Clinical Study Protocol

An Open-Label Extension Study of Reslizumab 110-mg Fixed, Subcutaneous Dosing in Patients 12 Years of Age and Older with Severe Eosinophilic Asthma

Study Number C38072-AS-30066

NCT03052725

Protocol Approval Date: 09 December 2016

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Safety Study (Phase 3)

IND number: 101,399; BLA number: TBD; EudraCT number: 2016-004661-23

Protocol Approval Date: 09 December 2016

Sponsor

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

Information regarding clinical laboratories and other departments and institutions is found in Protocol Appendix A

Confidentiality Statement

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for 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 legislation; and the sponsor's Standard Operating Procedures (SOPs).
This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Pharmaceuticals. The recipient agrees that no information contained herein may be published or disclosed without written approval from the sponsor.

INVESTIGATOR AGREEMENT

Original Protocol Dated 09 December 2016

IND number: 101,399; BLA number: TBD; EudraCT number: 2016-004661-23

EMA Decision number of Pediatric Investigation Plan: does not apply

Article 45 or 46 of 1901/2006: does not apply

An Open-Label Extension Study of Reslizumab 110-mg Fixed, Subcutaneous Dosing in Patients 12 Years of Age and Older with Severe Eosinophilic Asthma

Principal Investigator: [redacted]

Title: [redacted]

Address of Investigational Center: [redacted]

[redacted] France

Tel: [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 investigational medicinal product (IMP) 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 IMP and the conduct of the study. I agree to keep records on all patient information, IMPs 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
[redacted]	[redacted]	10 December 2016

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
[redacted]	[redacted]	09 December 2016

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 09 December 2016

IND number: 101,399; BLA number: TBD; EudraCT number: 2016-004661-23

EMA Decision number of Pediatric Investigation Plan: does not apply

Article 45 or 46 of 1901/2006: does not apply

An Open-Label Extension Study of Reslizumab 110-mg Fixed, Subcutaneous Dosing in Patients 12 Years of Age and Older with Severe Eosinophilic Asthma

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 and local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) 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 IMP and the conduct of the study. I agree to keep records on all patient information, IMPs shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations. In addition I will assume the responsibility of the coordinating investigator according to a separate contract.

Coordinating Investigator: [redacted]

Title: [redacted]

Address of Investigational Center: [redacted]

[redacted] France

Tel: [redacted]

Coordinating Investigator	Signature	Date
[redacted]	[redacted]	**10 December 2016**

CLINICAL STUDY PROTOCOL SYNOPSIS

Study C38072-AS-30066

Title of Study: An Open-Label Extension Study of Reslizumab 110-mg Fixed, Subcutaneous Dosing in Patients 12 Years of Age and Older with Severe Eosinophilic Asthma

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc.

Investigational New Drug (IND) Number: 101,399 **Biological License Application (BLA) Number:** TBD **EudraCT Number:** 2016-004661-23

EMA Decision number of Pediatric Investigation Plan: Does not apply

Article 45 or 46 of 1901/2006: Does not apply

Name of Test Investigational Medicinal Product (IMP): Reslizumab for subcutaneous (sc) injection, 110 mg/mL

EudraVigilance (EV) code for the IMP, if applicable: SUB96120

Type of the Study: Safety (Phase 3)

Indication: Add-on maintenance treatment of patients with severe asthma and an eosinophilic phenotype

Is this study conducted to investigate the New Use of an approved, marketed product? No

Number of Investigational Centers Planned: The study is planned to be conducted in approximately 140 investigational centers (centers that participated in Studies 30025 and 30027) worldwide.

Countries Planned: The study is planned to be conducted in ~12 countries.

Planned Study Period: The study is expected to start in March/Q1 2017 and complete in approximately November/Q4 2018.

Number of Patients Planned (total): Approximately 360 patients will be enrolled. There is no prespecified sample size for this open-label (OL) extension study. It is estimated that the majority of patients enrolled in eligible reslizumab safety and efficacy studies will rollover to this OL extension study.

Study Population: This study will enroll male and female patients 12 years of age and older with asthma who were randomized and completed the treatment period for a Phase 3 clinical study of reslizumab 110 mg sc (Study 30025 or 30027).

Primary, Secondary, and Tertiary Objectives and Endpoints

The **primary objective** of this study is to support the long-term safety of reslizumab 110 mg administered sc once every 4 weeks in patients 12 years of age and older with severe eosinophilic asthma whose asthma is inadequately controlled on standard-of-care treatment.

The primary endpoint is the frequency of adverse events including serious adverse events.

The secondary safety endpoints for this study include the following:

- clinical laboratory test results
  - hematology and chemistry results at baseline and at weeks 4 (chemistry only), 8, 24, and 36 or early withdrawal visit
- local tolerability at the injection site at approximately 1 hour after study drug administration every 4 weeks throughout the study (see Protocol Section 7.8)
- vital signs measurements every 4 weeks throughout the study
- concomitant medication usage every 4 weeks throughout the study

The **secondary objective** of this study is to evaluate the efficacy of reslizumab 110 mg administered sc once every 4 weeks in patients 12 years of age and older with severe eosinophilic asthma that is inadequately controlled on standard-of-care treatment.

The secondary efficacy endpoints for this study include the following:

- clinical asthma exacerbation (CAE) and healthcare utilization (HCU)-related endpoints
  - frequency of CAEs
  - frequency of asthma-specific hospital admissions
  - length of hospital stay and number of intensive care unit (ICU) days
  - frequency of asthma-specific emergency department visits
  - frequency of school/work days missed due to asthma
- change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV_1) measured using spirometry at weeks 0, 8, 24, and 36 or early withdrawal visit
- change in daily morning ambulatory FEV_1 from baseline at each week through week 36 or early withdrawal, as measured by the handheld spirometry device
- absolute and percent reduction in the daily oral corticosteroids (OCS) dose at weeks 20 and 36 or early withdrawal visit as compared with the dose at baseline (for patients on daily OCS at baseline)
- change from baseline in total inhalations of reliever bronchodilator medication (eg, short-acting beta-agonist [SABA]) measured using weekly averages until week 36 or early withdrawal visit
- change from baseline in Asthma Control Questionnaire (ACQ-6) score performed at weeks 0, 8, 24, and 36 or early withdrawal visit
- change from baseline in Asthma Quality of Life Questionnaire (AQLQ12+) score performed at weeks 0, 8, 24, and 36 or early withdrawal visit

[redacted]

The immunogenicity assessments for this study include the following:

- anti-drug antibody (ADA) measurement at baseline and at weeks 8, 24, and 36 or early withdrawal visit to evaluate the long-term immunogenicity of sc reslizumab
- ADA measurement at the end of study (EOS) visit (19 weeks after the final dose) to evaluate immunogenicity after study drug washout

Tertiary Objectives and Endpoints: No tertiary endpoints

Exploratory Objectives and Endpoints: No exploratory endpoints

General Design: This is a global, multicenter, OL extension study to obtain additional long-term safety data for sc administration of reslizumab treatment administered at a fixed dose of 110 mg in patients 12 years of age and older with severe eosinophilic asthma. The study consists of a screening/baseline visit (V1; seamless rollover patients; conducted on the same day as the end-of-treatment [EOT, week 52 or week 24, respectively] visit for patients who finished either Study 30025 or 30027) or a standalone screening visit (V0) for patients who did not seamlessly rollover from Study 30025 or 30027 (had a gap between placebo-controlled study EOT and start of OLE), followed by an OL treatment period, an EOT visit (V_{EOT}), a follow-up telephone call (V_{FU}) at 12 weeks after the EOT visit, and an EOS visit (V_{EOS}) for immunogenicity testing 19 weeks after the final dose of study drug administration. The duration of the OL treatment period will be 9 months (36 weeks).

