subject participation in the study. At doses much higher than the subject will receive in this study, radiation is known to increase the risk of developing cancer after many years. At the doses of radiation subjects will receive in this study, it is very likely that they will see no effects at all.

1.4.3. Overall Benefit and Risk Assessment for This Study

This is a research study exploring the effect of a single dose of reslizumab iv 3 mg/kg on biomarkers of lung inflammation. Therefore, no direct benefit to the participant is expected. However, information obtained from this study may benefit patients in the future by establishing the validity of a non-invasive measure of lung inflammation for asthma research purposes and for clinical assessment of severe eosinophilic asthma.

1.5. Selection of Drugs and Doses

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

1.5.1. Justification for Dose of Active Drug

The dose to be evaluated in this double blind study is 3.0 mg/kg administered every 4 weeks as per the US PI for CINQAIR (reslizumab).

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 the patients 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) Harmonised Tripartide Guideline for Good Clinical Practice (GCP) 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, Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice 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 clinical 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 clinical study in accordance with the protocol will be documented in separate clinical study agreements with the sponsor and other forms as required by national competent 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 clinical study; and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the involved clinical study personnel 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 PI.

The principal investigator has the overall responsibility for the conduct and administration of the clinical study and for contacts with study management, with the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and with competent authorities.

1.7. Study Population and Justification

This study will include 5 healthy control (HC) subjects and 10 patients with asthma. Males and females, from the ages of 18 through 50 years with asthma and current blood eosinophil levels of at least 400/µL, using ≥440 mcg of fluticasone equivalent and an allowed 2nd asthma controller (eg, long-acting β-agonist [LABA]), will be recruited.

Enrollment will include a minimum of 2 and a maximum of 3 female HC subjects and a minimum of 4 and a maximum of 6 female patients with eosinophilic asthma.

1.8. Location and Study Duration

This study is planned to be conducted in the US at 1 clinical investigational center [redacted] and 1 radiology center [redacted]. It is expected to start in 4th quarter 2016 and have a duration of approximately 2 years.

2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1. Purpose of the Study

The purpose of the study is to demonstrate that reslizumab reduces lung inflammation in patients with eosinophilic asthma.

2.2. Study Objectives

2.2.1. Primary Objective

There are 2 related primary objectives of this study:

1. To establish that positron emission tomography (PET)/computerized tomography (CT) imaging of the lung can reliably distinguish healthy, non-asthmatic volunteers and patients with severe asthma with an eosinophilic phenotype (initial validation).
2. If the utility of PET/CT scanning is established as per objective 1: to show that reslizumab produces a reduction in signal intensity (reduction in lung inflammation) in patients with severe asthma with an eosinophilic phenotype.

2.2.2. Secondary Objectives

The secondary objectives of the study are:

- to demonstrate a correlation between the benefit observed on imaging (PET/CT) with:
  - reductions blood eosinophil counts
  - improvement in clinic visit lung function
  - reductions in fractional exhaled nitric oxide (FeNO)
  - improvements in Asthma Quality of Life questionnaire (AQLQ) scores

2.2.3. Exploratory Objectives

Exploratory objectives are:

- to demonstrate a correlation between changes in the lung PET/CT signal produced by reslizumab and serum biological markers of asthmatic inflammation
- to demonstrate a correlation between changes in the lung PET/CT signal produced by reslizumab and other lung function variables including forced vital capacity (FVC), peak expiratory flow rate (PEFR) and forced expiratory flow at the 25% point to the 75% point of forced vital capacity ($FEF_{25\%-75\%}$)
- to demonstrate that reslizumab produces greater reductions in inflammation of whole-body lymph nodes and bone marrow than placebo as seen on PET/CT
- for those patients that can produce sputum, to demonstrate an association between changes in sputum eosinophil numbers produced by reslizumab and the lung PET/CT signal produced by reslizumab

2.3. Study Endpoints

2.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to week 4 in global lung glycolysis (GLG) (GLGΔ).

The supportive primary efficacy endpoint is the change from baseline to week 4 in lung parenchyma (LP) standardized uptake value (SUV) mean.

2.3.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- the change from baseline to week 4 in blood eosinophil counts
- the change from baseline to week 4 in FEV_1
- the change from baseline to week 4 in FeNO
- the change from baseline to week 4 in AQLQ

2.3.3. Exploratory Endpoints

The exploratory endpoints of this study are:

- biological markers of inflammation and asthma (blood):
  - immunoglobulin E (IgE)
  - dipeptidyl peptidase 4 (DPP4)
  - 25-hydroxy vitamin D
  - eotaxin-1, -2, and -3
  - thymus and activation regulated chemokine (TARC)
  - monocyte chemoattractant protein-1 (MCP-1) and MCP-4
  - group 2 innate lymphoid cells (ILC2)
- lung function variables:
  - FVC
  - PEFR
  - $FEF_{25\%-75\%}$
- the global uptake of FDG in the lymph nodes and bone marrow as measured by the PET-CT imaging parameters indicated for the primary efficacy variable
- sputum eosinophils for those patients that can produce sputum

2.3.4. Safety Endpoints

The safety endpoints are:

- occurrence of adverse events throughout the study
- vital signs (pulse, respiratory rate, and blood pressure) throughout the study
- clinical laboratory evaluations throughout the study
- physical examination findings throughout the study
- use of concomitant medication throughout the study

3. STUDY DESIGN

3.1. General Design and Study Schematic Diagram

This is a 7-week, single-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of reslizumab administered at 3.0 mg/kg in adult patients with eosinophilic asthma. The study will consist of a screening period (up to 21 days), a 6-week, double-blind treatment/assessment period, and a follow-up telephone contact (7±3 days after last visit).

All subjects who participate in this study will consent at [redacted] prior to undergoing any study procedures. After consent is obtained, all participants will undergo all tests and procedures required for eligibility, including sputum and blood eosinophil level assessments. Patients with asthma (does not apply to HC subjects) must have a screening blood eosinophil count of ≥400 cells/µL to be included. A maximum of 3 screening blood eosinophil assessments will be conducted. If the 1st assessment yields a blood eosinophil level below 400 cells/µL patients with asthma may return for a 2nd assessment of blood eosinophil level after 7 days. A 3rd and final assessment will be performed 7 days after the 2nd assessment, if necessary (eg, if the blood eosinophil level remains <400 cells/µL at the 2nd assessment).

The patient must maintain their usual asthma controller regimen without change throughout the screening and study 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 and cannot undergo randomization. A patient may be rescreened for this reason 1 time only. If a patient experiences an asthma exacerbation requiring treatment with systemic steroids, they will only be allowed to be rescreened 6 weeks after completion of treatment. All patients that have to be rescreened must be stable on other asthma medications for 30 days prior to rescreening.

The DEAR study is designed in 2 parts. Part 1 is a validation step whereby the sponsor wishes to determine (1) the intrapatient reproducibility in the GLG measure, and (2) the difference in the GLG measure between individual patients with severe asthma with an eosinophilic phenotype (1-by-1) and the entire HC group. Limits for both the reproducibility within patients and difference among the 2 groups have been provided by subject matter experts.

Part 2 will be a 7-week double-blind evaluation of patients with severe asthma with an eosinophilic phenotype that have been randomized to receive a single dose of either placebo or reslizumab at 3 mg/kg.

Part 1

Within 7 days (±3 days) of eligibility being confirmed, participants will have a PET/CT scan as per the PET/CT scan protocol described in Part 2 below. Participants will return to the [redacted] 7 days (±3) after the first PET/CT scan (taken during visit 2) for a second PET/CT scan following the same procedures described above. HC subjects (n=5) may also have a second sputum induction and blood sample collection at [redacted] with 1 day of the 2nd PET/CT scan, if feasible (preferred but not required). Healthy subjects will be considered

complete at this time. Only after all 5 HCs have completed the study will patients with asthma be screened.

If the relative difference in GLG (based on the average of the 2 measurements) between healthy and asthma patients will be ≥5%, then the asthma patients will be randomized.

A 10% variability (measured as relative difference between first measurement and second measurement) between PET/CT scans as measured by GLG within each group will be considered as the maximum allowed variability. The part 1 criteria have been set at these levels to observe a difference between the healthy subjects and patients with asthma and to ensure intra-group reproducibility; the criteria are based on the investigators' prior experience. If these exploratory criteria are not met (eg, 8 or more patients do not meet the criteria to enter Part 2 [inclusion criteria k and l]), then the study will be reevaluated.

Part 2

If eligible (eg, if inter- and intra-group GLG variability criteria are met), patients will be randomized. This may occur at any time after confirmation of eligibility and up to the time of dosing. Patients will return to [redacted] for baseline clinical, serological, and biochemical measures at the Clinical Research Center (CRC) according to standard procedures. Once these are completed, patients will receive either placebo or reslizumab and will receive the infusion at [redacted]. Any new serious adverse events, reslizumab-related adverse events, and new concomitant medications will be reported.

All planned PET/CT scans (weeks 2, 4, and 6) should be scheduled at the time of randomization. Within 2 weeks (±3 days) of the infusion, patients will return to [redacted] for clinical tests and procedures. Within 3 days of this visit, patients will undergo a PET/CT scan at the [redacted]. Patients repeat the clinical tests and procedures at weeks 4 and 6 post-infusion. Each visit at [redacted] will be followed by a PET/CT scan at the [redacted] as described above.

PET/CT scan procedure

A PET/CT scan consent will be signed before any PET/CT scan procedures are initiated. Patients will undergo a whole-body FDG 18 F-PET/CT scan using the standard protocol (Section 6.1.1).

Image Analysis

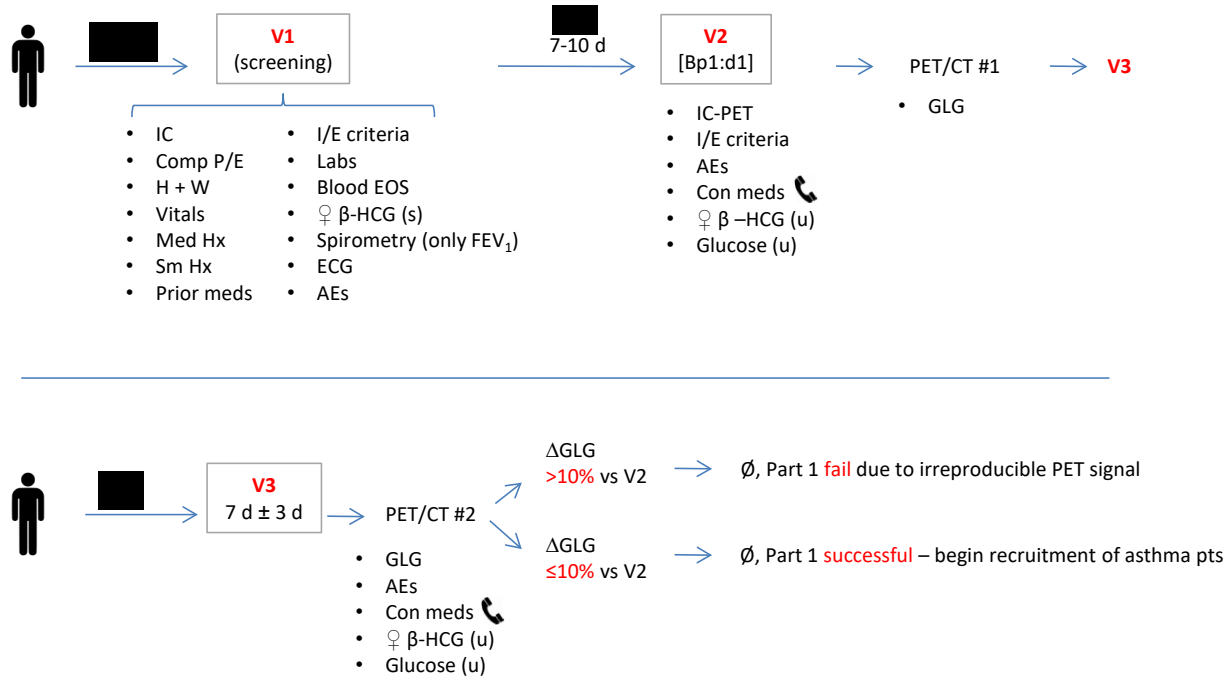
Axial, sagittal, and coronal PET reconstructions will be interpreted, with and without attenuation correction, using non-contrast CT images for anatomical correlation. The investigators plan to measure global and regional inflammation within the lung, lymph nodes and bone marrow by utilizing quantitative parameters based on both volume and SUV. Standardized uptake value is a well validated measure which normalizes FDG uptake by any particular object/tissue volume by the administered dose and either total body weight or total body surface area. Regions of interest (ROIs) will be drawn manually around the outer boundaries of the lung on every transverse slice passing through the lung on fused FDG PET/CT images from each subject. The trachea and main stem bronchi will be excluded from the ROIs to capture only the inflammation in the lung parenchyma. Lung sectional mean standardized uptake value (sSUV mean) and the area of the lung ROI will be recorded from each slice. Subsequently, the sectional lung volume (sLV) will be calculated from each slice by multiplying the lung ROI area (in centimeters squared) by 0.4 (slice thickness 4 mm). The sectional lung glycolysis (sLG) will be determined by multiplying

sLV and lung sSUV mean from each slice. The lung volume (LV) will be calculated by adding all the sLV from slices passing through the lung, and the GLG will be determined by adding all the sLG from slices passing through the lung. Finally, the lung SUV mean will be calculated by dividing the GLG by the LV. Applying this methodology to different tissues or regions of the lungs will allow us to determine average and global SUV measures for the following tissues: whole lung parenchyma, right and left lung parenchyma, trachea, bronchi, and right and left bronchi. These regions will be delineated in the CT images by using the image segmentation techniques. These tissue volumes will be registered with the PET images as outlined below for the estimation of SUVs within these regions. Similar methodology will be applied to the lymph nodes and bone marrow.

The assessments and procedures performed during each study visit are detailed in Table 2 and Section 3.14. If a patient elects to withdraw (or is discontinued from treatment by the investigator), every attempt will be made to continue the assessments subsequent to his/her withdrawal from the study (see Section 4.4).

