- 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)

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

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

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

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.

- 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

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	

  - 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%

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)

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.

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.

- 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.

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.

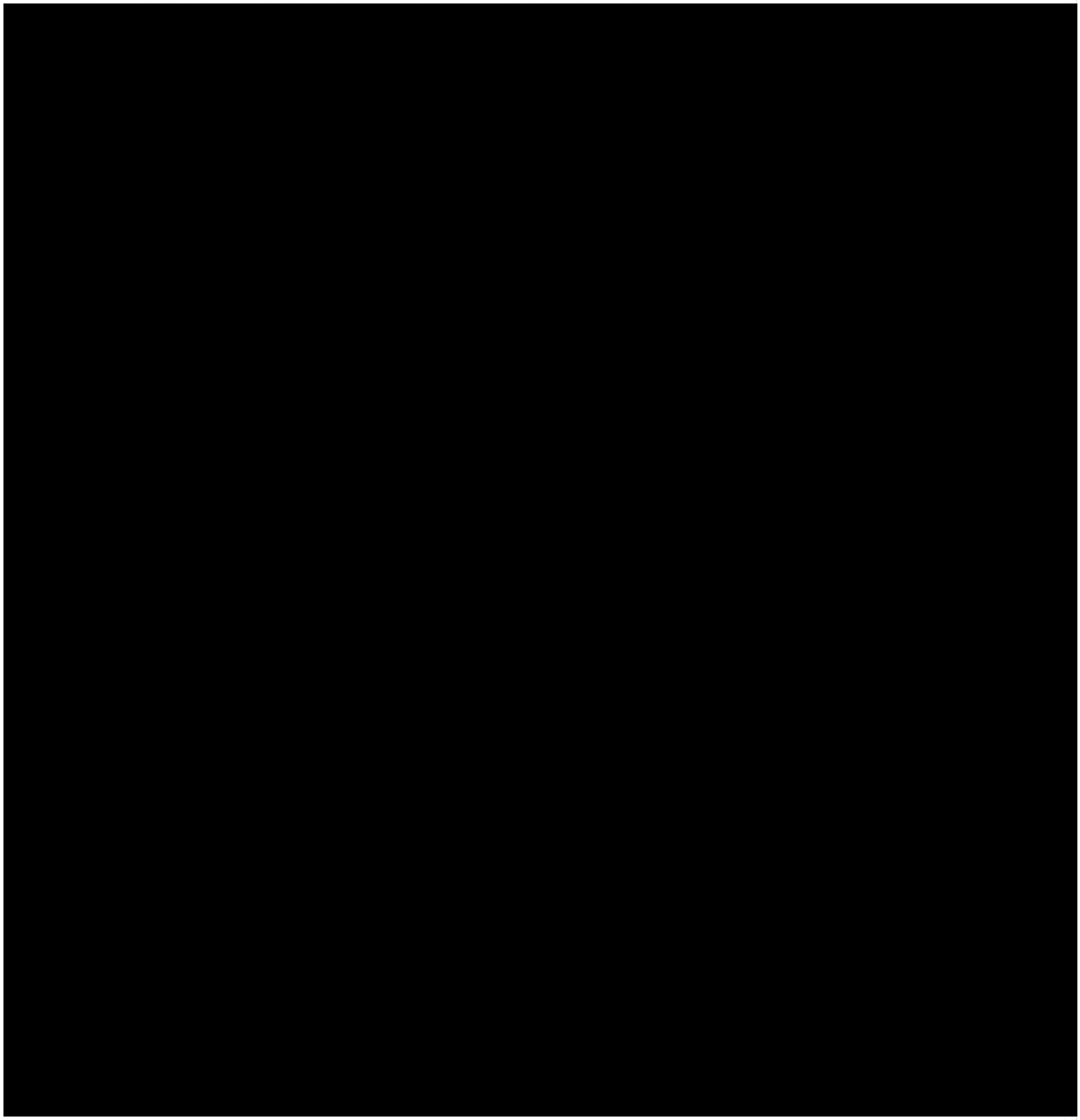
12.3. Confidentiality Regarding Study Patients

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



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.

- 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

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

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

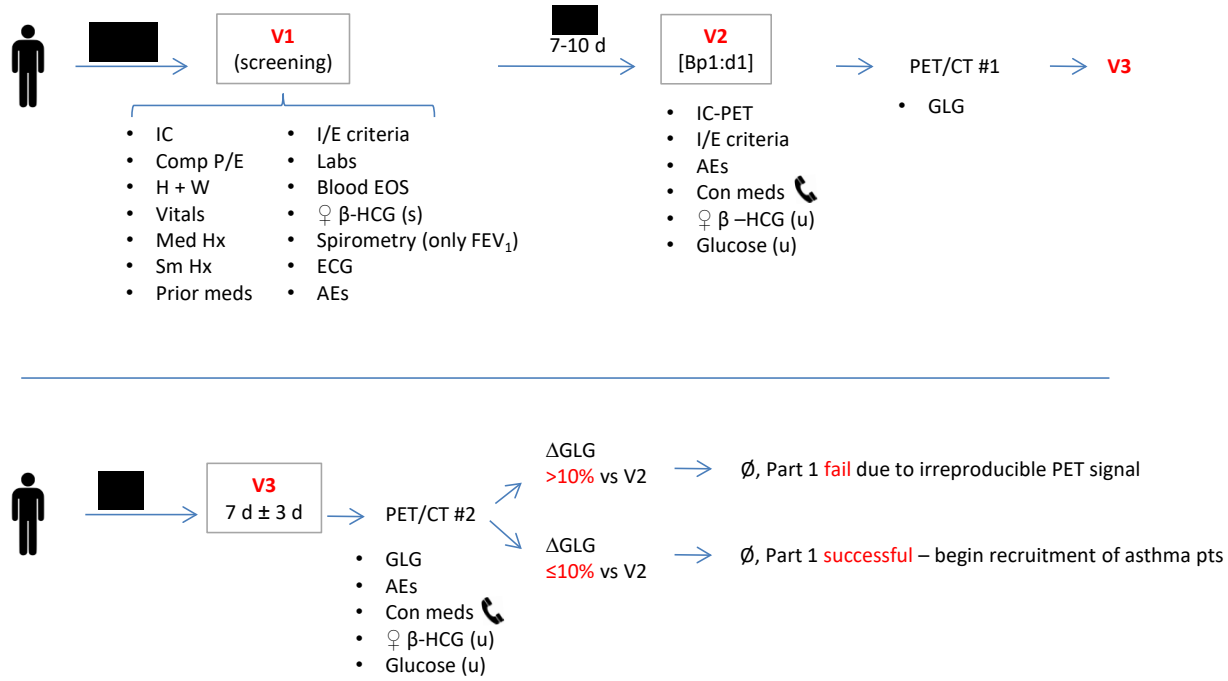
Within 7 days (±3 days) of eligibility being confirmed, participants will have a PET/CT scan as per the PET/CT scan protocol described in Part 2 below. Participants will return to the [redacted] 7 days (±3) after the first PET/CT scan (taken during visit 2) for a second PET/CT scan following the same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

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

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

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.

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).

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

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).

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.

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.

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.

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.

APPENDIX B. ASTHMA QUALITY OF LIFE QUESTIONNAIRE

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