Study patients will be deemed eligible only if they meet all inclusion criteria and no exclusion criteria are fulfilled. Patients currently enrolled in Studies 30025 and 30027 will be required to complete their respective treatment periods before being eligible for this study. In addition, adolescents (a patient 12 through <18 years of age) from Study 30025 must also complete the 12-week early follow-up visit (off study drug) before transferring to this OL study.

There may be a gap in study drug administration for some patients due to completion of Study 30025 or 30027 before the initiation of the OL extension study (non-seamless rollover). Patients with a gap between the EOT visit for Study 30025 or 30027 will complete a V0 screening visit. Adolescents (a patient 12 through <18 years of age) from Study 30025 can complete the V0 screening visit of Study 30066 the same day as the 12-week early follow-up visit for Study 30025. Any patient who did not rollover seamlessly from Study 30025 or 30027 will participate in a 7-day run-in period where baseline measures for asthma control and spirometry will be established. During screening/baseline, informed consent (and assent for patients under 18 years of age according to local Institutional Review Board/Independent Ethics Committee requirements) will be obtained. Any blood tests completed by adolescents at the 12-week early follow-up visit for Study 30025 can be used for the V0 screening visit of Study 30066 and do not need to be repeated.

During the treatment period, patients will receive reslizumab by sc injection at a dosage of 110 mg every 4 weeks (28 days ±7 days) for 32 weeks in the study center. Patients will return to the study center every 4 weeks relative to baseline during OL treatment.

After study drug administration, each patient will remain at the study center for a minimum of 1 hour for observation.

After each administration, the patient will be required to use a study-provided handheld electronic diary (eDiary)/spirometry device, which will ask questions post-injection to evaluate for any new symptoms that may have developed during the 24-hour period after IMP administration. The patient

will complete a question regarding new symptoms on the eDiary device the evening after the IMP administration and the following morning. This is in addition to the PEF (AM and PM), FEV_1 measurements (AM only), and recording of rescue inhaler use that are performed every day during the treatment period.

A full physical examination will be completed at screening and at EOT. Other safety evaluations will be performed at every visit when study drug is administered: adverse event inquiry, vital sign measurement, assessment of injection site, concomitant medication use, and urine pregnancy test. Additional evaluations including clinical chemistry, hematology, and ADA measurements will be performed throughout the study according to the schedule of procedures and assessments (see Protocol Table 1). Patients will also be monitored for asthma exacerbations throughout the study (see Protocol Section 6.1.1).

Asthma control measures will be assessed as part of this OL extension study to evaluate the long-term effect of sc reslizumab. These will include CAE assessment (including HCU), pre-bronchodilator spirometry, questionnaires including the ACQ-6 and AQLQ12+, and change in OCS dose for those on maintenance therapy. For patients previously enrolled in Study 30027, maintenance prednisone will no longer be provided by the sponsor. Asthma control including asthma exacerbations and related HCU will be assessed at every study visit during the treatment period. Spirometry will be performed daily through the use of a handheld spirometry device. Pre-bronchodilator spirometry will be analyzed at baseline and weeks 8, 24, and 36 or in the event of an early withdrawal. Questionnaires will be completed as follows: ACQ-6 and AQLQ12+ will be completed at baseline and at weeks 8, 24, and 36 or early withdrawal visit. Concomitant medications will be recorded at all visits during the treatment period and will include OCS dose if participants are on maintenance corticosteroids. In an effort to standardize a patient's maintenance therapy, it is encouraged that the investigators prescribe prednisone/prednisolone as the maintenance corticosteroid preparation if deemed necessary.

Patients will have final procedures and assessments performed at the EOT visit. Patients who withdraw before the completion of the study will have EOT procedures and assessments performed at their early withdrawal visit. All patients will have a follow-up telephone assessment 12 weeks after the EOT visit. The EOT visit includes home pregnancy testing, an adverse event assessment, and a concomitant medication inquiry. There will then be an EOS visit for immunogenicity testing 19 weeks after the final dose of study drug administration.

Measurement of ADAs will be performed on samples collected at baseline and at weeks 8, 24, and 36 or early withdrawal visit to evaluate the potential long-term immunogenicity of sc reslizumab and on samples collected at the EOS visit (19 weeks after final dose) to evaluate immunogenicity after study drug washout. A blood sample will also be collected in the event of withdrawal from the study or upon observation of any severe hypersensitivity reaction (eg, anaphylaxis). An unscheduled sample can also be drawn after a serious adverse event if the investigator or sponsor considers appropriate. Drug levels may be measured in the serum samples collected for ADAs to help inform ADA analysis. If a patient is found to have a positive ADA status after at least 2 doses of study drug in this OL study, the patient may be scheduled to complete an EOT visit. This testing may be done to enhance early data collection on potential washout samples. A summary of ADA results in previous clinical experience is outlined in Protocol Section 1.2.2.4.

Study procedures and assessments with their time points are shown in Protocol Table 1. The study schematic diagram is shown in Protocol Figure 1.

Brief Summary of Study Design for the Trial Registry(s): See the above "General Design" section.

Method of Randomization and Blinding: This is a nonrandomized OL extension study that includes patients who were randomized and completed the treatment period of a Teva-sponsored double-blind, placebo-controlled study (Study 30025 or 30027) of sc administration of reslizumab in severe eosinophilic asthma.

Investigational Medicinal Products: Dose, Pharmaceutical Form, Route of Administration, and Administration Rate:

Test IMP: Reslizumab for sc injection will be provided as a sterile solution in a pre-filled syringe (PFS) containing 110 mg (1.0 mL) reslizumab per syringe and formulated at 110 mg/mL in [redacted] sodium acetate, with [redacted] sucrose, [redacted] polysorbate 80, and pH 5.5 buffer. Reslizumab will be administered with the PFS subcutaneously at a dose of 110 mg (1.0 mL) every 4 weeks.

Reference IMP: Not applicable.

Placebo IMP: Not applicable.

Duration of Patient Participation and Maximal Exposure to IMP: This study will consist of a standalone screening visit if necessary (V0), a screening/baseline visit (V1), an OL treatment period of 36 weeks including an EOT visit 4 weeks after the final reslizumab dose administration (or early withdrawal), and a follow-up telephone assessment 12 weeks after the EOT visit. For immunogenicity testing only, there will be an EOS visit 19 weeks after the final dose of reslizumab is administered. Patients are expected to complete the entire duration of the study. This final visit for immunogenicity testing will be considered the end of the trial for the purposes of end-of-trial notification.

Study Duration: The study treatment period duration is 36 weeks. The study's entire duration is approximately 53 weeks (including up to a 2-week screening period, the 36-week treatment period, the follow-up telephone assessment, and the EOS visit).

End of Study: EOS is defined as when the last patient completes his/her last study visit (EOS visit).

Plans for Treatment or Care after the Patient Has Ended Participation in the Study: Patients will return to the care of their primary physician and/or asthma specialist after the end of this study.

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

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

b. Male or female patient 12 years or older with eosinophilic asthma who was previously randomized and completed the treatment period in either of the double-blind, placebo-controlled studies (Study 30025 or 30027) for sc reslizumab and who by the assessment of the Principal Investigator can safely participate in this study.