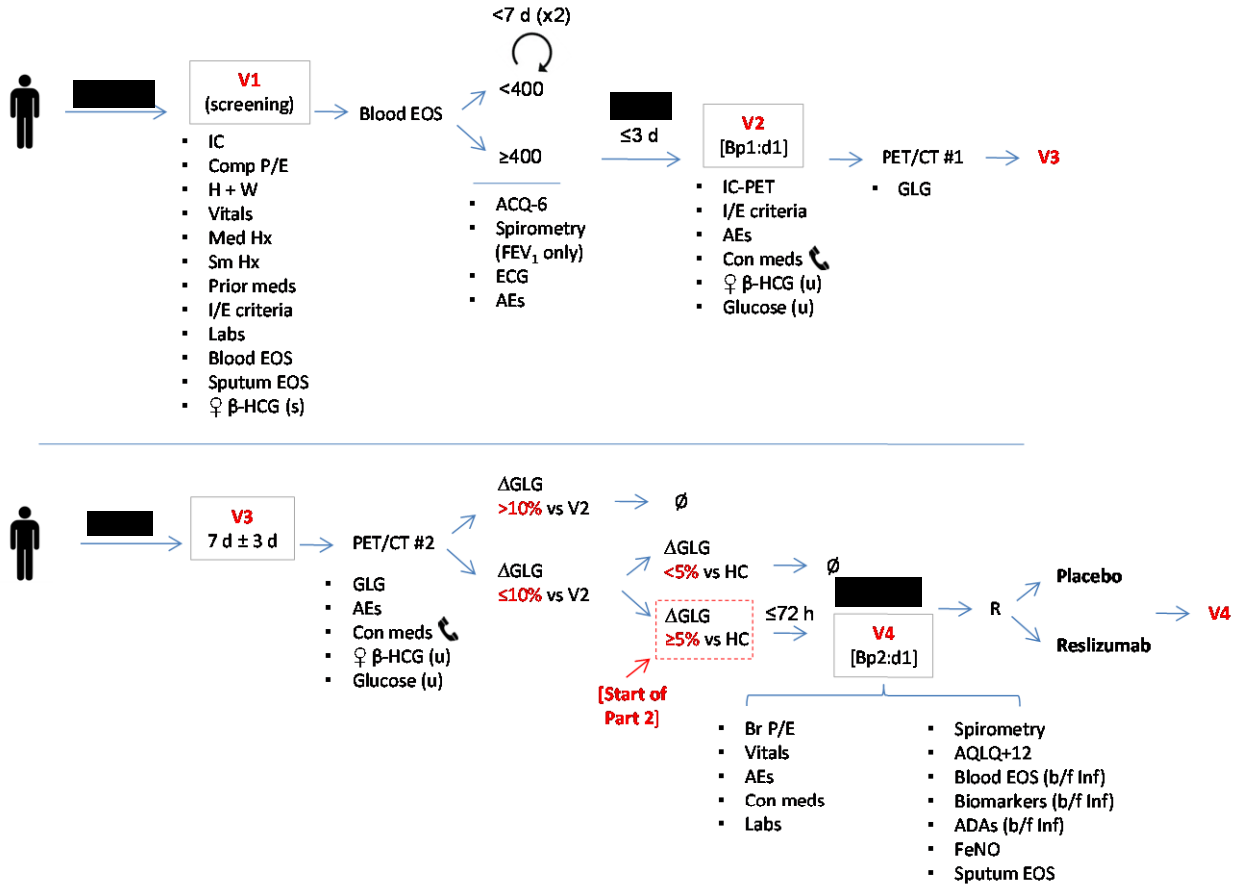
Schemas presenting the walk-through of the study are shown in Figure 1, Figure 2, and Figure 3.

Figure 1: Health Control Subjects-Study Flow



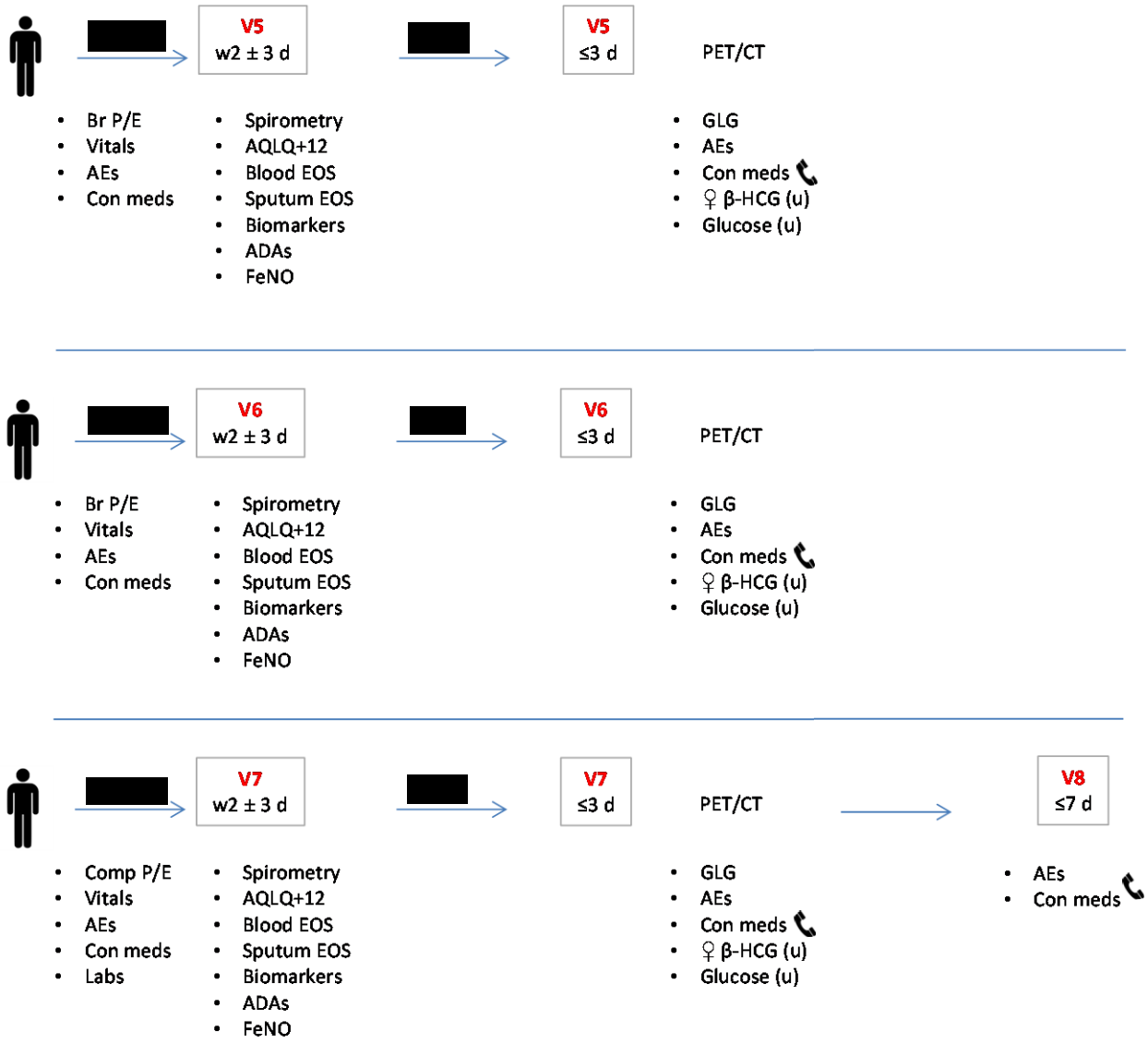
AE=adverse event; β-HCG=beta-human chorionic gonadotropin; Bp1=baseline Part 1; Comp=complete; Con=concomitant; CT=computerized tomography; d=day; ECG=electrocardiography; EOS=eosinophils; FEV_1=forced expiratory volume in 1 second; GLG=global lung glycolysis; H=height; Hx=history; IC=informed consent; I/E=inclusion/exclusion; Labs=laboratory samples; Med=medical; meds=medications; P/E=physical exam; [redacted]; PET=positron emission tomography; pts=patients; [redacted]; s=serum; Sm=smoking; u=urine analysis; V=visit; W=weight

Figure 2: Patients with Asthma-Study Flow: Part 1



ACQ=Asthma Control Questionnaire; ADA=anti-drug antibody; AE=adverse event; AQLQ=Asthma Quality of Life Questionnaire; β-HCG=beta-human chorionic gonadotropin; b/f=before; Bp1=baseline Part 1; Bp2=baseline Part 2; Br=brief; Comp=complete; Con=concomitant; CT=computerized tomography; d=day; ECG=electrocardiography; EOS=eosinophils; FeNO=fractional exhaled nitric oxide; FEV_1=forced expiratory volume in 1 second; GLG=global lung glycolysis; H=height; h=hour; HC=healthy control subjects; Hx=history; IC=informed consent; I/E=inclusion/exclusion; inf=infusion; Labs=laboratory samples; Med=medical; meds=medications; P/E=physical exam; [redacted]; PET=positron emission tomography; R=randomization; [redacted]; s=serum; Sm=smoking; u=urine analysis; V=visit; W=weight

Figure 3: Patients with Asthma-Study Flow: Part 2



ADA=anti-drug antibody; AE=adverse event; AQLQ=Asthma Quality of Life Questionnaire; β-HCG=beta-human chorionic gonadotropin; Br=brief; Comp=complete; Con=concomitant; CT=computerized tomography; d=day; EOS=eosinophils; FeNO=fractional exhaled nitric oxide; GLG=global lung glycolysis; Labs=laboratory samples; meds=medications; P/E=physical exam[redacted]; PET=positron emission tomography; [redacted]; u=urine analysis; V=visit; w2=week 2.

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
Conducting the study	To date, there has been no report of direct visualization of whole lung inflammation in asthmatic patients treated with placebo versus an anti-IL-5 therapy. In addition, there has been no report on the rapidity by which an anti-IL-5 therapy can affect whole lung inflammation in asthmatic patients.
Study population	Patients with eosinophilic asthma and HCs, males and females that are between the ages of 18 and 50. Patient with asthma must have a current blood eosinophil levels of at least 400/μL on ≥440 μg of fluticasone-equivalent and a LABA or any allowed additional treatment to control asthma symptoms.
Study design	Single-center, placebo-controlled, double-blinded, parallel-group, imaging study as Part 1 (validation) and Part 2 (evaluation)
Investigational product dosage regimen and duration of treatment	Reslizumab (CEP-38072), 3.0 mg/kg, iv, 1 administration only
Choice of comparison drug(s) (placebo, active, reference)	Placebo
Number of subjects (including number per treatment group)	Fifteen in Part I (5 as HCs, including a minimum of 2 and a maximum of 3 females, and 10 patients with eosinophilic asthma, including a minimum of 4 and a maximum of 6 females). The latter group will advance to Part 2 with 5 patients randomized to placebo and 5 patients randomized to reslizumab.
Key inclusion and exclusion criteria	See above
Treatment blinding (ie, rationale for blinded or open-label design)	Each patient will be assigned a unique identifier number and all reference to the patient will be using this identifier. Double-blinding is important to ensure that the treatment effect of reslizumab is truly ascribed to the treatment.
Primary analysis (measure, variable, time point, statistical test)	The primary efficacy variable is the update of FDG in the whole lung between placebo- and reslizumab-treated patients as measured by ΔGLG. The supportive primary efficacy variable will be the ΔLP SUV mean. All measurements made at 2 baseline visits and at weeks 2, 4, and 6 post-randomization. The ΔGLG will be described using descriptive statistics. No statistical testing will be conducted.
Inclusion of ancillary studies: PK, PD, immunogenicity	A number of biomarkers will be evaluated to monitor whether they change as part of the response to treatment. Anti-drug antibodies will be evaluated for all patients.

Area	Rationale
Key safety measures	Key safety measures include: • inquiries about adverse events • clinical laboratory evaluations • vital signs (pulse, respiratory rate, and blood pressure) • physical examination findings • inquiries about use of concomitant medication

anti-hIL-5=anti-human interleukin-5; FDG=fludeoxyglucose; ΔGLG=change from baseline in global lung glycolysis; HC=healthy control; iv=intravenous; LABA=long-acting beta-agonist; LP=lung parenchyma; OCS=oral corticosteroids; PD=pharmacodynamic; PK=pharmacokinetics; SUV=standardized uptake value

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

GLG will be measured at 2 baseline visits and at weeks 2, 4, and 6 (all ±3 days) post randomization.

3.3.2. Secondary Efficacy Measures and Time Points

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

- blood eosinophil counts from baseline to weeks 2, 4, and 6 (all ±3 days)
- FEV_1 from baseline to weeks 2, 4, and 6 (all ±3 days)
- FeNO measurements from baseline to weeks 2, 4, and 6 (all ±3 days)
- AQLQ scores from baseline to weeks 2, 4, and 6 (all ±3 days)

3.4. Safety Measures and Time Points

Patient safety will be assessed by standard asthma management and physician practice. If a patient experiences an asthma exacerbation during Part 1, they will be treated with oral corticosteroids (OCS) for a period of 2 weeks, followed by a 6-week observation period without OCS to ensure asthma control. Stable patients will then re-enter the study at the time point of the exacerbation.

The following safety measures will be implemented during the study:

- occurrence of adverse events throughout the study
- vital signs (pulse, respiratory rate, and blood pressure) throughout the study
- clinical laboratory evaluations throughout the study
- physical examination findings throughout the study

- use of concomitant medication throughout the study

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

3.5. Pharmacokinetic Measures and Time Points

Pharmacokinetics will not be assessed in this study.

3.6. Exploratory Efficacy Measures and Time Points

The exploratory efficacy measures and time points are:

- biological markers of inflammation and asthma:
  - IgE
  - DPP4
  - 25-hydroxy vitamin D
  - eotaxin-1, -2, and -3
  - TARC
  - MCP-1 and MCP-4
  - ILC2
- lung function variables:
  - FVC
  - PEFR
  - $FEF_{25\%-75\%}$
- the global uptake of FDG in the lymph nodes and bone marrow as measured by the PET/CT imaging parameters indicated for the primary efficacy variable
- for those patients that can produce sputum, to demonstrate a correlation between reductions in inflammation by reslizumab with a reduction in sputum eosinophils

All variables will be measured at 1 (biomarkers only) or 2 baseline visits and at weeks 2, 4, and 6 post-randomization.

3.7. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. After the 2 baseline PET/CT scans and successful completion of all requirements (Part 1), patients will be randomly assigned 1:1 in a double-blind fashion to receive either placebo or iv 3.0 mg/kg reslizumab.

In order to maintain the blind, each patient will be assigned a unique identifier number and all reference to the patient will be by using this identifier.

Patients will be randomly assigned to treatment groups by means of a computer-generated randomization list. The specifications for randomization will be under the responsibility and

oversight of Teva Global Statistics. The output of the randomization process will be a patient randomization list.

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 ADA sample analysis and an un-blinded person who will be responsible for randomization assignment. Additionally, in order to maintain the study blind, blood and sputum eosinophil levels assessed after study drug administration will not available to investigators, their blinded staff, the sponsor, and blinded members of the clinical research organization. There will be un-blinded data management, un-blinded site staff, and an un-blinded CRA who will not sit on the study team and be responsible for un-blinded eosinophil data.

3.8. Maintenance of Randomization and Blinding

3.8.1. Maintenance of Randomization

Patient randomization codes will be maintained in a secure location at the service provider contracted to generate the codes. At the time of analysis (after the end of study), after receiving unblinding request from Teva statistician, the service provider will provide the unblinded treatment assignment according to the processes defined in the relevant Standard Operating Procedure (SOP).

3.8.2. Blinding/Unblinding

For information about personnel who may be aware of treatment assignments, see Section 3.7. These individuals will not be involved in conduct of any study procedures or assessment of any adverse events.

An envelope containing individual sealed envelopes that correspond to each study drug package will be provided to the investigational center. The envelopes will contain the randomization number and the name and dose (if applicable) of the study drug for each patient. In case of a serious adverse event, pregnancy, or in cases when knowledge of the study drug assignment is needed to make treatment decisions, the investigator may open the patient's envelope and unblind the patient's drug assignment as deemed necessary, mainly in emergency situations. 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. All envelopes must be returned to the sponsor at the completion of the study. Breaking of the treatment code can always be performed by the investigational center 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 on 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 an adverse event defined as a 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 broken (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 the investigator and for other personnel involved in the conduct of the study, and analysis and reporting of the data.

3.8.3. Data Monitoring Committee

A Data Monitoring Committee will not be used during this study.

3.9. Drugs Used in the Study

A description of administration procedures is given in Section 5.1.

Additional details may be found also be found in the current US PI for reslizumab (CINQAIR 2016) and for FDG 18 (FDG 2014).

3.9.1. Investigational Product

Reslizumab will be provided as a sterile solution for infusion presented as 100 mg (10 mL) per vial, formulated at 10 mg/mL in 20 mM sodium acetate, 7% sucrose, pH 5.5 buffer.

The contents of the label will be in accordance with all applicable local regulatory requirements.

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

3.9.2. Placebo

Placebo will be provided as a sterile solution of 20 mM sodium acetate, 7% sucrose, pH 5.5 buffer.

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

3.9.3. Fludeoxyglucose F 18

Fludeoxyglucose F 18 injection will be provided as a ready to use isotonic, sterile, pyrogen free, clear, colorless citrate buffered solution. Each mL will contain between 0.740 to 7.40 gigabecquerel (20.0 to 200 millicurie [mCi]) of 2-deoxy-2-[^{18}F]fluoro-D glucose at the end of synthesis (EOS), 4.5 mg of sodium chloride and 7.2 mg of citrate ions. The pH of the solution will be between 5.5 and 7.5. The solution will be packaged in a multiple-dose glass vial and will not contain any preservative.

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

3.10. Drug Supply and Accountability

3.10.1. Drug Storage and Security

3.10.1.1. Reslizumab and Placebo

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.

3.10.1.2. Fludeoxyglucose F 18

Receipt, transfer, handling, possession, or use of FDG is subject to the radioactive material regulations and licensing requirements of the US Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate.

The FDG vial must be stored upright in a lead shielded container at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Store and dispose of FDG in accordance with the regulations and a general license, or its equivalent, of an Agreement State or a Licensing State. The expiration date and time are provided on the container label. Use FDG within 12 hours from the EOS time.

3.10.2. Drug Accountability

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

The investigator is responsible for ensuring that deliveries of study drug and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the CFR or national and 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 or designee.

3.11. Duration of Patient Participation and Justification

This study will consist of Part 1, a 21-day PET/CT screening period, and Part 2 (only patients with asthma), a 6 week double blind treatment/assessment period followed by a 7-day follow up period. See Section 12.4 for the definition of the end of study.

3.12. Stopping Rules and Discontinuation Criteria

Other than in the event a participant becomes pregnant, there are no formal rules for early termination of this study. During the conduct of the study, serious adverse events will be reviewed by Teva in an ongoing basis (see Section 7.1.5) as they are reported to Teva by the investigational center to identify safety concerns.

The study may be terminated by the sponsor for reasons including, but not limited to, a safety concern.

Termination of patient participation is required in Part 2 in the event of an asthma exacerbation. Should this happen, additional patients will be enrolled until 10 patients (including at least 4 female patients) have completed all 3 post-reslizumab/placebo PET/CT scans.

A patient may discontinue participation in the study at any time for any reason (eg, lack of efficacy, withdrawal of consent, and adverse event); every effort should be undertaken to find out the reason for discontinuation. The investigator or sponsor can withdraw a patient from the

study at any time for any reason (eg, protocol violation or deviation as defined in Section 11.1.2, noncompliance, or adverse event).

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

If data are processed from other institutions or means (eg, clinical laboratory, central image center, or electronic diary data) the results will be sent to the investigational center, where they will be retained and transcribed to the CRF. All data from other institutions will be available to the investigator.

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

3.14. Study Procedures and Assessments

Study procedures and assessments with their time points are summarized in Table 2. Detailed by-visit information is provided starting with Section 3.14.1. Detailed descriptions of each assessment are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (other assessments).

Table 2: Study Procedures and Assessments

Study period	**Part 1**			**Part 2**				**Follow-up**
Visit number	**V1**[a]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**
Allowed time windows	**Up to -21 days**	**0 days**	**±3 day(s)**	**Within 3 days of V3**	**±3 day(s)**	**±3 day(s)**	**±3 day(s)**	**Up to +7 days**
Procedures and assessments	**Screening** [redacted]	**Baseline (day 1)** [redacted]	**W1 (day 8)** [redacted]	**Baseline (day 1)** [redacted]	**W2 (day 15 from V4)**	**W4 (day 29 from V4)**	**W6 (day 43 from V4)/early termination**	**W7**
Informed consent	X	X						
Medical history	X							
Smoking history	X							
Prior medication and treatment history	X							
Complete physical examination[b]	X						A	
Brief physical examination[b]				A	A	A		
Vital signs measurement[bc]	X			A	A	A	A	
Inclusion and exclusion criteria	X	X						
Clinical chemistry[bd]	X			A			A	
Urine/serum β HCG test for women of child bearing potential[be]	X	X	X	A	A	A	A	
Hematology (eosinophils)[f]	X			A	A	A	A	
Sputum sampling for eosinophils[g]	X			A	A	A	A	
Urinalysis[h]	X	X	X		A	A	A	
PET/CT scan [redacted][i]		X	X		A	A	A	
ACQ-6 for entry criterion	A							
Electrocardiography[b]	X							
Spiromety	X			A	A	A	A	

Study period	**Part 1**			**Part 2**				**Follow-up**
Visit number	**V1**[a]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**
Allowed time windows	**Up to -21 days**	**0 days**	**±3 day(s)**	**Within 3 days of V3**	**±3 day(s)**	**±3 day(s)**	**±3 day(s)**	**Up to +7 days**
Procedures and assessments	**Screening** [redacted]	**Baseline (day 1)** [redacted]	**W1 (day 8)** [redacted]	**Baseline (day 1)** [redacted]	**W2 (day 15 from V4)**	**W4 (day 29 from V4)**	**W6 (day 43 from V4)/early termination**	**W7**
ADA[bj]				A	A		A	
Blood collection for biomarker analysis[b]				A	A	A	A	
AQLQ				A	A	A	A	
Randomization				A[k]				
Study drug infusion				A				
Adverse event inquiry	X	X	X	A	A	A	A	A
Concomitant medication inquiry	X	X	X	A	A	A	A	A

[a] screening visit (visit 1) will take place up to 21 days before the V2 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 FEV_1.

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

[c] Vital signs measurements will include blood pressure, pulse, respiratory rate, body temperature, and blood oxygen saturation (SpO_2). Height and weight measurements are required only at screening visit.

[d] The clinical chemistry will include a complete metabolic panel.

[e] A serum β-HCG pregnancy test will be performed at V1 only, for all participating women of childbearing potential. Urine β-HCG tests will be performed, for all participating women of childbearing potential, at V2, V3, V5, V6, and V7, prior to performance of PET/CT scan.

[f] Hematology will include a complete blood count with differential. The results of the differential blood tests performed after study drug administration will be blinded. If there is a medical need to review these results, the investigator will contact the medical monitor.

[g] The results of the sputum eosinophil assessments performed after study drug administration will be blinded. If there is a medical need to review these results, the investigator will contact the medical monitor.

[h] A complete urinalysis will be performed at the screening visit, visit 4, and visit 7; a urine dipstick test for glucose will be performed prior to each PET/CT scan.

[i] Patients should be observed for 1 hour following completion of PET/CT scan.

[j] Blood samples for ADA assessment will be collected at baseline (before study drug administration) and other scheduled time points, and upon observation of any severe hypersensitivity reaction (eg, anaphylaxis).

[k] Randomization can occur any time from determining that the patient qualifies for Part 2 up to study drug infusion. Patient qualification is based on meeting both of the following 2 steps: 1) ΔGLG ≤10% versus V2 [for reproducibility] and 2) ΔGLG≥5% versus HC [for signal] to study drug infusion.

A=patients with asthma only; ACQ-6=6-item Asthma Control Questionnaire; ADA=anti-drug antibodies; AQLQ=Asthma Quality of Life Questionnaire; β-HCG= beta human chorionic gonadotropin; CBC=complete blood count; CT=computerized tomography; GLG=gloal lung glycolysis; HC=healthy control subjects only; IP=investigational product; PET=positron emission tomography; [redacted]; V=visit; W=week; X=patients with asthma and healthy control subjects.

3.14.1. Procedures for Screening and Enrollment (Visit 1)

A signed and dated informed consent form will be obtained before any screening procedures commence (see Section 12.1). Assessments conducted as part of routine medical care and performed during the screening period may be used in place of the protocol-specific assessments. In addition, disease-specific assessments performed within a specified time frame before informed consent may be used for the study. Patients 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 assigned number of the investigational center, and the last 3 digits will be assigned at the investigational center (eg, if the number assigned to the country is 01, the 3rd patient screened at 5th investigational center would be given the number of 01005003).

The screening visit (visit 1) will take place not more than 3 weeks before the Part 1 baseline visit (visit 2). The following procedures will be performed at visit 1:

- Obtain written informed consent before any study-related procedures are performed
- Review inclusion and exclusion criteria
- Review medical history
- Review medication history
- Review smoking history
- Perform clinical laboratory tests (chemistry, hematology, and urinalysis). Patients with an eosinophil count <400/μL may be retested up to 2 additional times within the 21-day screening period. Patients must have an eosinophil level ≥400/μL to complete screening.
- Perform serum pregnancy test (for women of childbearing potential)
- Perform complete physical examination including height and weight
- Assess vital signs, including blood pressure (BP), pulse, respiratory rate (RR), body temperature, and blood oxygen saturation level (SpO_2)
- Perform ECG
- Perform spirometry
- Collect sputum sample
- Complete ACQ-6 (patients only, not HC subjects)
- Inquire about adverse events
- Inquire about concomitant medication usage
- Inform patients of study restrictions and compliance requirements

3.14.2. Procedures Before Study Drug Treatment (Part 1 Baseline [Visit 2, Day 1])

Patients who meet the inclusion and exclusion criteria and complete the assessments at visit 1 will continue to visit 2 (up to 3 days after completing the screening procedures).

The following procedures will be performed at visit 2:

- Confirm patient meets inclusion and exclusion criteria
- Ensure written informed consent is in place before any procedures at the [redacted] are performed
- Perform urine pregnancy test (for women of child bearing potential)
- Perform urine glucose test
- Perform PET/CT scan
- Observe for 1 hour after completion of PET/CT scan
- Inquire about concomitant medication usage
- Inquire about adverse events

3.14.2.1. Week 1 (Visit 3)

The following procedures/assessments will be performed at visit 3, day 8 (±3 days):

- Perform urine pregnancy test (for women of child bearing potential)
- Perform urine glucose test
- Perform PET/CT scan
- Observe for 1 hour after completion of PET/CT scan
- Inquire about concomitant medication usage
- Inquire about adverse events

Healthy subjects are considered complete at this point and do not need to return for any follow up visits.

3.14.3. Procedures During Study Drug Treatment

3.14.3.1. Part 2 (Week 1 [Visit 4])

Randomization may occur at any time from determining that the patient qualifies for Part 2 up to study drug infusion. Patient qualification is based on meeting both of the following 2 steps: 1) $\Delta GLG \leq 10\%$ versus V2 (for reproducibility) and 2) $\Delta GLG \geq 5\%$ versus HC (for signal). Patients will be assigned a permanent, unique randomization number and a treatment number. These 2 assigned numbers will be entered in the CRF.

On Part 2, day 1 (within 72 hours of the PET/CT scan), the following procedures will be performed:

- Inquire about adverse events

- Inquire about concomitant medication usage
- Perform brief physical examination
- Assess vital signs (as described in Section 3.14.1)
- Perform urine pregnancy test (for women of child bearing potential)
- Perform clinical laboratory tests (chemistry, urinalysis, and hematology).
- Collect sputum sample.
- Administer the AQLQ+12
- Collect blood sample for serum ADA assay
- Collect blood sample for biomarkers analyses
- Perform spirometry

Once the above procedures have been performed, study drug infusion will occur. Any adverse events that occurred, or concomitant medications that were administered, during the visit will be recorded.

Observe patients for 1 hour after completion of study drug infusion.

3.14.3.2. Weeks 2, 4, and 6 (Visits 5, 6, and 7)

The following procedures/assessments will be performed at weeks 2, 4, and 6 (visits 5, 6, and 7):

The following procedures will be performed at the CRTC of the [redacted]:

- Perform urine pregnancy test (for women of child bearing potential)
- Perform urine glucose test
- Perform PET/CT scan
- Observe for 1 hour after completion of PET/CT scan

Up to 72 hours after the PET/CT scan, the following procedures will be performed:

- Inquire about adverse events
- Inquire about concomitant medication usage
- Perform clinical laboratory tests (chemistry [week 6, visit 7 only], urinalysis [week 6, visit 7 only], and hematology). The results of the differential blood tests performed after study drug administration will be blinded. If there is a medical need to review these results, the investigator will contact the medical monitor.
- Collect sputum sample. The results of the sputum eosinophil assessments performed after study drug administration will be blinded. If there is a medical need to review these results, the investigator will contact the medical monitor.
- Perform physical examination:
  - brief exam at week 2 (visit 5) and week 4 (visit 6)

  - complete exam at week 6 (visit 7) only
- Assess vital signs, including BP, pulse, RR, body temperature, and SpO_2
- Administer the AQLQ+12
- Obtain blood sample for serum ADA assay (weeks 2 and 6 [visits 5 and 7] only)
- Obtain blood sample for biomarkers analyses
- Perform spirometry

3.14.4. Procedures After Study Drug Treatment

Patients who participate in the study in compliance with the protocol for at least 6 weeks from the start of Part 2 will be considered to have completed the study. See Section 12.4 for the definition of the end of study.

For patients who complete the study or withdraw prematurely, final evaluations will be performed at an end-of treatment visit or as soon as possible thereafter. Procedures for patients who withdraw prematurely from the study are described in Section 4.4. Patients should be treated with standard of care after termination of the study as appropriate.

Patients with ongoing adverse events will be monitored as described in Section 7.1.2. Otherwise, visit 7 will be the last study visit.

3.14.4.1. Telephone Follow-Up (Visit 8, Up To 7 Days After Visit 7)

The following procedures/assessments will be completed at the follow-up contact (visit 8, week 7, up to 7 days after visit 7):

- Inquire about adverse events.
- Inquire about concomitant medication usage.

3.14.5. Unscheduled Visits

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

Procedures performed during unscheduled visits include the following:

- concomitant medication inquiry
- vital signs measurements
- adverse event inquiry
- review study compliance

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

4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be enrolled are not granted by Teva (see Section 11.1.2).