   Adolescents from Study 30025 must also complete the early follow-up visit before being eligible for this study.

c. Unless surgically sterile or postmenopausal, female patients must have a negative urine pregnancy test at baseline. Definitions of sterile and postmenopausal are given in Protocol Appendix E.

d. Females of childbearing potential (not surgically sterile or postmenopausal) must have an exclusively same-sex partner or use a medically acceptable method of contraception and must agree to continue the use of this method for the duration of the study and for 5 months after discontinuation of the study drug. Acceptable methods of contraception include intrauterine device, steroidal contraceptive (oral, implanted, transdermal, or injected), barrier method with spermicide, abstinence, bilateral tubal occlusion, and partner vasectomy.

e. The patient must be willing and able to comply with study restrictions and willing to return to the investigational center for the follow-up procedures and assessments as specified in this protocol.

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

a. Patient has received any intravenous or sc reslizumab administration in any previous clinical trial other than Studies 30025 and 30027.

b. Patient withdrew early (discontinued from treatment) from either of the placebo-controlled reslizumab studies, Studies 30025 and 30027, for any reason.

c. The patient has any clinically significant, uncontrolled medical condition (treated or untreated) that would interfere with the study schedule or procedures and interpretation of efficacy results or would compromise the patient's safety.

d. The patient has another confounding underlying lung disorder (eg, chronic obstructive pulmonary disease, interstitial lung disease, bronchiectasis eosinophilic granulomatosis with polyangiitis [also known as Churg-Strauss syndrome], or allergic bronchopulmonary aspergillosis).

e. The patient has a known/diagnosed hypereosinophilic syndrome.

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

g. The patient is a pregnant or lactating woman or intends to become pregnant during the study or within 5 months after the last dose of study drug. Administration of IMP will be discontinued for any female patient who becomes pregnant during the study.

h. The patient required treatment for an asthma exacerbation within 4 weeks of screening or during the screening. (Note: This is required only in patients who did not rollover seamlessly from Study 30025 or 30027, ie, had a gap between placebo-controlled study EOT and screening for Study 30066 [including adolescents from Study 30025 who must also complete the early follow-up visit].)

   Patients who did not rollover seamlessly from Study 30025 or 30027 may be considered for rescreening if they are excluded from study participation for not satisfying this criterion. A patient may be rescreened for this reason 1 time only. The duration between the first visit during the screening period and the rescreening must be >30 days.

i. The patient is a current smoker (ie, has smoked within the last 6 months before screening) or has a smoking history ≥10 pack-years.

j. The patient is currently using any systemic immunosuppressive or immunomodulatory biologic (eg, anti-immunoglobulin E monoclonal antibody [mAb] or other mAb [eg, mepolizumab, benralizumab, dupilumab] or soluble receptors) or non-biologic (eg, methotrexate or cyclosporine), except maintenance oral corticosteroids for the treatment of asthma (up to and including 40 mg of prednisone daily or equivalent every-other-day dosing). Note: Previous use of such agents that occurred >5 half-lives from the initial screening visit may be allowed.

k. The patient participated in a clinical study other than approved Teva reslizumab studies within 30 days or 5 half-lives of the investigational drug before screening, whichever is longer.

l. The patient has a history of an immunodeficiency disorder including human immunodeficiency virus (HIV).

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

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

o. The patient has a history of allergic reaction or hypersensitivity to any component of the study drug.

p. The patient is expected to be poorly compliant with study procedures or visits.

q. The patient is a vulnerable patient (eg, a patient who is or may be for any reason unable to take care of himself or herself, unable to protect himself or herself against significant harm or exploitation, or kept in detention).

Statistical Considerations: The enrolled analysis set includes all patients who were enrolled in the study, regardless of whether or not the patient took study drug. The safety analysis set will include all patients who received at least 1 dose of reslizumab in this study. All efficacy and safety summaries will be performed on the safety analysis set. For all variables, only the observed data from patients will be used in the statistical analyses; that is, there is no plan to estimate missing data. All analyses will be descriptive. No inferential statistics are planned.

Sample Size Rationale: The sample size for this OL extension study is not based on power considerations. The sample size is determined by the number of patients anticipated to rollover from the 2 double-blind, placebo-controlled, Phase 3 studies of reslizumab sc (Studies 30025 and 30027). The objective of this study is primarily safety oriented; therefore, no formal hypothesis testing is planned. Patients completing at least the full treatment periods of Studies 30025 and 30027 (or through at least the early follow-up visit for adolescents from Study 30025) are eligible for enrollment in this study.

Analysis of Primary Endpoint: Patient counts and percentages will be provided for the frequency of patients with at least 1 adverse event.

Analysis of Secondary Endpoints: Secondary safety endpoints include clinical laboratory tests, local injection site reactions, vital signs measurements, and concomitant medication usage. Secondary efficacy endpoints include CAE and HCU-related events, change from baseline in pulmonary function tests, absolute and percent reduction in the daily OCS dose (for patients on daily OCS at baseline), change from baseline in total inhalations of reliever bronchodilator medication (eg, SABA), and change from baseline in patient-reported outcome questionnaires (ACQ-6 and

AQLQ12+). Other efficacy endpoint includes the change in daily morning ambulatory FEV_1 from baseline at each week through week 36 or early withdrawal and the change in AM (morning) as measured by the handheld spirometry device.

The safety analysis set will be used for all safety and efficacy analyses. Baseline for clinic-based efficacy and safety variables measured and summarized over time will be defined as the last observation recorded before administration of the first dose of reslizumab in this OL extension study.

For continuous variables, a descriptive summary will be provided. The summary statistics will include n, mean, standard deviation (SD), standard error, median, minimum, and maximum. For categorical variables, patient counts and percentages will be provided.

Primary Efficacy Analysis: As per "Secondary Endpoints" section above.

Sensitivity Analysis: No sensitivity analyses are planned.

Secondary Efficacy Analysis: As per "Secondary Endpoints" section above.

Safety Analyses: Safety analyses will be performed on the safety analysis set.

Safety assessments and time points are provided in Protocol Table 1. For all clinic-based safety variables measured and summarized over time, baseline will be defined as the last observation recorded before administration of the first dose of reslizumab in this OL extension study.

For continuous variables of safety measures, descriptive statistics (n, mean, SD, 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.

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 reslizumab.

Multiple Comparisons and Multiplicity: This study is descriptive in nature. There are no plans to conduct any formal inferential statistics as part of this study.

Analysis of Exploratory/Other Endpoints: Not applicable.

Tolerability Analysis: Tolerability will be assessed via the overall on-treatment safety profile and patient disposition characteristics.

Pharmacokinetic Analysis: Pharmacokinetic parameters will be assessed in the context of ADA samples in this study.

Pharmacodynamic Analysis: See below in "Biomarker Analysis" section.

Pharmacokinetic/Pharmacodynamic Analysis: Not applicable.

Biomarker Analysis: The biomarker measure includes blood eosinophils. Blood eosinophil data will be listed. Summaries will be provided, if appropriate.

Immunogenicity Analysis: ADA status will be listed. ADA status will be correlated with variables of safety, if appropriate.

Ancillary Studies Analysis: Not applicable.

Planned Interim Analysis: There will be a planned data cut with statistical output produced before the supplemental Biologics License Application submission.