4.1. Patient Inclusion Criteria

Healthy subjects and patients may be enrolled in this study only if they meet all of the following criteria:

a. Male or female, 18 through 50 years of age.

b. Females that are either surgically sterile, are 2 years postmenopausal, or have a negative pregnancy test beta-human chorionic gonadotropin at screening (serum) and all PET/CT imaging visits (urine).

c. Females of childbearing potential (not surgically sterile or 2 years postmenopausal), have to use a medically accepted method of contraception and have to agree to continue to use of this method for the duration of the study and for 5 months after study drug administration. Acceptable methods of contraception include barrier method with spermicide, abstinence, intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted, and injected). Note: partner sterility alone is not acceptable for inclusion in the study.

d. Subjects and patients with less that 10-pack year history of smoking.

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

e. Male or female, 18 through 50 years of age, with a previous diagnosis of asthma.

f. Patients taking inhaled fluticasone at a dosage of at least 440 mcg daily, or equivalent.

g. The patient's baseline asthma therapy regimen (including, but not limited to, inhaled corticosteroids, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, or cromolyn) must be stable for 30 days prior to screening and judged by their treating physician to be able to continue without dosage changes throughout the study.

h. Patients with a blood eosinophil level of at least 400/µL at screening. Patients with a blood eosinophil level below 400/µL will be given 2 additional screening opportunities to determine blood eosinophil levels.

i. Patients with airway reversibility of at least 12% to β-agonist administration.

j. Patients with an ACQ score of at least 1.5 at either screening or baseline visits.

Patients may be included in Part 2 of the study only if they also meet the following, additional criteria:

k. the intrapatient reproducibility, taken as sequential GLG measures on visits 2 and 3 (Table 2), differs by only ≤10%

l. the intragroup variability (signal window), taken as a difference in the 2 subcriteria (below) to be ≥5%:

- the mean GLG of healthy controls determined by taking the mean of the average GLG for visits 2 and 3 for each healthy control.
- the mean GLG of each single patient with severe asthma with an eosinophilic phenotype, taken as sequential GLG measures on visits 2 and 3 (Table 2).

4.2. Patient Exclusion Criteria

Healthy subjects and patients will be excluded from participating in this study if they meet any of the following criteria:

a. Patients requiring treatment with oral, intramuscular, or iv corticosteroids within 6 weeks of the Part 1 baseline visit.

b. Patients with any other confounding underlying lung disorder including but not limited to: bronchiectasis, chronic obstructive pulmonary disorder, smoking ≥10 pack year history, pulmonary fibrosis, emphysema, cystic fibrosis, and lung cancer.

c. Patients with a blood glucose level at screening or baseline greater than or equal to 150 mg/dL.

d. Patients diagnosed with diabetes mellitus.

e. Patients with pulmonary conditions and blood eosinophilia other than eosinophilic asthma including, but not limited to: Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis and hypereosinophilic syndrome.

f. Patients with clinically meaningful comorbidity that can interfere with the study schedule or procedures, or compromise the patient's safety.

g. Patients that are current smokers (ie, have smoked within the last 12 months prior to screening).

h. Patients using systemic immunosuppressive, immunomodulating, or other biologic agents (including, but not limited to, anti-IgE mAb, methotrexate, cyclosporin, interferon-α, or anti–tumor necrosis factor mAb) within 6 months prior to screening.

i. Patients who have previously received an anti-hIL-5 mAb (eg, reslizumab, mepolizumab [Nucala]) or anti-IL-5 receptor mAb (eg, benralizumab).

j. Patients who had concurrent infection or disease that may preclude assessment of active asthma.

k. Patients with a history of concurrent immunodeficiency (human immunodeficiency virus or acquired immunodeficiency syndrome or congenital immunodeficiency).

l. Patients that had an active parasitic infection within 6 months prior to screening.

m. Patients with a history of exposure to water-borne parasites within 6 weeks prior to screening or during the screening period or a history of diarrheal illness of undetermined etiology within 3 months prior to screening or during the screening period

n. Any patient who had an infection requiring the following:
   - an admission to the hospital for at least 24 hours within 4 weeks prior to screening or during the screening period
   - treatment with iv antibiotics within 4 weeks prior to screening or during the screening period
   - treatment with oral antibiotics within 4 weeks prior to screening or during the screening period

o. Patients with any disorder that may interfere with drug absorption, distribution, metabolism, or excretion (including gastrointestinal surgery).

p. Female subjects who are pregnant or breast-feeding or considering becoming pregnant during the study or within 5 months after reslizumab dosing.

q. Known hypersensitivity to study drug or to FDG/contrast agents.

r. Treatment with metformin.

s. Compromised renal function.

4.3. Justification for Key Inclusion and Exclusion Criteria

4.4. Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki, each patient is free to withdraw from the study at any time. The investigator also has the right to 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 3.8, 3.12, 3.14.4, 5.4, and 7.1.8.

Should a patient decide to withdraw after administration of study drug(s), or should the investigator decide to withdraw the patient, all efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given as to why the patient is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed to the CRF. 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 clinically significant abnormal laboratory test result, monitoring will be continued 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 specific event or test result must be recorded on the source documentation and transcribed to the CRF.

All assessments should be performed according to the protocol.

A patient who is has been identified as a potential participant but does not complete the screening period may be replaced with another eligible patient to ensure that at least 10 asthma patients (with at least 4 females) are evaluable for post-reslizumab PET/CT.

5. TREATMENT OF PATIENTS

5.1. Drugs Administered During the Study

5.1.1. Reslizumab

At the Part 2 baseline visit, patients will be randomly assigned to treatment with reslizumab or to the placebo treatment group. Reslizumab (3.0 mg/kg) or matching placebo will be administered by iv infusion, over 20 to 50 minutes, at the baseline visit. Patients will be observed for 1 hour after administration of study drug/placebo. Additional administration information may be found in Section 2 of the US PI for reslizumab (CINQAIR 2016).

Study drug will be administered by qualified study personnel who will ensure that the study drug is administered in accordance with the protocol.

A more detailed description of the reslizumab drug product is provided in Section 3.9.

5.1.2. Fludeoxyglucose F 18

Prior to each PET/CT scan, FDG will be administered by iv infusion.

Fludeoxyglucose F 18 will be administered by qualified study personnel who will ensure that the study drug is administered in accordance with the protocol.

5.2. Restrictions

Medications prohibited before 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 Medication or Treatment

Any prior or concomitant medication, treatment, or procedure a patient has had within 4 weeks before screening and up to the end of 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.

- Patients should refrain from using reliever inhalers for 6 hours before any study visit that includes spirometry or airway reversibility testing, including the screening visit.
- If a patient is taking LABAs, these should be withheld for 12 hours before any study visit that includes spirometry or airway reversibility testing, including the screening visit.

The following medications will not be allowed during this study:

- Any immunosuppressive or immunomodulatory agents (biological and non biological), including, but not limited to systemic steroids, methotrexate, cyclosporine, and interferon (excluding maintenance allergen immunotherapy)

- All biologic therapies, including, but not limited to omalizumab (Xolair®), mepolizumab (Nucala), benralizumab, lebrikizumab, and anti-tumor necrosis factor monoclonal antibodies
- All nonbiologic investigational drugs
- Inhaled nicotine (including electronic cigarettes)

The following medications are allowed as *prior medications*, with the restrictions as noted:

- Treatment with systemic corticosteroids must have been stopped at least 6 weeks prior to the Part 1 baseline visit
- Treatment with systemic immunosuppressive, immunomodulating, or other biologic agents (including, but not limited to, anti-IgE mAb, methotrexate, cyclosporin, interferon-α, or anti–tumor necrosis factor mAb) must have been stopped at least 6 months prior to screening
- Baseline asthma therapy regimen (including, but not limited to, inhaled corticosteroids, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, or cromolyn) must be stable for 30 days prior to screening and judged by their treating physician to be able to continue without dosage changes throughout the study.

5.4. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance. A check of study drug compliance will be performed during each visit after the initial dispensation of study drug; and study drug accountability records will be completed. 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 total blood volume to be collected for each patient in this study is approximately 164.5 mL (Table 3).

Table 3: Blood Volumes

Type of samples	Volume per sample (mL)	Total number of samples	Total volume (mL)
Clinical laboratory	15.5	5[a]	77.5
Biomarkers	18	4	72
ADA	5	3	15
Total	**38.5**	**12**[a]	**164.5**

[a] A single clinical laboratory sample will be collected from the healthy control subjects, at the screening visit.
ADA=anti-drug antibody.

6. ASSESSMENT OF EFFICACY

6.1. Primary Efficacy Measure and Justification

The primary efficacy measure for this study is the change in GLG as assessed by PET/CT. Part 1 of the study will validate this measure by comparing this assessment between HC subjects and patients with eosinophilia asthma. In Part 2, only patients with eosinophilic asthma will be assessed for GLG at 2, 4, and 6 weeks, after randomization to placebo or treatment with a single dose of reslizumab.

6.1.1. Positron Emission Tomography/Computerized Tomography Scans

Patients must fast for 8 hours prior to the scan. Blood glucose level will be measured before the administration of FDG. Blood glucose level should not exceed 150 mg/dL at the time of injection. Whole-body, head-to-toe PET/CT image acquisition will begin about 120 minutes after iv administration of 7 mCi of the radioisotope fluorine-18 (^{18}F)-FDG. PET/CT image acquisition will take 30 to 40 minutes. In total, patients will spend about 3 hours in the PET center per each imaging visit. Patients will be asked to return in 2 days for a repeat FDG-PET/CT scan to be used as technical replicates in Part 1. Because ^{18}F has a half-life of 109 minutes and is effectively fully decayed within a few hours of administration, FDG will be re-administered during the follow up visits and PET/CT imaging will be performed following the same protocol described above.

Each FDG-PET/CT scan will deliver about 800 millirem (mrem) of radiation to the patient. Because patients will undergo 5 PET/CT scans, it is estimated that patients will receive a total radiation of 4000 mrem, which is within yearly limits set by the [redacted]

To minimize radiation-absorbed dose to the bladder, adequate hydration should be encouraged to permit frequent voiding during the first few hours after iv administration of FDG injection. This may be achieved by having patients drink at least an 8 oz glass of water prior to drug administration. To help protect themselves and others in their environment, patients should take the following precautions for 12 hours after injection: whenever possible, a toilet should be used and should be flushed several times after each use and hands should be washed thoroughly after each voiding or fecal elimination. If blood, urine or feces soil clothing, the clothing should be washed separately.

6.1.2. Image Analysis

Axial, sagittal, and coronal PET reconstructions will be interpreted, with and without attenuation correction, using non-contrast CT images for anatomical correlation. The investigators plan to measure global and regional inflammation within the lung, lymph nodes and bone marrow by utilizing quantitative parameters based on both volume and SUV. SUV is a well validated measure which normalizes FDG uptake by any particular object/tissue volume by the administered dose and either total body weight or total body surface area. Regions of interest (ROIs) will be drawn manually around the outer boundaries of the lung on every transverse slice passing through the lung on fused FDG PET/CT images from each subject. The trachea and main

stem bronchi will be excluded from the ROIs to capture only the inflammation in the lung parenchyma. Lung sectional mean standardized uptake value (sSUV mean) and the area of the lung ROI will be recorded from each slice. Subsequently, the sLV will be calculated from each slice by multiplying the lung ROI area (in centimeters squared) by 0.4 (slice thickness 4 mm). The sLG will be determined by multiplying sLV and lung sSUV mean from each slice. The LV will be calculated by adding all the sLV from slices passing through the lung, and the GLG will be determined by adding all the sLG from slices passing through the lung. Finally, the lung SUV mean will be calculated by dividing the GLG by the LV. Applying this methodology to different tissues or regions of the lungs will allow us to determine average and global SUV measures for the following tissues: whole lung parenchyma, right and left lung parenchyma, trachea, bronchi, and right and left bronchi. These regions will be delineated in the CT images by using the image segmentation techniques. These tissue volumes will be registered with the PET images as outlined below for the estimation of SUVs within these regions. Similar methodology will be applied to the lymph nodes and bone marrow.

6.1.3. Calculations

The radiology center will determine the following:

GLG is the total FDG uptake in the whole lung.

An ROI is drawn around lung boundary in each axial slice. SUVmean and area of each ROI is recorded. Using the formula: area*slice thickness the volume of each slice is calculated. Then SUVmean of each slice is multiplied by the volume of the corresponding slice, which will represent the total FDG uptake in one slice. This number for each slice is summed together to provide GLG of that lung.

$$GLG=\sum_{1}^{n}(area * slice\ thickness\ * SUVmean)$$

n=number of slices

Intra-patient variability (reproducibility measure):

Below is the calculation to determine the intra-patient variability between PET/CT scans as measured by GLG for HCs and patients with eosinophilic asthma. The accepted variability within each group is ≤10% and will be as follows:

Relative difference of GLG=(GLG2-GLG1)/GLG1

Relative difference of GLG=(GLG4-GLG3)/GLG3

1= First time point (HCs)

2= Second time point (HCs)

3= First time point (patients with eosinophilic asthma)

4= Second time point (patients with eosinophilic asthma)

Variability between HC group and individual patients with eosinophilic asthma:

The planned method to assess whether the difference in GLG (ΔGLG) between HC subjects, as a group, and individual patients with eosinophilic asthma is ≥5% and will be as follows:

For Females:

Relative difference of GLG=($GLG6_i$-GLG5f)/GLG5f

For Males:

Relative difference of GLG=($GLG6_i$-GLG5m)/GLG5m

5=average of 1 and 2

6=average of 3 and 4

$GLG6_i$ will be calculated for each individual patient using his/her two measurements, and if that amount is ≥5%, than the patient will be randomized.

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

6.3. Asthma Control Questionnaire

The ACQ-6 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-6 has a possible score ranging from 0 to 6, and the total score is the mean of all responses (Appendix A).

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).

7. ASSESSMENT OF SAFETY

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

- Adverse events throughout the study
- Clinical laboratory test results (serum chemistry, hematology, and urinalysis) throughout the study
- Vital signs (pulse, respiratory rate, body temperature, blood pressure, and SpO_2) throughout the study
- Physical examination findings throughout the study
- Concomitant medication usage throughout the study

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

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

In this study, any adverse event occurring after the clinical study patient has signed the 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. 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 (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 test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, require medical treatment or further diagnostic work up, or are considered by the investigator to be clinically significant (Note: Abnormal laboratory test results at

the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)

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.

7.1.2. Recording and Reporting of 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 1 week after visit 6 (week 6), approximately 7 weeks after the single dose of reslizumab. 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 to 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 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 occurring in a patient after the end of the study should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

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”. 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, on the Serious Adverse Event Form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; or until the patient is referred for continued care to a 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 to 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 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 after 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:

- results in death

- is life-threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event which hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission 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 the patient signed the informed consent form will not be considered serious adverse events, unless there was worsening of the preexisting condition during the patient's participation in this study.
- results in persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- is 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 (RSI) by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The RSI for this study is the US prescribing information for reslizumab and for FDG.