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LIST OF ABBREVIATIONS

Abbreviation	Term
ACQ-6	Asthma Control Questionnaire
ADA	anti-drug antibody
ADR	adverse drug reaction
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AQLQ12+	Asthma Quality of Life Questionnaire
AST	aspartate aminotransferase (SGOT)
BUN	blood urea nitrogen
CAE	clinical asthma exacerbation
CFR	Code of Federal Regulations
CPK	creatine phosphokinase
CRF	case report form (any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
CSR	clinical study report
ECG	electrocardiogram
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FSH	follicle stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GPSP	Global Patient Safety and Pharmacovigilance
HCU	healthcare utilization
HCG	human chorionic gonadotropin
HEENT	Head, Eyes, Ears, Nose, and Throat
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICS	inhaled corticosteroids

Abbreviation	Term
ICU	intensive care unit
ID	identification
IEC	Independent Ethics Committee
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
iv	intravenous
LABA	long-acting beta-agonist
LPLV	Last Patient Last Visit
LSO	local safety officer
MA	Marketing Authorisation
mAb	monoclonal antibody
n	number
OCS	oral corticosteroid
OL	open-label
PD	pharmacodynamics
PEF	peak expiratory flow
PFS	pre-filled syringe
PI	principal investigator
PK	pharmacokinetics
RSI	reference safety information
SABA	short-acting beta-agonist
sc	subcutaneous
SD	standard deviation
SE	standard error
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedures
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
WBC	white blood cell
WOCBP	women of childbearing potential

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

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

Currently, inhaled corticosteroids (ICSs) are the most effective treatment agents for the long-term control of asthma (EPR-3 2007, GINA 2016). For patients whose asthma is not adequately controlled on daily ICS alone, the addition of long-acting beta agonists (LABAs) and/or other controller therapies often provides additional control. There are currently very few options for patients whose asthma is inadequately controlled on ICS/LABA. The most severely affected patients with asthma may require daily oral corticosteroid (OCS) doses to maintain asthma control (GINA 2016). Long-term use of daily OCS may be associated with the severe adverse effects of an iatrogenic Cushing's syndrome, including increased risk of infections, impaired growth in children, hyperglycemia, low bone density, elevated blood pressure, cataracts, and adrenal insufficiency (Stanbury and Graham 1998, Walsh et al 2001). Risk may be decreased by maintaining patients on the lowest possible dose of OCS and utilization of corticosteroid-sparing strategies.

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

Therapies directed against IL-5 or its receptor (mepolizumab, reslizumab, and benralizumab) work by reducing eosinophil counts in the circulation and in the airway and have recently met a clinical proof of concept (reduction in asthma exacerbations, improved Asthma Control Questionnaire [ACQ-6] scores, or improved lung function) in Phase 2 and Phase 3 studies in primarily adult populations with asthma and elevated sputum or blood eosinophils (Castro et al 2011, Haldar et al 2009, Molfino et al 2012, Nair et al 2009, Ortega et al 2014, Pavord et al 2012).

Reslizumab is a humanized anti-human IL-5 monoclonal antibody (mAb) of the immunoglobulin G4/κ isotype being developed for the treatment of asthma in patients with elevated blood eosinophils. Confirmatory Phase 3 safety and efficacy studies for administration of reslizumab by the intravenous (iv) route have concluded the clinical portion; results are notable for a significant reduction in clinical asthma exacerbations (CAEs) as well as improved lung function. Reslizumab by the iv route has been approved by the following Health Authorities: Food and Drug Administration (FDA) approval date: 23 March 2016; European Medicines Agency Summary of Opinion date: 23 June 2016; and Health Canada Notice of Compliance Letter date: 20 July 2016.

The safety profile accumulated throughout the clinical development of reslizumab has demonstrated that reslizumab has a favorable benefit-risk profile in treating patients with asthma and elevated blood eosinophils. Studies 30025 and 30027 are being conducted to further investigate the safety and

effectiveness of subcutaneous (sc) reslizumab administration. The purpose of this study is to support the long-term safety of reslizumab 110 mg administered sc once every 4 weeks in patients 12 years of age and older with severe eosinophilic asthma whose asthma is inadequately controlled on standard-of-care treatment.

1.2. Findings from Nonclinical and Clinical Studies

Brief summaries of nonclinical pharmacology, pharmacokinetics (PK), and toxicology studies and clinical studies are provided in the following sections. More detailed information is provided in the Investigator's Brochure (IB).

1.2.1. Nonclinical Studies

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

In vivo, reslizumab showed biological activity in several species, including mice, guinea pigs, rabbits, and monkeys. 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 after dosing in mice and for up to 6 months in monkeys. The effects of reslizumab on eosinophilia in mice were additive with the effects of prednisolone.

Nonclinical studies in male cynomolgus monkeys, mice, and rats were performed to assess the absolute bioavailability of reslizumab after single and multiple sc doses. It was found that absolute bioavailability after sc administration of reslizumab was high (>75%) in all species. Administration of sc reslizumab in these studies was well tolerated. Mild, focal, intramuscular macrophage infiltrates were found at the injection site in 1 monkey dosed with sc reslizumab. In addition, an acute sc irritation study in rats found that sc administration of reslizumab produced minimal to mild gross local tissue irritation. After sc administration in nonclinical studies, approximately 20% to 50% of animals tested positive for anti-reslizumab antibodies. The antibody response correlated with decreased serum concentrations in some, but not all, of these animals.

Further details may be found in the current IB.

1.2.2. Clinical Studies

Currently, available data with the sc formulation are limited to the data from a Phase 1 study (Study C38072/1107, hereby referred to as Study 1107). Study 1107 was a Phase 1, open-label (OL), parallel-group study to assess the absolute bioavailability of reslizumab after administration of a single 220-mg sc dose to healthy subjects (45 subjects). The PK, safety and tolerability, immunogenicity, and pharmacodynamics (PD) of reslizumab after a single sc or iv 220-mg dose to healthy non-Japanese subjects and a single 220-mg sc dose to healthy Japanese subjects were characterized.

No deaths or serious adverse events occurred in this study. No subject discontinued the study due to adverse events in Study 1107. There were no noteworthy differences in the type, incidence, or severity of adverse events based on route of administration or ethnicity. Overall, 10 non-Japanese subjects (33%) who received iv reslizumab, 13 non-Japanese subjects (43%) who received sc

reslizumab, and 6 Japanese subjects (40%) who received sc reslizumab reported at least 1 adverse event.

None of the adverse events were considered treatment related. For the sc formulation, the most frequent adverse events were hordeolum, drug withdrawal headache (secondary to per protocol caffeine withdrawal), and insomnia in 2 subjects each; all other adverse events occurred in 1 subject. For the iv formulation, the most frequent adverse events were drug withdrawal headache (secondary to per protocol caffeine withdrawal) and presyncope in 2 subjects each. Most of these adverse events were mild in severity, and none were severe. The adverse event "insomnia" was described as headache secondary to lack of sleep/insomnia. No subject experienced an injection site reaction or hypersensitivity reactions. No deaths, serious adverse events, or withdrawal due to adverse events were reported.

Studies C38072-PK-10069 and C38072-PK-10071 are ongoing PK studies of sc reslizumab, and full summarized safety data have not yet been produced.

There are currently 2 ongoing Phase 3, double-blind, placebo-controlled, parallel-group studies of reslizumab 110-mg sc once-every-4-weeks fixed dosing in patients with asthma and elevated eosinophil count (Study C38072-AS-30025) and in patients with OCS-dependent asthma and elevated blood eosinophil count (Study C38072-AS-30027). These studies do not have data available at the time of this protocol.

Since the available data on the sc formulation is limited to Study 1107, the clinical safety data presented in the following sections are from the iv formulation clinical program. As described below, iv reslizumab was generally well tolerated over the range of doses evaluated (ie, from 0.03 through 3.0 mg/kg).

1.2.2.1. Clinical Pharmacology Studies

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

1.2.2.2. Clinical Safety and Efficacy Studies

The Phase 3 BREATH program in adult and adolescents with asthma evaluated the safety and efficacy of reslizumab administered iv every 4 weeks at 3.0 mg/kg (16-week Studies C38072/3081 and C38072/3084, 52-week Studies C38072/3082 and C38072/3083, and OL safety extension Study C38072/3085) and 0.3 mg/kg (Study 3081 only) [Castro et al 2015, Bjermer et al 2016, Corren et al 2016]. 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-6 and Asthma Symptom Utility Index) were observed for patients with eosinophilic asthma defined by a screening blood eosinophil count ≥400 cells/μL (Studies 3081, 3082, and 3083). In patients with asthma without an elevated blood eosinophil count (Study 3084),

reslizumab produced nonsignificant improvements in lung function and other measures of efficacy. In contrast, in patients with blood eosinophil count ≥400 cells/μL, reslizumab produced significant improvements in lung function and other measures of efficacy.

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

The safety of reslizumab was evaluated in adults and in children in clinical studies summarized in the current IB. Single or multiple doses of iv reslizumab from 0.03 through 3.0 mg/kg were well tolerated with a common adverse event profile similar to that of placebo. The majority of adverse events were generally mild to moderate in severity, and most adverse events were assessed to be unrelated to study drug as determined by the investigator. The following summary relates to integrated adverse event data of the 5 completed placebo-controlled asthma studies (ie, Studies Res-5-0010, 3081, 3082, 3083, and 3084) that assessed the 3.0-mg/kg iv dose and every-4-weeks dosing regimen (up to 52 weeks). Serious adverse event and death cases from the OL Study 3085 are also included in the relevant sections.

Severe systemic reactions (including anaphylaxis) and myalgia are considered adverse drug reactions (ADRs) of iv reslizumab.

1.2.2.2.1. Common Adverse Events

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

1.2.2.2.2. 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 group (9%). The serious adverse event reported with the highest incidence was asthma (preferred terms: asthma, asthma crisis, and status asthmaticus), which was reported by 24 patients (3%) in the placebo group and 24 patients (2%) in the reslizumab 3.0-mg/kg group.

1.2.2.2.3. Deaths

There were 4 deaths in the iv BREATH program: 1 death occurred in a placebo-treated patient and 3 deaths (1 patient died due to progressive anal cancer; 1 patient died due to hemoptysis, aspiration pneumonia, nervous system disorder, and cardio-respiratory arrest; and 1 patient died at home and cardiac arrest was reported as the cause of death, considered not assessable by the investigator) occurred in the OL study (Study C38072/3085). None of the deaths were considered related to reslizumab.

1.2.2.2.4. Laboratory Findings

No clinically meaningful changes in vital signs measurements, electrocardiogram, or physical examination findings were noted in the completed studies. Overall, laboratory test values were similar in patients treated with reslizumab and placebo, with the exception of transient creatine phosphokinase (CPK) elevations and a decrease in eosinophil counts in the reslizumab-treated groups.

Transient CPK elevations in patients with normal baseline CPK values were observed in 20% of reslizumab-treated patients versus 18% of placebo-treated patients during routine laboratory assessments. The PK/PD analyses that were conducted to examine serum levels versus CPK levels did not show an exposure-response relationship that would indicate that reslizumab exposure is associated with CPK elevation.

The decreases in eosinophil counts in the reslizumab groups were considered dose related and expected in view of the mechanism of action of reslizumab. Small decreases in the mean values of total white blood cell (WBC) counts were also observed in some studies and were assessed as reflecting the decrease in the eosinophil component of differential cell counts. The mean values of eosinophil and WBC counts returned to baseline values at the end of study (EOS) follow-up visit (4 months after the final dose of reslizumab).

1.2.2.2.5. Adverse Drug Reactions

Anaphylaxis related to reslizumab infusion has been reported and is considered an ADR. Early in the drug development, all cases of anaphylaxis occurred in the eosinophilic esophagitis studies and were deemed by the investigator as related to known food allergies and not to reslizumab.
Three infusion-related reactions, reported as anaphylaxis, occurred during or shortly after reslizumab infusion in the BREATH program and were characterized variously by skin or mucosal involvement, dyspnea, wheezing, gastrointestinal symptoms, and chills. The 3 events were treated at the study center without subsequent complications, and patients were withdrawn from the study.

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

1.2.2.3. Additional Safety Considerations

1.2.2.3.1. Malignancy

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

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

In the combined placebo-controlled studies and long-term, OL, safety extension Study C38072/3085, malignancies were reported in 21 reslizumab-treated patients. These included 5 cases of

non-melanoma skin cancer. Most malignancies were diagnosed within less than 6 months after starting reslizumab treatment, and in 5 cases, there was a previous medical history of malignancy.

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

1.2.2.3.2. Infections

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

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

1.2.2.3.3. Pregnancy

The safety of reslizumab in pregnant women or developing fetus has not been studied, but nonclinical and clinical studies raised no specific concerns. In the iv BREATH clinical program, there were 10 pregnancies, 2 of which occurred during the screening period of the study and 8 in patients receiving reslizumab. All cases resulted in discontinuation of treatment and withdrawal from the study. Of the 8 on-treatment pregnancies, outcomes are known for 7 patients: 2 ended in elective abortions and 5 concluded with live births of infants with no malformations (1 male baby had a neonatal jaundice that was reported as an unrelated adverse event and was assessed as a physiological jaundice). Information about 1 pregnancy case was not available.

1.2.2.4. Immunogenicity

Treatment emergent anti-drug antibody (ADA) responses were observed in 5% of reslizumab (3.0 mg/kg)-treated 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 (positive at only 1 time point) and were not associated with an effect on reslizumab concentration, eosinophil count, or specific clinical manifestations (including hypersensitivity reactions). There was no observed association of ADA response with adverse events.

Additional information regarding benefits and risks to patients may be found in the IB.

1.3. Known and Potential Benefits and Risks to Patients

1.3.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s)

The PK, PD, immunogenicity, and safety of iv reslizumab over the dose range of 0.03 through 3.0 mg/kg have been characterized in 14 studies in patients with asthma and in healthy subjects.

Results from clinical studies indicate improved asthma control (ACQ and forced expiratory volume in 1 second [FEV_1]), quality of life (Asthma Quality of Life Questionnaire [AQLQ]), and a medically meaningful decreased rate of CAEs with reslizumab.

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

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

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

There are limited safety data regarding sc administration of reslizumab. In Study 1107, 45 healthy subjects received a single 220-mg sc injection of reslizumab. All adverse events were mild to moderate in severity. There were no deaths, serious adverse events, treatment-related adverse events, or withdrawals due to adverse events reported in this study. Studies 10069, 10071, 30025 and 30027 are ongoing, and data from these studies are not yet available.

Additional information regarding benefits and risks to patients may be found in the IB.

In summary, the benefit and risk assessment for reslizumab is favorable after review of the outlined data.