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) that occur during the study period (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 treatment of that patient has ended 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 (contact information is in the Clinical Study Personnel Contact Information section); the LSO will forward the report to the sponsor's Global Patient Safety and Pharmacovigilance.

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 medication (including doses, routes of administration, 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)
  - autopsy findings (if available)

The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

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.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigator 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 and Pharmacovigilance will distribute the Council for International Organizations of Medical Sciences form/Extensible Markup Language file to the LSO for submission to the competent 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 national and local regulations.

Blinding will be maintained for all clinical study personnel. Therefore, in case of a SUSAR, only the LSO will receive 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).

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 the appropriate competent authorities (and IEC/IRB, as appropriate).

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

- 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 all 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, and parasitic helminth and opportunistic infections. 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).

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 C). 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.

Blood samples for ADA testing should be taken in any case where hypersensitivity is suspected to be related to study drug/placebo administration.

7.1.7.2. Creatine Phosphokinase/Muscular Adverse Events Case Report Form

Potentially clinically significant 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× ULN (Grade 3 based on the FDA "Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials").

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 Sponsor's Authorized Representative as soon as possible of each patient who is being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

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

7.1.9. Overdose of Study Drug

Any dose of study drug (whether the investigational product, reference treatment, or 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 3.8.

Any administration of medication that is not in accordance with the study protocol should be reported on the CRF, either as a violation or as a deviation, in the patient's source documents, regardless of whether an adverse event occurs as a result. See Section 7.3 for additional information.

7.1.10. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must

contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol 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

Any female patient becoming pregnant during the study will discontinue study medication.

All pregnancies of women participating in the study that occur during the study, or within 5 months after study medication infusion, are to be reported immediately to the individual identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO) with the completed pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (Section 7.1.5.3).

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

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

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

7.3. Medication Error and Special Situations

Any administration of study medication that is not in accordance with the study protocol should be reported on the CRF either as a violation, if it meets the violation criteria specified in the protocol (Section 11.1.2), or as a deviation, in the patients source documents, regardless of whether an adverse event occurs as a result. All instances of incorrect medication administration should be categorized on the CRF as “Non-Compliance to investigational medicinal product (IMP)”.

Types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.

3. Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.
4. Abuse: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.
6. Occupational exposure: Exposure to a medicinal product, as a result of one's professional or non-professional occupation.

7.4. Clinical Laboratory Tests

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

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that has significantly worsened (according to investigator's medical judgment) from the baseline 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. Any adverse clinical laboratory result 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.

7.4.1. Serum Chemistry, Hematology, and Urinalysis

Clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be performed at the time points detailed in Table 2. Clinical laboratory tests will be performed using the local laboratory. Specific laboratory tests to be performed are provided in Table 4.

Table 4: Clinical Laboratory Tests

Serum Chemistry	Hematology	Urinalysis
calcium phosphate sodium potassium chloride creatinine glucose blood urea nitrogen (BUN) cholesterol (low density lipoprotein [LDL]/high density lipoprotein [HDL]/total)[a] triglycerides[a] uric acid alanine aminotransferase (ALT) aspartate aminotransferase (AST) lactate dehydrogenase (LDH) gamma-glutamyl transpeptidase (GGT) alkaline phosphatase bicarbonate or carbon dioxide creatinine phosphokinase total protein albumin total bilirubin direct bilirubin indirect bilirubin	hemoglobin hematocrit red blood cell (RBC) count RBC indices platelet count white blood cell (WBC) count, and differential count and percentage – absolute neutrophil count (ANC) – polymorphonuclear leukocytes (neutrophils) – lymphocytes – eosinophils – monocytes – basophils – atypical lymphocytes – other (to include band granulocytes) international normalized ratio (INR)	protein glucose ketones blood (hemoglobin) pH specific gravity microscopic – bacteria – red blood cells (RBCs) – white blood cells (WBCs)

[a] Assessed at the screening visit only

7.4.2. Other Clinical Laboratory Tests

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

7.4.2.1. Human Chorionic Gonadotropin Tests

Human chorionic gonadotropin tests in serum will be performed for all women at screening (visit 1) and, in urine, before study drug administration and before each PET/CT scan as specified in Table 2. Any female patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.

7.5. Vital Signs

Vital signs (blood pressure, respiratory rate, body temperature, pulse, and SpO_2) will be measured at the time points detailed in Table 2. All vital signs results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Before blood pressure and pulse 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 clinically significant will be recorded on the source documentation, transcribed to the CRF as an adverse event, and monitored as described in Section 7.1.2.

7.6. Electrocardiography

A 12-lead ECG will be conducted at screening (visit 1). ECGs should be obtained before other assessments (eg, blood draw and pulmonary function testing). The ECG will be interpreted by the investigator (or qualified physician) as normal or abnormal. If the ECG is read as abnormal the investigator will specify the abnormality and indicate whether or not the abnormality is clinically significant (yes or no). Clinically significant abnormal ECG findings at screening should be recorded as part of the medical history.

7.7. Physical Examinations

Physical examinations, including height (to be obtained at the screening visit only) and weight, will be performed at the time points detailed in Table 2. The "full" physical examination should include the following organ systems: General appearance; Head, Eyes, Ears, Nose, and Throat; 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; Head, Eyes, Ears, Nose, and Throat; Chest and Lung; and Heart. Any physical examination finding that is judged by the investigator as clinically significant will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

7.8. Concomitant Medication or Treatment

Use of concomitant medication or treatment will be monitored throughout the study. Details of prohibited medications are found in Section 5.3.

7.9. Methods and Time Points of Assessing, Recording, and Analyzing Safety Data

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

Procedures for recording safety data are discussed in Section 13.1 and methods of analyses are discussed in Section 9.7.2.

8. ASSESSMENT OF BIOMARKERS AND IMMUNOGENICITY

8.1. Assessment of Exploratory Biomarkers

8.1.1. Immunoglobulin E

8.1.1.1. Background

Immunoglobulin (IgE) is synthesized by plasma cells as an immune reaction to parasites such as helminths (Erb 2007). IgE also has an essential role in type I hypersensitivity, which manifests various allergic diseases, such as allergic asthma, most types of sinusitis, allergic rhinitis, food allergies, and specific types of chronic urticaria and atopic dermatitis (Gould et al 2003). Immunoglobulin E also plays a pivotal role in responses to allergens, such as anaphylatic drugs, bee stings, and antigen preparations used in desensitization immunotherapy.

It is well known that IgE, T-helper cell subset 2 (Th2)-derived cytokines, and eosinophils play a major role in the development of chronic airway inflammation, which is observed even in subjects with mild disease (Busse 2000, Holloway et al 2001, Novak and Bieber 2003, Pelaia et al 2012). Airway inflammation plays a central role in the pathogenesis of bronchial asthma and is associated with an increase in airway responsiveness to several trigger factors such as aeroallergens which induce bronchoconstriction in atopic asthma patients, acting sometimes in cooperation with other trigger factors such as viruses and air pollution (Martinez and Vercelli 2013).

It is estimated that more than 50% of asthma has an allergic background and about 50% of patients with severe asthma have allergic-atopic asthma (Masoli et al 2004, Wenzel 2006), although many previously published data demonstrated that the severe phenotype is less frequent in atopic adult-onset asthma (Wenzel 2006, ENFUMOSA 2003, Moore et al 2007).

The development of the first anti-IgE antibody has been a significant advance in the treatment of allergic asthma. In 2005, Humbert and colleagues examined the benefits of omalizumab (anti-IgE, Xolair®) as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (Humbert et al 2005). The INNOVATE trial reported that the rate of clinically significant asthma exacerbations, after adjusting for an observed imbalance in asthma exacerbation history prior to randomization, was significantly reduced by 26.2% with omalizumab versus placebo.

Overall, there are many therapeutic benefits of anti-IgE antibodies. These include serum IgE levels diminishing by greater than 95% compared to before treatment and consequently weakening early and late phase reactions (Fahy et al 1997, Milgrom et al 1999). The 2014 Cochrane review (Normansell et al 2014) and other systematic reviews identify that omalizumab significantly reduces asthma exacerbations, and specifically that there was a reduction in the rate of exacerbations from 26% to 16% when comparing patients given a placebo to patients receiving omalizumab (Norman et al 2013, O'Byrne 2013).

Despite all these advances, the effect of anti-IL5 therapy on the levels of IgE has never been studied. In this protocol, we wish to evaluate the quantity of IgE in peripheral blood and sputum and determine whether any changes occur following the administration of reslizumab.

8.1.1.2. Specimen Sampling and Handling

Blood samples for assessment of IgE will be collected and processed using the procedures in place at the investigational center [redacted]

8.1.2. Dipeptidyl Peptidase-4

8.1.2.1. Background

The protein encoded by the dipeptidyl peptidase-4 (DPP4) gene is an antigenic enzyme expressed on the surface of most cell types and is associated with immune regulation, signal transduction and apoptosis (Chen 2006).

The best known immunostimulatory activity of DPP4 is its contribution to T lymphocyte activation (Zhong et al 2013). Recently, it was reported that DPP4 has a proliferative effect on vascular smooth muscle cells (Ervinna et al 2013) and could be involved in airway remodeling by inducing the production of extracellular matrix proteins such as fibronectin (Shiobara et al 2016).

Although DPP4 has recently been demonstrated to be induced by IL-13 in normal human bronchial epithelial cells (Zhen et al 2007), the contribution of IL-5 is currently unknown and the effect of anti-IL-5 therapy on the expression of DPP4 has never been studied. In this protocol, we wish to evaluate levels of DPP4 in peripheral blood and sputum and determine whether any changes occur following the administration of reslizumab.

8.1.2.2. Specimen Sampling and Handling

Blood samples for assessment of DPP4 will be collected and processed using the procedures in place at the investigational center [redacted]

8.1.3. 25-Hydroxy Vitamin D

8.1.3.1. Background

The relationship between low levels of vitamin D and declining lung function has been demonstrated in a number of clinical trials, observational studies and real-world evidence data (Poon et al 2013, Brumpton et al 2016).

Black and Scragg evaluated data from the Third National Health and Nutrition Examinations Survey, which conducted a cross-sectional 6-year study on 14,091 participants. Eligible subjects had undergone spirometry and a measurement of serum 25-hydroxy vitamin D level. After adjustment for age, gender, height, body mass index, ethnicity, and smoking history, they observed a significant difference in mean FEV_1 and mean FVC among participants with the highest quintile of serum 25-hydroxy vitamin D level (≥85.7 nmol/L) compared with the lowest quintile (≤40.4 nmol/L; $p < 0.0001$) (Black and Scragg 2005).

The HUNT study reported on the association between low 25-hydroxyvitamin D levels and lung function decline in adults with asthma and whether this association was modified by smoking status or ICS use in a period spanning 11 years. Participants with low 25-hydroxyvitamin D (<50 nmol/L) had more decline in the lung function measurements of FEV_1 and FVC when compared

with those with high 25-hydroxyvitamin D (≥50 nmol/L). The associations were stronger in never smokers and non-ICS users (Brumpton et al 2016).

Mechanistically, the beneficial effects of vitamin D on asthma can be proposed through several pathways. T-helper type 9 lymphocytes play an important role in the pathogenesis of asthma. Vitamin D can decrease inflammatory cytokines such as interleukin (IL)-9, IL-5, and IL-13 in these cells (Keating et al 2014). Steroid resistance is a major challenge in the treatment of asthma and vitamin D can overcome this resistance by generating IL-10-secreting regulatory T cells (Xystrakis et al 2006) and down-regulating the expression of fractalkine, a gene causing steroid resistance (Banerjee et al 2008). Even a combination of vitamin D and dexamethasone were more effective in decreasing the inflammatory cytokines than dexamethasone alone (Keating et al 2014, Chambers et al 2015). Interestingly, patients with glucocorticoid-resistant asthma were should to have significantly reduced levels of 25-hydroxyvitamin D and elevated levels of vitamin D-binding protein (VDBP) raising the possibility that serum VDBP may be a useful noninvasive biomarker to predict steroid resistance in asthma patients (Jiang et al 2016).

As more evidence accumulates linking 25-hydroxyvitamin D to glucocorticoid resistance in asthma, little is known of the effects of an anti-IL5 therapy on the levels of 25-hydroxyvitamin D. In this protocol, we wish to evaluate levels of vitamin D in peripheral blood and sputum and determine whether any changes occur following the administration of reslizumab.

8.1.3.2. Specimen Sampling and Handling

Blood samples for assessment of 25-hydroxy vitamin D will be collected and processed using the procedures in place at the investigational center [redacted]

8.1.4. Eotaxin-1, -2, and -3

8.1.4.1. Background

Eotaxin-1 (also known as CCL11) is a small cytokine belonging to the CC chemokine family. Eotaxin-1 selectively recruits eosinophils by inducing their chemotaxis, and, therefore, is implicated in allergic responses (Jose et al 1994; Ponath et al 1996; Garcia-Zepeda et al 1996a). Increased expression of eotaxin in bronchoalveolar lavage and airways of asthmatics contributes to the chemotaxis of eosinophils to the site of inflammation (Lamkhioued et al 1997). Eotaxin-2 (CCL24) also belongs to the CC chemokine family and elevated levels of eotaxin-2 have been seen in patients with aspirin-exacerbated respiratory disease, such as asthma (Palikhe et al 2010). Lastly, eotaxin-3 (CCL26) is chemotactic for eosinophils and basophils and is expressed by several tissues including heart, lung and ovary, and in endothelial cells that have been stimulated with the cytokine IL-4 (Shinkai et al 1999; Guo et al 1999).

Eosinophilia in lung tissue is driven by IL-5, which supports the development of eosinophils in the bone marrow, and by the recruitment of eosinophils to the lung mucosa and interstitium via production of eotactic chemokines such as eotaxins 1, 2 and 3 (CCL11, CCL24 and CCL26, respectively) (Lambrecht and Hamad 2015). In animal models, an iv injection of IL-5 in guinea pigs induces an acute increase in circulating eosinophils, and this amplifies tissue recruitment induced by locally administered eotaxin (Conroy and Williams 2001).

Although the role of the eotaxin family has been demonstrated as a chemotactic agent for eosinophils, the effect of anti-IL5 therapy on the expression of these eotaxins has never been studied. In this protocol, we wish to evaluate levels of eotaxins-1, -2, and -3 in peripheral blood and sputum and determine whether any changes occur following the administration of reslizumab.

8.1.4.2. Specimen Sampling and Handling

Blood samples for assessment of eotaxin-1, -2, and -3 will be collected and processed using the procedures in place at the investigational center [redacted]

8.1.5. Thymus and Activation Regulated Chemokine

8.1.5.1. Background

Thymus and activation regulated chemokine (TARC), also known as CCL17, is a small cytokine belonging to the CC chemokine family. TARC specifically binds and induces chemotaxis in T-cells, specifically Th2-type, and elicits its effects by interacting with the chemokine receptor CCR4 (Imai et al 1996, Imai et al 1997). It is expressed in dendritic cells and possibly in macrophages.