1.3.2. Overall Benefit and Risk Assessment for this Study

In completed Phase 3 clinical studies involving patients with moderate to severe asthma and elevated blood eosinophil count, iv reslizumab, when compared with placebo, demonstrated a significant reduction in the annual rate of asthma exacerbations over 52 weeks along with improved lung function, symptom scores, and quality-of-life scores. Reslizumab was generally well tolerated over the dose range of 0.03 to 3.0 mg/kg. The majority of adverse events in reslizumab-treated patients

were mild to moderate in severity; considered to be unrelated to study drug treatment, as determined by the investigator; and (as expected) associated with their underlying asthma disease. There were no significant differences in the adverse event profile between patients treated with reslizumab and patients treated with placebo with the exception of the following ADRs: "acute systemic reactions (including anaphylaxis)" and "myalgia." Three anaphylactic reactions related to reslizumab infusions were reported during the iv BREATH asthma program; none of the patients tested positive for ADA. All cases resolved without complications with standard treatment, and treatment with reslizumab was permanently discontinued. Myalgia (without evidence for muscle injury) was reported at a slightly higher rate in the reslizumab 3.0-mg/kg group (1%) than in the placebo group (0.5%).

The double-blind, placebo-controlled, Phase 3 efficacy and safety studies of reslizumab 110 mg administered sc every 4 weeks are ongoing. Study 30066 is an open-label study, and all patients will be on active drug.

Consideration of the accumulated data on the clinical effects of reslizumab in patients with asthma suggests that patients with elevated blood eosinophil count benefit the most from anti-human IL-5 therapy. Given the mechanism of action, the known PK and PD profile, and predicted reslizumab exposures based on modeling and simulation, it is expected that the sc formulation will be well tolerated and will produce a clinically meaningful effect. Based on the large and established safety and efficacy database for iv reslizumab, which is approved and indicated for severe eosinophilic asthma, Teva anticipates a favorable benefit-risk profile for sc reslizumab at a fixed dose of 110 mg in patients with severe asthma and elevated blood eosinophil counts that are inadequately controlled on standard-of-care ICS-based treatment regimens.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary, Secondary, and Tertiary Study Objectives and Endpoints

The primary, secondary, and tertiary study objectives and endpoints are as follows:

Objectives	Endpoints
The **primary objective** of this study is to support the long-term safety of reslizumab 110 mg administered sc once every 4 weeks in patients 12 years of age and older with severe eosinophilic asthma that is inadequately controlled on standard-of-care treatment.	The primary endpoint is frequency of all adverse events including serious adverse events.
	The secondary safety endpoints for this study include the following: • clinical laboratory test results – hematology and chemistry results at baseline and at weeks 4 (chemistry only), 8, 24, and 36 or early withdrawal visit • local tolerability at the injection site at approximately 1 hour after study drug administration every 4 weeks throughout the study • vital signs measurements every 4 weeks throughout the study • concomitant medication usage every 4 weeks throughout the study
The **secondary objective** of this study is to evaluate the efficacy of reslizumab 110 mg administered sc once every 4 weeks in patients 12 years of age and older with severe eosinophilic asthma that is inadequately controlled on standard-of-care treatment.	The secondary efficacy endpoints for this study include the following: • clinical asthma exacerbation (CAE) and healthcare utilization (HCU)-related endpoints – frequency of CAEs – frequency of asthma-specific hospital admissions – length of hospital stay and number of ICU days – frequency of asthma-specific emergency department visits – frequency of school/work days missed due to asthma • change from baseline in pre-bronchodilator FEV_1 measured using spirometry at weeks 0, 8, 24, and 36 or early withdrawal visit • change in daily morning ambulatory FEV_1 from baseline at each week through week 36 or early withdrawal, as measured by the handheld spirometry device • absolute and percent reduction in the daily OCS dose at

Objectives	Endpoints
	weeks 20 and 36 or early withdrawal visit as compared with the dose at baseline (for patients on daily OCS at baseline) • change from baseline in total inhalations of reliever bronchodilator medication (eg, short-acting beta-agonist) measured using weekly averages until week 36 or early withdrawal visit • change from baseline in ACQ-6 score performed at weeks 0, 8, 24, and 36 or early withdrawal visit • change from baseline in AQLQ12+ score performed at weeks 0, 8, 24, and 36 or early withdrawal visit
	[redacted]
	The immunogenicity assessments for this study include the following: • ADA measurement at baseline and at weeks 8, 24, and 36 or early withdrawal visit to evaluate the long-term immunogenicity of sc reslizumab • ADA measurement at the EOS visit (19 weeks after the final dose) to evaluate immunogenicity after study drug washout
No tertiary or exploratory objectives.	No tertiary or exploratory endpoints.

ACQ-6=Asthma Control Questionnaire; ADA=anti-drug antibody; AQLQ12+=Asthma Quality of Life Questionnaire; EOS=end of study; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; ICU=intensive care unit; OCS=oral corticosteroids; [redacted]; SABA=short-acting beta-agonist; sc=subcutaneous

2.1.1. Justification of Primary Endpoint

The primary objective of this study is to support and obtain additional long-term safety data for sc administration of reslizumab treatment administered at a fixed dose of 110 mg in patients 12 years of age and older with severe eosinophilic asthma. The primary endpoint is the frequency of all adverse events including serious adverse events experienced in patients administered sc reslizumab. The study design includes standard assessments that will help inform the overall safety profile of reslizumab, as well as adverse events of interest including systemic reactions (including anaphylaxis and administration site reactions), malignancy, infections (including parasitic helminthic and opportunistic infections), ADA, and musculoskeletal/CPK abnormalities. This comprehensive data collection methodology will allow for a robust analysis of patient safety during the study.

3. STUDY DESIGN

3.1. General Design and Study Schematic Diagram

This is a global, multicenter, OL extension study to obtain additional long-term safety data of reslizumab treatment administered sc at a fixed dose of 110 mg in patients 12 years of age and older with severe eosinophilic asthma.

The study consists of a screening/baseline visit (V1; seamless rollover patients; conducted on the same day as the end-of-treatment [EOT, week 52 or week 24, respectively] visit for patients who finished either Study 30025 or 30027) or a standalone screening visit (V0) for patients who did not seamlessly rollover from Study 30025 or 30027 (had a gap between placebo-controlled study EOT and start of OLE; Section 4.1 and Appendix B.1), followed by an OL treatment period, an EOT visit (V_{EOT}), a follow-up telephone call (V_{FU}) at 12 weeks after the EOT visit, and an EOS visit (V_{EOS}) for immunogenicity testing 19 weeks after the final dose of study drug administration. The duration of the OL treatment period will be 9 months (36 weeks).

Study patients will be deemed eligible only if they meet all inclusion criteria and no exclusion criteria are fulfilled. Patients currently enrolled in Studies 30025 and 30027 will be required to complete their respective treatment periods to be eligible for this study. In addition, adolescents (patients 12 through <18 years of age) from Study 30025 must also complete the 12-week early follow-up visit (off study drug) before transferring to this OL study.

There may be a gap in study drug administration for some patients due to completion of Study 30025 or 30027 before the initiation of the OL extension study (non-seamless rollover). Patients with a gap between the EOT visit for Study 30025 or 30027 will complete a V0 screening visit. Adolescents (a patient 12 through <18 years of age) from Study 30025 can complete the V0 screening visit of Study 30066 the same day as the 12-week early follow-up visit for Study 30025. Any blood tests completed by adolescents at the 12-week early follow-up visit for Study 30025 can be used for the V0 screening visit of Study 30066 and do not need to be repeated. Any patient who did not rollover seamlessly from Study 30025 or 30027 will participate in a 7-day run-in period where baseline measures for asthma control and spirometry will be established. This screening assessment and run-in period will be completed within the 2 weeks prior to visit 1.

During screening/baseline, informed consent (and assent for patients under 18 years of age according to local Institutional Review Board/Independent Ethics Committee [IRB/IEC] requirements) will be obtained. This will be conducted at the EOT visit of Study 30025 or 30027 (seamless rollover patients) or at the standalone screening visit (V0) for non-seamless rollover patients with a gap in study drug administration (those who have previously completed Study 30025 or 30027, but are not screened on the same day as the EOT visit.

During the treatment period, patients will receive reslizumab by sc injection at a dosage of 110 mg every 4 weeks (28 days ±7 days) for 32 weeks in the study center. Patients will return to the study center every 4 weeks relative to baseline during OL treatment.

After study drug administration, each patient will remain at the study center for a minimum of 1 hour for observation. If during post-study drug observation the patient develops clinical symptoms, vital signs should be collected and the patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.6.1.1.

After each administration, the patient will be required to use a study-provided handheld electronic diary (eDiary)/spirometry device that will ask questions post-injection to evaluate for any new symptoms that may have developed during the 24-hour period after investigational medicinal product (IMP) administration. The patient will complete a question regarding new symptoms on the eDiary device the evening after the IMP administration and the following morning. This is in addition to the peak expiratory flow (PEF; AM and PM), FEV_1 measurements (AM only), and recording of rescue inhaler use that are performed every day during the treatment period.

A full physical examination will be completed at screening and at EOT. Other safety evaluations will be performed at every visit when the study drug is administered: adverse event inquiry, vital signs measurement, assessment of injection site, concomitant medication use, and urine pregnancy test. Additional evaluations, including clinical chemistry, hematology, and ADA measurements, will be performed throughout the study according to the schedule of procedures and assessments (Table 1). Patients will also be monitored for asthma exacerbations throughout the study (Section 6.1.1).

Asthma control measures will be assessed as part of this OL extension study to evaluate the long-term effect of sc reslizumab. These will include CAE assessment (including healthcare utilization [HCU]), pre-bronchodilator spirometry, questionnaires (including ACQ-6 and AQLQ12+), and change in OCS dose for those on maintenance therapy. Asthma control including asthma exacerbations and related HCU will be assessed at every study visit during the treatment period. Spirometry will be performed daily through the use of a handheld spirometry device. Concomitant medications will be recorded at all visits during the treatment period and will include OCS dose if participants are on maintenance corticosteroids (Appendix I). For those patients previously enrolled in Study 30027, maintenance prednisone will no longer be provided by the sponsor. In an effort to standardize a patient's maintenance therapy, it is encouraged that the investigators prescribe prednisone/prednisolone as the maintenance corticosteroid preparation if deemed necessary.

Patients will have final procedures and assessments performed at the EOT visit. Patients who withdraw before the completion of the study will have EOT procedures and assessments performed at their early withdrawal visit. All patients will have a follow-up telephone assessment 12 weeks after the EOT visit. The EOT visit includes home pregnancy testing, adverse event assessment, and concomitant medication inquiry. There will then be an EOS visit for immunogenicity testing 19 weeks after the final dose of study drug.

Measurement of ADAs will be performed on samples collected at baseline and at weeks 8, 24, and 36 or early withdrawal visit to evaluate the potential long-term immunogenicity of sc reslizumab, and on samples collected at the EOS visit (19 weeks after the final dose) to evaluate immunogenicity after study drug washout. A blood sample will also be collected in the event of withdrawal from the study or upon observation of any severe hypersensitivity reaction (eg, anaphylaxis). An unscheduled sample can also be drawn after a serious adverse event if the investigator or sponsor considers appropriate. Drug levels may be measured in the serum samples collected for ADAs to help inform ADA analysis. If a patient is found to have a positive ADA status after at least 2 doses of study drug in this OL study, the patient may be scheduled to complete an EOT visit. This testing may be done to enhance early data collection on potential washout samples. A summary of ADA results in previous clinical experience is outlined in Section 1.2.2.4.

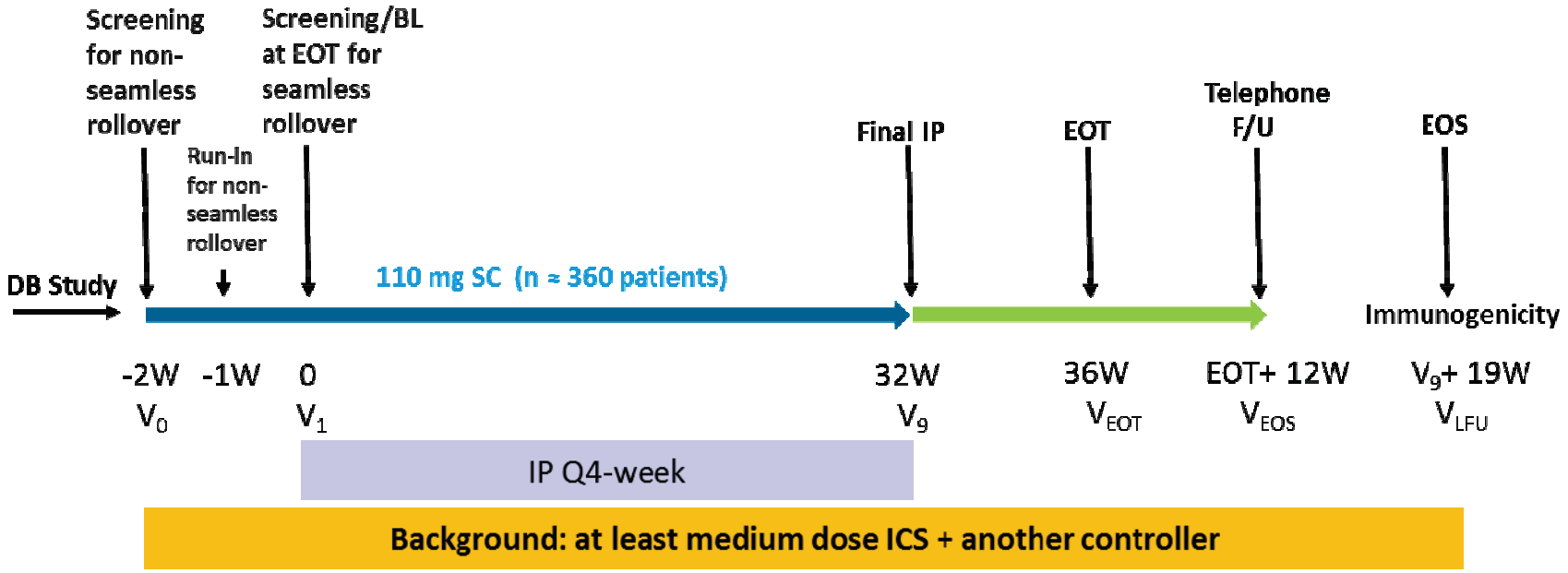
An unscheduled visit may be performed at any time during the study at the patient's request or as deemed necessary by the investigator. The date and reason for the unscheduled visit as well as any other data obtained (eg, adverse events, concomitant medications and treatments, and results from

procedures or tests) will be recorded on the case report form (CRF) and noted within the patient's source notes.

Study procedures and assessments with their time points are shown in Table 1.

The study schematic diagram is presented in Figure 1.

Figure 1: Overall Study Schematic Diagram



DB=double-blind; BL=baseline; EOS=end of study; EOT=end of treatment; F/U=follow-up; ICS=inhaled corticosteroids; IP=investigational product; n=number; Q=every; SC=subcutaneous; V=visit; W=week

3.2. Planned Number of Patients and Countries

Approximately 360 patients will be enrolled in this study who have rolled over to this OL extension study from their participation in Studies 30025 and 30027.

The study is planned to be conducted in approximately 12 countries in approximately 140 investigational centers (centers that participated in Studies 30025 and 30027). The study is expected to start in March/Q1 2017 and last until approximately November/Q4 2018.