In 2001, Kawasaki and colleagues demonstrated that TARC was constitutively expressed in the lung and was up-regulated in allergic inflammation. A specific antibody against TARC attenuated ovalbumin-induced airway eosinophilia and diminished the degree of airway hyperresponsiveness with a concomitant decrease in Th2 cytokine levels and eosinophil-chemotactic chemokine expression in the lung (Kawasaki et al 2001).

Despite these advances, the in vivo pathophysiological roles of TARC remain largely unknown and the effect of anti-IL-5 therapy on the expression of TARC has never been studied. In this protocol, we wish to evaluate levels of TARC in peripheral blood and sputum and determine whether any changes occur following the administration of reslizumab.

8.1.5.2. Specimen Sampling and Handling

Blood samples for assessment of TARC will be collected and processed using the procedures in place at the investigational center [redacted]

8.1.6. Monocyte Chemoattractant Protein-1 and -4

8.1.6.1. Background

Monocyte chemoattractant protein 1 (MCP-1) and 4 (MCP-4) are also known as CCL2 and CCL13, respectively, and belong to the CC chemokine family. Monocyte chemoattractant protein-1, RANTES, MCP-3, and eotaxin have been shown to be increased in the epithelium and bronchial mucosa in patients with asthma compared with normal control subjects (Sousa et al 1994, Humbert et al 1997). Monocyte chemoattractant protein-1 is also increased in bronchoalveolar lavage (BAL) fluids from patients with asthma (Lamkhioued et al 1997, Rozyk et al 1997) and is released into the BAL fluid following endobronchial antigen challenge of patients with allergic asthma (Holgate et al 1997).

MCP-4 has been shown to be expressed in a limited number of human disease tissue. We have found that MCP-4 mRNA is expressed in the epithelium and submucosa of nasal biopsies obtained from patients with both allergic and nonallergic sinusitis and allergic rhinitis (Garcia-Zepeda et al 1996b, Mendez-Enriquez and Garcia-Zepada 2013, Kalayci et al 2004). MCP-4 is broadly active on immune cells implicated in the pathogenesis of asthma. The levels of MCP-4 protein in the BAL correlate with eosinophil influx. MCP-4 plays a role in the recruitment and activation of eosinophils in the airway of patients with asthma and thus the pathogenesis of this disease.

Monocyte chemoattractant protein-1 and MCP-4 have demonstrated as a chemotactic agent for eosinophils, however the effect of anti-IL-5 therapy on the expression of these chemokines has never been studied. In this protocol, we wish to evaluate levels of MCP-1 and MCP-4 in peripheral blood and sputum and determine whether any changes occur following the administration of reslizumab.

8.1.6.2. Specimen Sampling and Handling

Blood samples for assessment of MCP-1 and MCP-4 will be collected and processed using the procedures in place at the investigational center [redacted]

8.1.7. Type 2 Innate Lymphoid Cells

8.1.7.1. Background

Type 2 innate lymphoid cells (ILC2s) are a relatively novel family of haematopoietic effector cells which, like traditional Th2 cells, produce Th2-associated cytokines, including high amounts of IL-5 and IL-13 and, to a lesser extent, IL-4 (Walker et al 2013, Spits et al 2013). Recent studies have demonstrated the presence of ILC2s in nasal polyps of chronic rhinosinusitis, which are characterized by large numbers of eosinophils (Mjösberg et al 2011) as well as in lung and peripheral blood of patients with asthma (Begin and Nadeau 2014).

In a subset of patients with severe asthma, increased expression of epithelial-derived IL25, IL33 and thymic stromal lymphopoietin drives activation of ILC2s which, in turn, contributes to refractory eosinophilia (Licona-Limon et al 2013, Halim et al 2012). In addition, ILC2s may influence the polarization and activation of Th2 cells by their ability absorb and display antigens via MHC II presentation (Scanlon and McKenzie 2015).

The effect of anti-IL-5 therapy on the presence, distribution and/or activation of ILC2s in patients with eosinophilic asthma has never been studied. In this protocol, we wish to evaluate the number of ILC2 cells in peripheral blood and sputum by flow cytometry and determine whether any changes occur following the administration of reslizumab.

8.1.7.2. Specimen Sampling and Handling

Blood samples for assessment of ILC2s will be collected and processed using the procedures in place at the investigational center [redacted]

8.1.8. Shipment and Analysis of Samples

Biomarker samples will be stored, shipped, and processed using the procedures in place at the investigational center [redacted]

8.2. Immunogenicity Testing

8.2.1. Blood Sampling and Handling

Blood samples (5 mL) for assessment of ADA response will be taken before and after dosing at the time points indicated in Table 2. Unscheduled blood samples for anti-reslizumab antibody assessment will also be obtained from all patients experiencing a severe hypersensitivity reaction (eg, anaphylaxis).

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 2 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.

8.2.2. Shipment and Analysis of Samples

Serum samples for immunogenicity assessment for all patients 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 (CSR).

9.1. Sample Size and Power Considerations

This study is exploratory in nature; therefore, no formal hypothesis testing is planned. Based on clinical and practical considerations, 5 healthy subjects and 10 eosinophilic asthma patients (5 patients treated with reslizumab, 5 patients treated with placebo) is considered adequate for:

1. a validation of the ability of PET/CT to differentiate patients with eosinophilic asthma from HCs
2. an evaluation of the effect of reslizumab versus placebo on inflammation of the lungs.

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized patients. In this analysis set, treatment will be assigned according to 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/placebo. In this analysis set, treatment will be assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized.

The safety analysis set will be used for safety analyses of Part 2 of the study. In addition, safety analyses may present safety data from both Part 1 and Part 2 of the study as deemed necessary. For these analyses, the combined safety analysis set and enrolled analysis set (See Section 9.2.4) will be used.

9.2.3. Full Analysis Set

The full analysis set will include all patients in the ITT analysis set who receive at least 1 dose of study drug and have at least 1 postbaseline efficacy assessment.

9.2.4. Enrolled Analysis Set

The enrolled analysis set will include all patients enrolled to Part 1 of the study, including healthy subjects and patients with eosinophilic asthma.

9.3. Data Handling Conventions

For all variables, only the observed data from the patients will be used in the statistical analyses, ie, there is no plan to estimate missing data, unless otherwise specified.

9.3.1. Handling Withdrawals and Missing Data

Missing data will not be imputed, unless otherwise specified.

9.4. Study Population

Study population will be summarized for the ITT analysis set (see Section 9.2.1) as well as for the enrolled analysis set (see Section 9.2.4). 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 (and reason for not randomized), subjects/patients who are enrolled, patients who are randomized, patients randomized but not treated (and reason), patients in the ITT, safety, and full analysis sets, patients who complete the study, and patients who withdraw from the study will be summarized using descriptive statistics. Data from patients who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

9.4.2. Demographic and Baseline Characteristics

Patient and HC demographic and baseline characteristics, including medical history, prior medications and treatments, and ECG findings, will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation, 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

The efficacy endpoints for Part 2 of the study are discussed in Section 9.5.1 through Section 9.5.4.4.

9.5.1. Primary Endpoint

The primary efficacy endpoint is the change from baseline to week 4 in GLG (ΔGLG).

The supportive primary efficacy endpoint is the change from baseline to week 4 in LP SUVmean.

9.5.2. Secondary Endpoints

The secondary efficacy endpoints are:

- Change from baseline to weeks 2, 4, and 6 in blood eosinophil count
- Change from baseline to weeks 2, 4, and 6 in FEV_1
- Change from baseline to weeks 2, 4, and 6 in FeNO measurements

- Change from baseline to weeks 2, 4, and 6 in AQLQ scores

9.5.3. Exploratory Endpoints

The exploratory endpoints are:

- biological markers of inflammation and asthma:
  - IgE
  - DPP4
  - 25-hydroxy vitamin D
  - eotaxin-1, -2, and -3
  - TARC
  - MCP-1 and MCP-4
  - ILC2
- the global uptake of FDG in the lymph nodes and bone marrow as measured by the PET-CT imaging parameters indicated for the primary efficacy variable.
- sputum eosinophils for those patients that can produce sputum

9.5.4. Planned Method of Analysis

The ITT analysis set (see Section 9.2.1) will be used for summaries and the FAS will be used for all efficacy analyses. Summaries will be presented by treatment group.

9.5.4.1. Primary Efficacy Analysis

All imaging variables will be measured at 2 baseline visits and at weeks 2, 4, and 6 post-randomization.

Change in GLG from baseline to each of the postbaseline visits will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) by treatment group. The difference in means between reslizumab and placebo will be summarized and reported.

No inferential statistics will be used for primary analysis and endpoint.

9.5.4.2. Supportive to Primary Efficacy Endpoint Analysis

The same methods as described in Section 9.5.4.1 will be used to describe the supportive endpoints to the primary endpoint.

9.5.4.3. Secondary Efficacy Analysis

The same methods as described in Section 9.5.4.1 will be used to analyze the secondary endpoints.

In addition, correlation between each of the secondary endpoints and change from baseline to week 4 in GLG will be calculated. Spearman's Rho correlation will be used for this analysis. No

inferential statistics will be used for secondary endpoints and analyses. Additional details about secondary endpoints analyses may be detailed in the statistical analysis plan.

9.5.4.4. Exploratory Efficacy Analysis

Analysis of the exploratory endpoints will be detailed in the statistical analysis plan (to be finalized and signed before unblinding).

9.6. Multiple Comparisons and Multiplicity

No adjustments will be made for the preplanned multiple comparisons/endpoints.

9.7. Safety Endpoints and Analysis

Safety analyses will be performed on the safety analysis set (Section 9.2.2). Safety analyses for the combined safety analysis set and enrolled analysis set, presenting safety data for Part 1 and Part 2 of the study may be presented as deemed necessary.

9.7.1. Safety Endpoints

Safety measures and time points are provided in Table 2.

9.7.2. Safety Analysis

All adverse events will be coded using the Medical Dictionary for Regulatory Activities. 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 (overall and by severity). Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Changes in laboratory and vital signs measurement data will be summarized descriptively.

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

Newly occurring abnormalities in the physical examinations will be identified and listed.

For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will be provided as well.

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 CSR.

9.8. Tolerability Variables and Analysis

Since this is a single-dose study, tolerability is not specifically defined.

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

ADA information will be described for subjects who test positive. Samples from placebo-treated patients will not be analyzed.

9.11. Planned Interim Analysis

There will be no formal interim analysis.

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 CSR, or any combination of these, as appropriate, and in accordance with applicable national, local, and regional requirements and regulations.

10. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

The medical experts, study monitors, auditors, IEC/IRB, and inspectors from competent authority (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with national and 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 3.13).

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 national 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. The principal investigator at each investigational center, the coordinating investigator (if applicable), and the sponsor will sign the protocol amendment.

11.1.2. Protocol Violations

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the subjects of the study and/or (b) the scientific value of the study will be considered a protocol violation. Protocol violations may include non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to study drug administration; use of prohibited medications. Protocol violations will be identified and recorded by investigational center personnel in 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 documented approval from the medical expert. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

Changes in the inclusion and 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 inclusion and exclusion criteria was entered in 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 will be recorded.

11.2. Information to Study Personnel

The investigator is responsible for giving information about the study to all personnel 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 personnel become involved). The investigator must ensure that all study personnel are qualified by education, experience, and training to perform their specific task. These study personnel members must be listed on the investigational center authorization form, which includes a clear description of each personnel 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 personnel, including the investigator, and for ensuring they comply with the protocol. Additional information will be

made available during the study when new personnel members 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 are to visit the investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitor will contact 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 document [see Section 3.13]) 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 personnel 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 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, chemical, micro-biological quality, or characteristics of clinical drug supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product quality-related complaint include but are not limited to:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc)
- defective components
- missing or extra units (eg, primary container is received at the investigational center 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 quality related complaint by completing the product quality complaint form provided by Teva and emailing it to [redacted] within 2 business days 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 Teva for investigative evaluation 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 Teva for investigative evaluation whenever possible.

11.4.1. Product Quality Related Complaint Information Needed from the Investigational Center

In the event that the product quality 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, lot number, 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 adverse event Yes/No
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name (clinical study site) of person receiving the complaint

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

11.4.2. Handling of 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 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 due to product complaint, the protocol should be followed for recording and reporting (Section 7.1.2 and Section 7.1.5.3, respectively).

11.4.4. Documenting a Product Complaint

The investigator will record in the source documentation a description of the product complaint, and 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, GCP guidelines, and applicable regulatory requirements. The sponsor's Global Clinical Quality Assurance, independent of Global Clinical Development, is responsible for determining the need for (and timing of) an investigational center audit.

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

12. ETHICS

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

12.1. Informed Consent

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 oral information about the study will be provided in a language as nontechnical as practical to be 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 documents.

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 the informed 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 informed 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 participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

Patients will provide written informed consent prior to completing the PET/CT scans.

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

Before this study starts, the protocol will be submitted to each IEC/IRB for review. As required, the study will not start before the IEC/IRB for the investigational center gives 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 number.

Personal medical information may be reviewed for the purpose of patient safety or for verifying data in the source and transcribed to the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, Global Quality Assurance, or competent authorities. Personal medical information will always be treated as confidential.

12.4. Declaration of the End of Clinical Study

The last visit (visit 7) is defined as end of treatment (approximately week 6). This will be considered the end of the trial for the purposes of end of trial notification

12.5. Registration of the Clinical Study

In compliance with national and 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 by the study monitor using the data source, 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, electronic diary data, electronic patient-reported outcome Tablet), the results will be sent to the investigational center, where they will be retained but not entered in 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 in the clinical database. Laboratory test results will not be entered in the CRF unless otherwise specified 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 screening failure reason, demography, and adverse events from the time of informed consent will be entered in 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. Investigational 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 national and local laws, including, but not limited to:

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

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the CRO or sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational 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. After 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 signed 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 applicable legal provisions. The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions. Excluded from the insurance coverage 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 FDA 3454 form. 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 national, local, and regional requirements and regulations for registration and posting of results.

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

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

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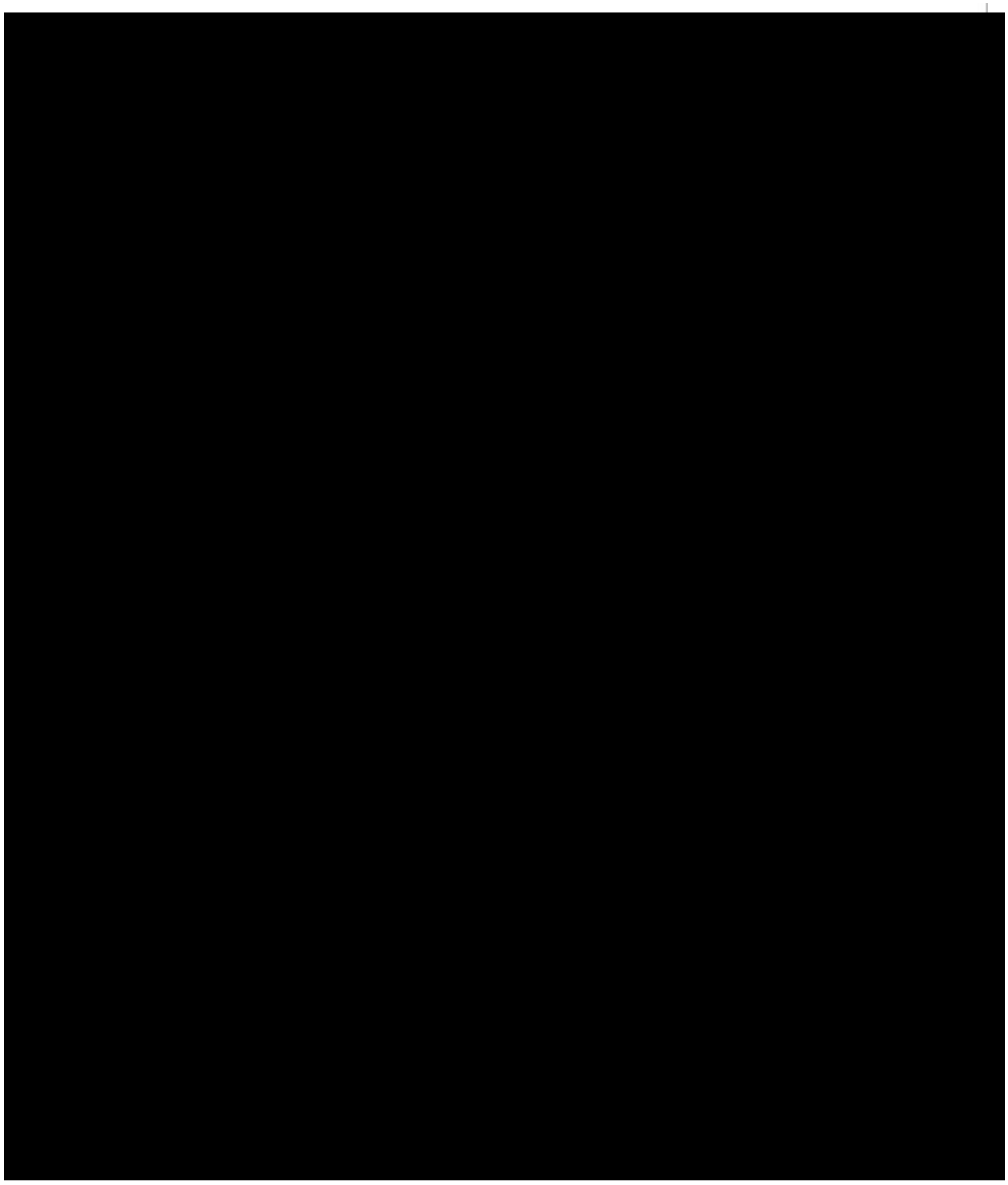
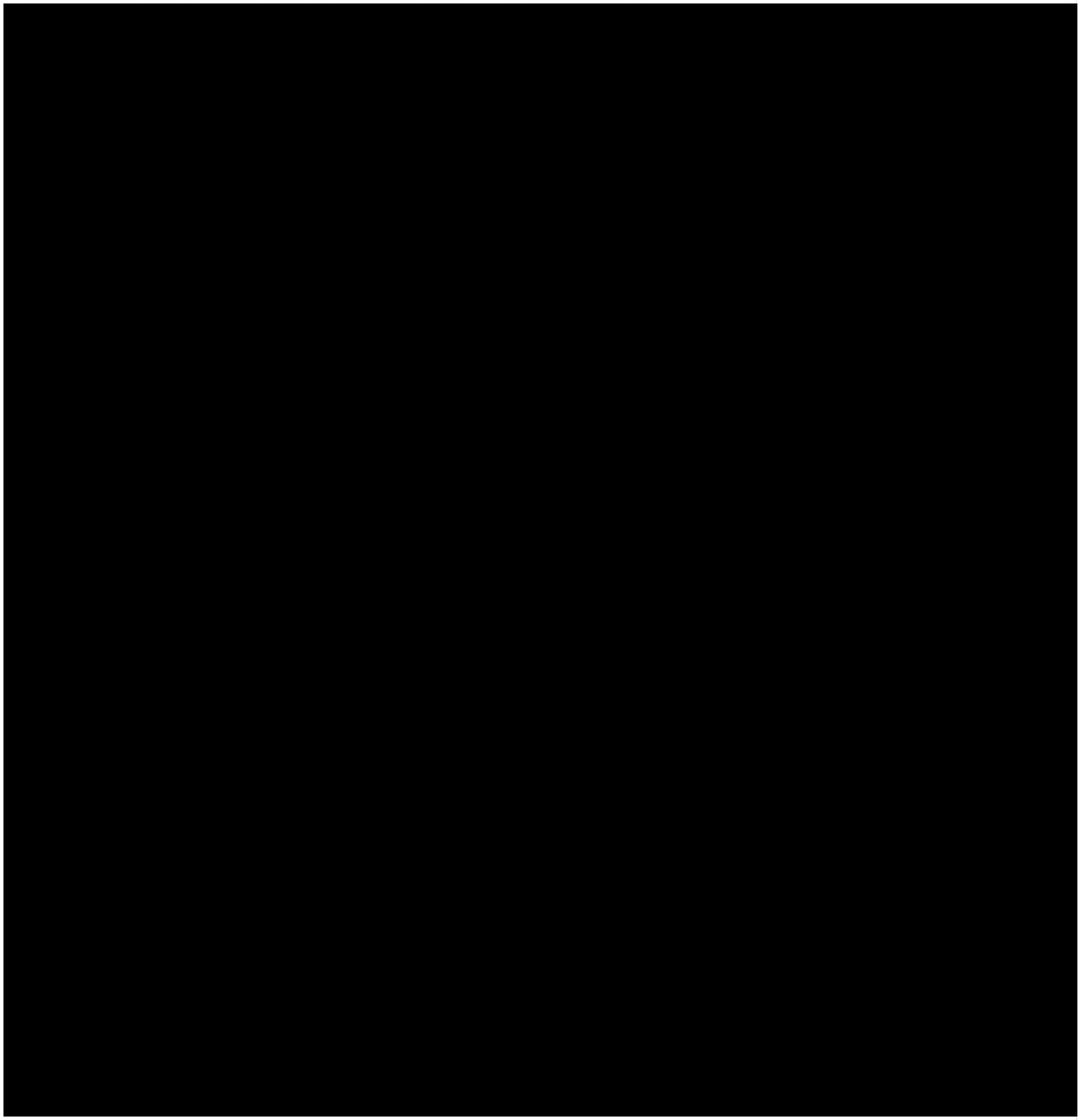
APPENDIX A. ASTHMA CONTROL QUESTIONNAIRE

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

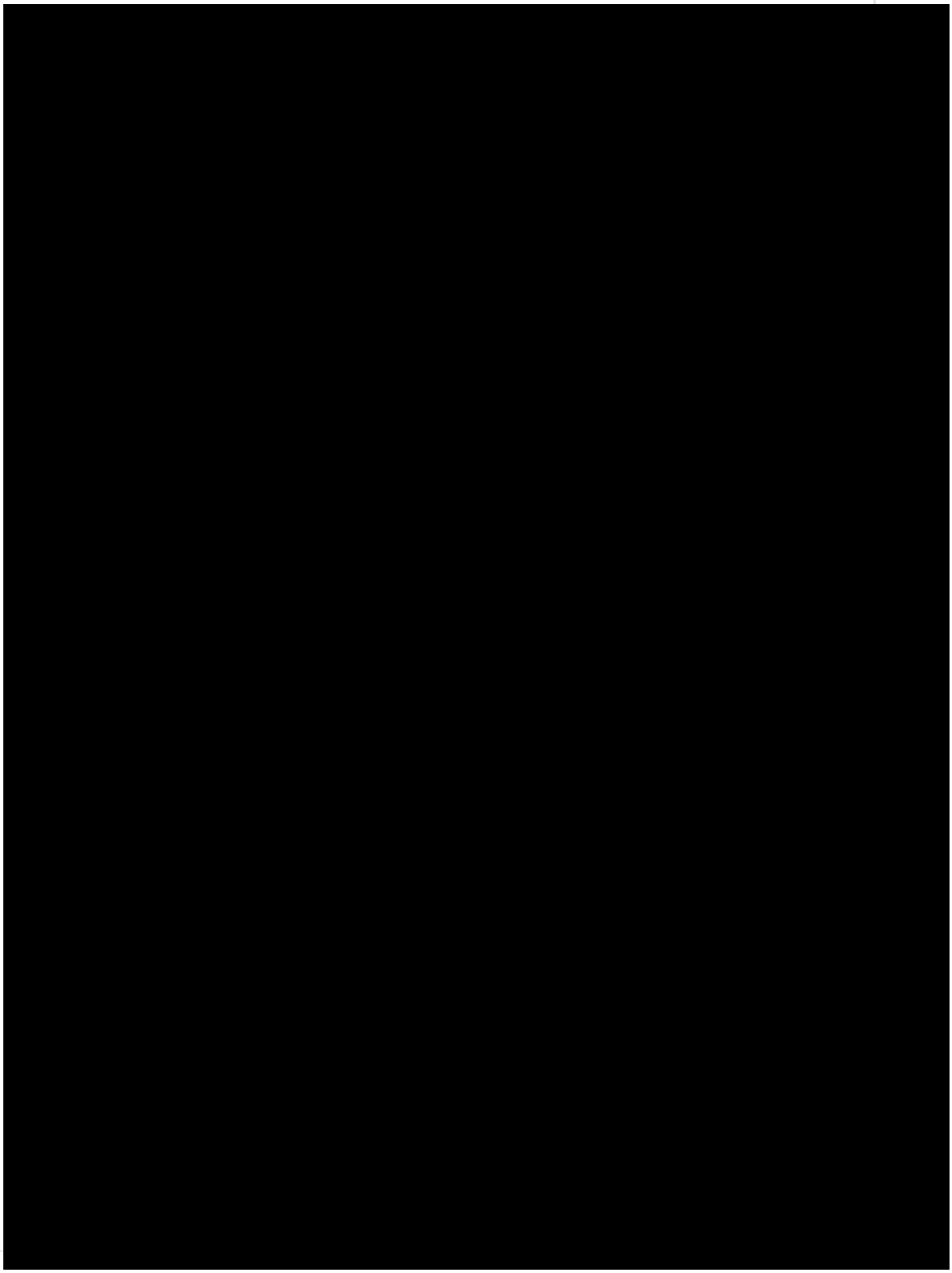


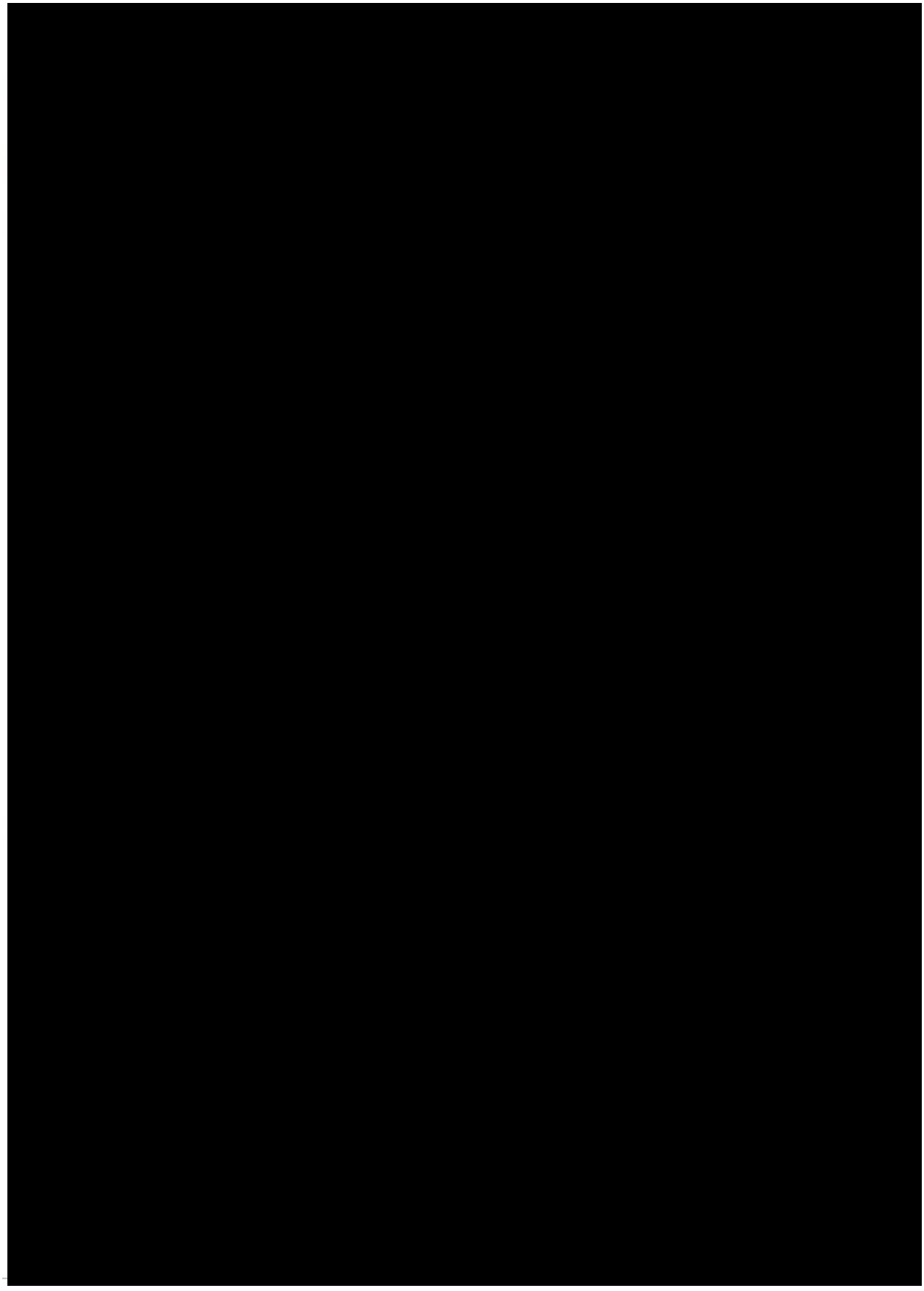


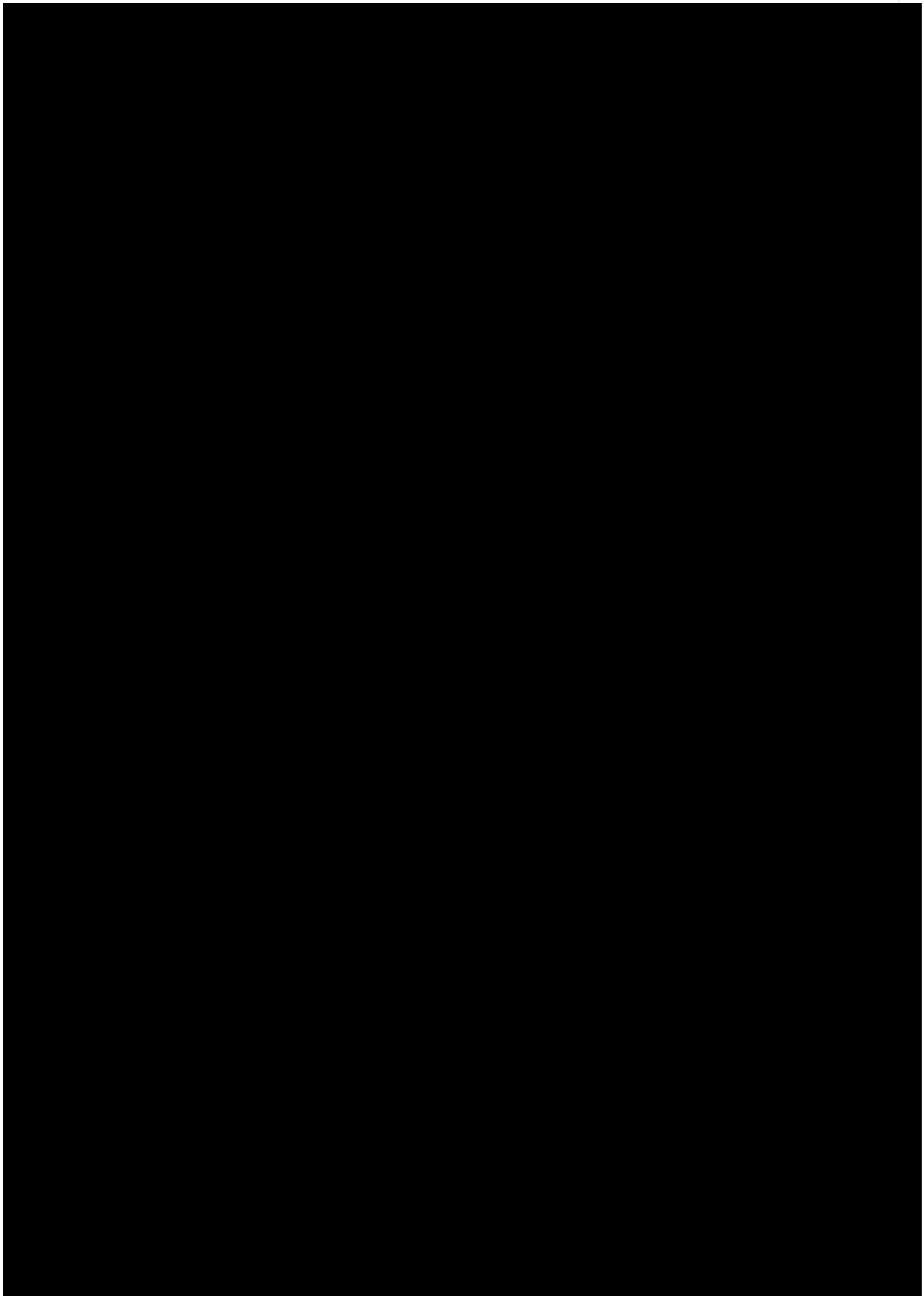
Source: Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902-7.

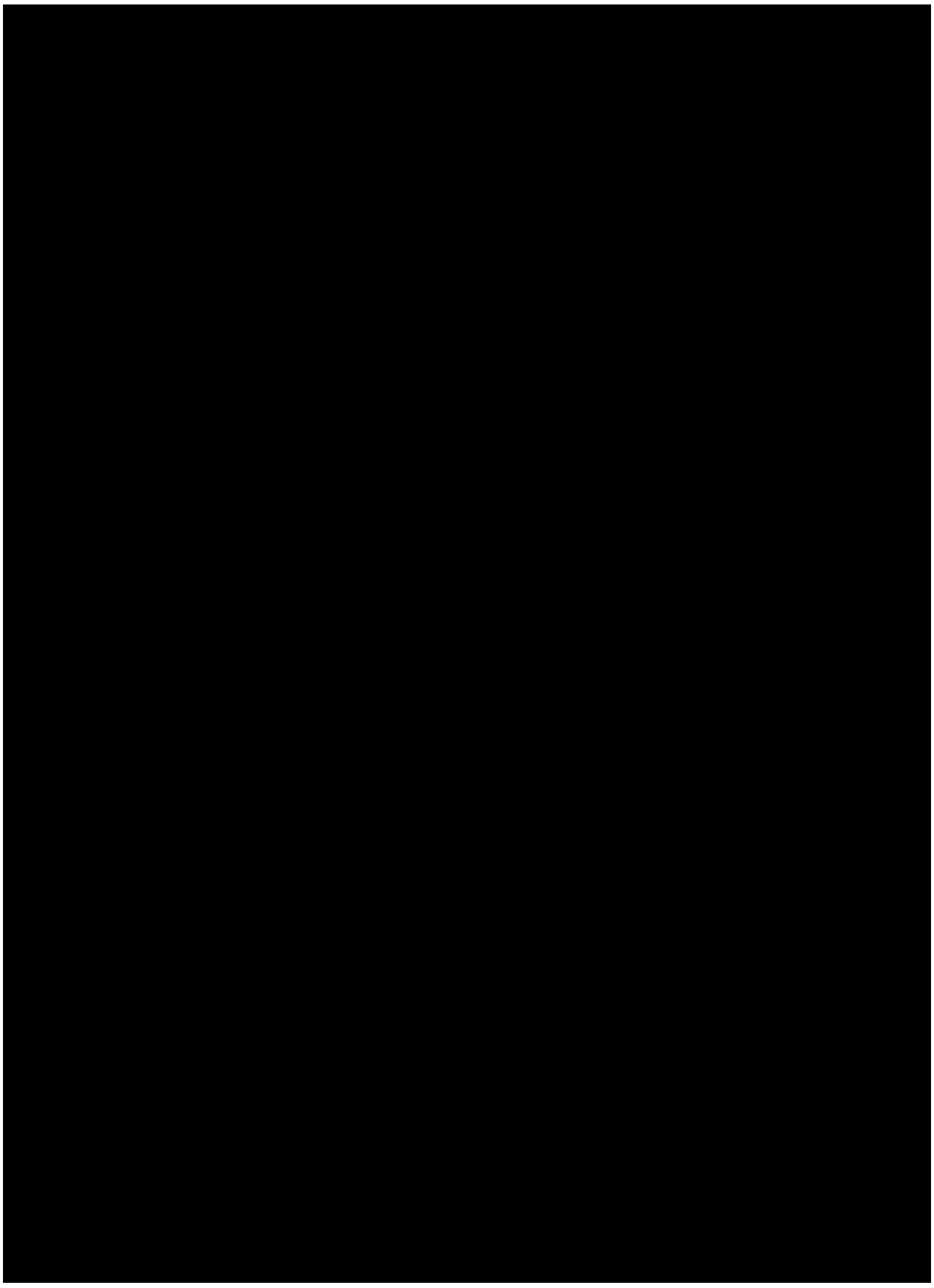
APPENDIX B. ASTHMA QUALITY OF LIFE QUESTIONNAIRE

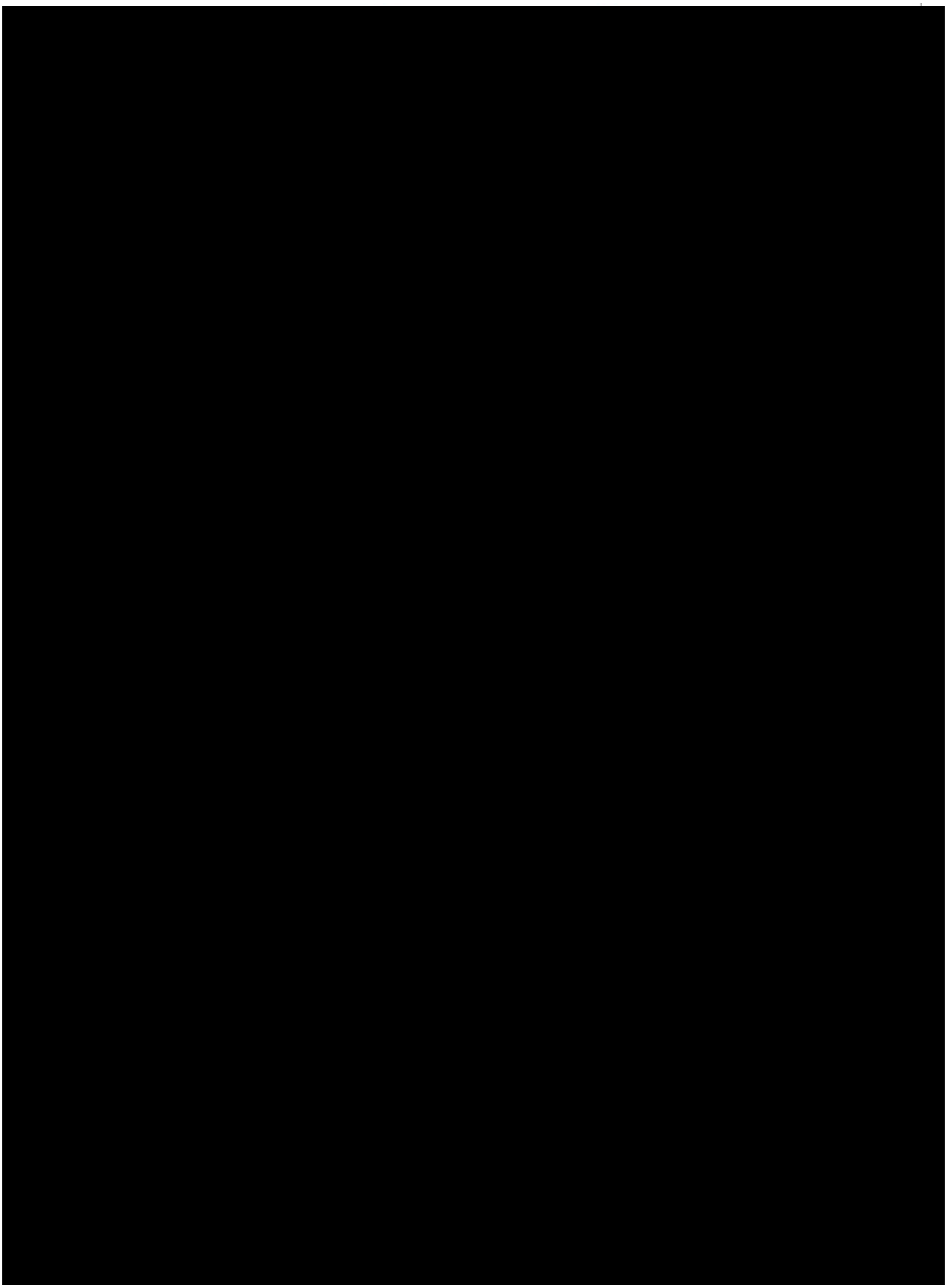
(Sample provided in this appendix is for reference only.)

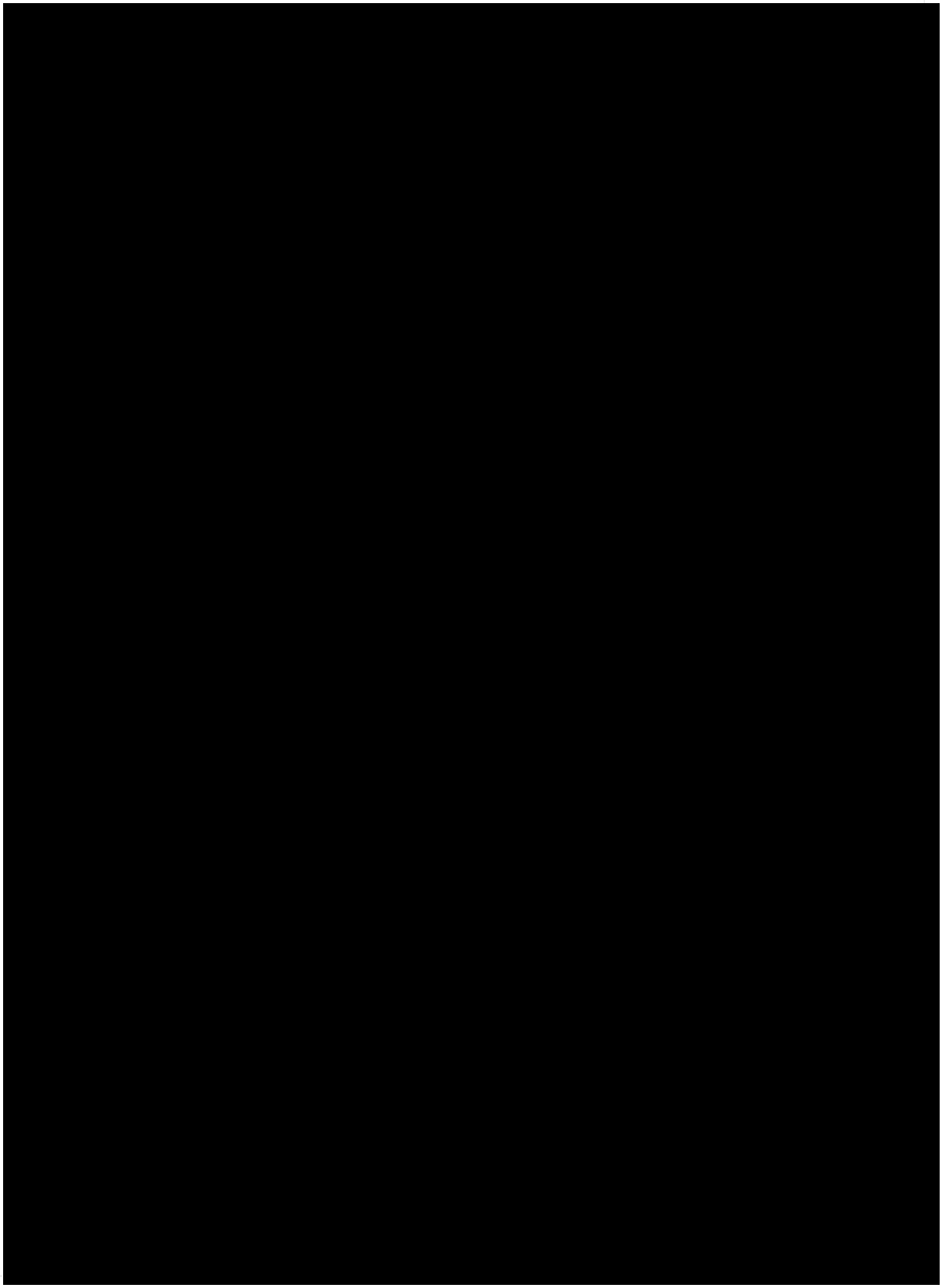












Source: Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health-related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax 1992;47:76 83.

APPENDIX C. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

Anaphylaxis is highly likely when the following criteria are fulfilled:

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)

Source: Modified from Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium [reprint in Ann Emerg Med 2006;47(4):373-80; PMID: 16546624]. J Allergy Clin Immunol 2006;117(2):391-7.