3.3. Justification for Study Design and Selection of Population

This study is a global, multicenter, OL, extension study to obtain additional long-term safety data of reslizumab treatment administered sc at a fixed dose of 110 mg in patients 12 years of age and older with severe eosinophilic asthma. This study will increase the length of patient exposure for patients previously exposed to reslizumab for up to an additional 9 months beyond the placebo-controlled studies (Studies 30025 and 30027).

The population selected for this study is considered representative of the asthma population with severe eosinophilic asthma. This study will enroll male and female patients 12 years of age and older with severe eosinophilic asthma who were randomized and completed the treatment period for a Phase 3 clinical study of reslizumab 110 mg sc (Studies 30025 and 30027). Note that adolescents (patients 12 through <18 years of age) from Study 30025 must also complete the 12-week early follow-up visit (off study drug) before transferring to this OL study.

3.4. Stopping Rules for the Study

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

Other than pregnancy, there are no formal rules for study drug discontinuation in this study due to safety concerns. During the conduct of the study, serious adverse events and adverse events of special interest will be reviewed by the sponsor (Section 7.1.5.3.2) as they are reported from the investigational center to identify safety concerns.

If a patient is found to have a positive ADA status after at least 2 doses of study drug in this OL study, the patient may be scheduled to complete an EOT visit. This testing would be done to enhance early data collection on potential washout samples.

The investigator and/or sponsor can withdraw a patient from the study for reasons including, but not limited to, a change in the medical condition or an adverse event that alters the patient's benefit/risk (eg, pregnancy, a related severe hypersensitivity reaction, or related severe myalgia/muscle event), a protocol violation or deviation as defined in Section 7.1.9 or Section 7.3, or noncompliance.

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

3.5. Patient Completion

Patients who participate in the study in compliance with the protocol for 36 weeks of OL treatment will be considered to have completed the treatment period. Patients who complete the

EOS visit (week 51) will be considered as having completed the study. See Section 3.6 for the definition of the end of the study.

3.6. End of the Clinical Study

Last Patient Last Visit (LPLV) of the treatment period is defined as the EOT. The EOS visit for immunogenicity testing only will be performed 19 weeks (±2 weeks) after the final dose of study drug (approximately week 51). This will be considered the end of the trial for the purposes of end of trial notification.

3.7. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented in Table 1. Detailed descriptions of each method of procedures and assessments are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (other assessments). Study procedures and assessments by visit are listed in Appendix B.

Table 1: Study Procedures and Assessments

Study period	**Screening**		**Open-label treatment period**											
Visit number	**V0[a] Screening for non-seamless enrollees**	**Run-in for non-seam-less enrollees**	**V1[a] Screening /baseline**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V_{EOT} EOT or early with-drawal**	**V_{FU} Follow-up telephone assessment**	**V_{EOS} EOS**
Procedures and assessments	**W-2 -14d to ≤-7d**	**-7d to 0d**	**W0**	**W4 ±7d**	**W8 ±7d**	**W12 ±7d**	**W16 ±7d**	**W20 ±7d**	**W24 ±7d**	**W28 ±7d**	**W32 ±7d**	**W36 ±7d**	**W48 (EOT +12W) ±14d**	**W51 (V9 +19W) ±14d**
Informed assent/consent	X		X											
Medication history	X		X											
Inclusion and exclusion criteria	X		X											
Pregnancy testing	X[b]		X[c]	X	X	X	X	X	X	X	X	X	X	
Hematology (CBC with differential) (prior to IMP administration)	X		X[c]		X				X			X		
Serum chemistry tests with CPK[d] (prior to IMP administration)	X		X[c]	X	X				X			X		
Blood for ADA[e]			X[c]		X				X			X		X
Full physical examination[f]	X		X[c]									X		
ECG[f]	X		X[c]									X		
Vital signs[f]	X		X[c]	X	X	X	X	X	X	X	X	X		
Height and weight	X											X		
Pre-bronchodilator spirometry[g]			X[c]		X				X			X		
ACQ-6			X[c]		X				X			X		
AQLQ12+			X[c]		X				X			X		

Table 1: Study Procedures and Assessments (Continued)

Study period	**Screening**		**Open-label treatment period**											
Visit number	**V0[a] Screening for non-seamless enrollees**	**Run-in for non-seam-less enrollees**	**V1[a] Screening /baseline**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V_{EOT} EOT or early with-drawal**	**V_{FU} Follow-up telephone assessment**	**V_{EOS} EOS**
Procedures and assessments	**W-2 -14d to ≤-7d**	**-7d to 0d**	**W0**	**W4 ±7d**	**W8 ±7d**	**W12 ±7d**	**W16 ±7d**	**W20 ±7d**	**W24 ±7d**	**W28 ±7d**	**W32 ±7d**	**W36 ±7d**	**W48 (EOT +12W) ±14d**	**W51 (V9 +19W) ±14d**
Assess asthma control including asthma exacerbations and related HCU: step-down background medication (eg, OCS) if clinically appropriate[h]	X		X[c]	X	X	X	X	X	X	X	X	X		
Provide/collect handheld electronic diary/spirometry device; reinforce diary and PEF/spirometry compliance	X		X	X	X	X	X	X	X	X	X	X		
Patient daily use of handheld electronic diary/spirometry device		X →												
Adverse event inquiry	X		X[c]	X	X	X	X	X	X	X	X	X	X	
Concomitant medication inquiry[i]	X		X[c]	X	X	X	X	X	X	X	X	X	X	
IMP administration			X	X	X	X	X	X	X	X	X			
Injection site assessment[j]			X	X	X	X	X	X	X	X	X			

[a] Visit 1 (screening/baseline) will take place at the EOT visit for patients seamlessly rolling over from Studies 30025 and 30027. Any patient who did not rollover seamlessly from Study 30025 or 30027 will be seen first at an earlier screening visit (V0) in order to complete informed consent and eligibility criteria procedures before completing all other procedures and IMP administration at V1. Adolescents (a patient 12 through <18 years of age) from Study 30025 can complete the V0 screening visit of Study 30066 the same day as the 12 week early follow up visit for Study 30025. Additionally, any patient who did not rollover seamlessly from Study 30025 or 30027 will participate in a 7-day run-in period where baseline measures for asthma control and spirometry will be established. The screening period (including run in) will be up to a maximum of 14 days. Patients who complete the screening assessments of informed assent/consent, medication history, and inclusion and exclusion criteria at V0 do not need to repeat them at V1. Any assessments that are performed at V0 do not need to be repeated at V1 if completed within the previous 14 days (including blood tests completed by adolescents at the 12 week early follow up visit for Study 30025).

[b] Beta-human chorionic gonadotropin serum pregnancy tests will be performed at V0 for patients who did not seamlessly rollover (female patients who are not postmenopausal or surgically sterile only). Urine pregnancy testing will be performed at all other visits for all female patients who are not postmenopausal or surgically sterile only. Note: FSH level will be obtained from serum chemistry test as required to determine postmenopausal status. Please see the Laboratory Manual for further information.
[c] These assessments may have been done as part of the EOT visit of Study 30025 or 30027 if patient seamlessly enters open-label study.
[d] If a potentially clinically significant CPK level (≥3.1× ULN) occurs, please refer to Protocol Section 7.1.6.1.2 for further management.
[e] For ADA collection, a blood sample will also be collected in the event of withdrawal from the study or upon observation of any severe hypersensitivity reaction (eg, anaphylaxis). An unscheduled sample can also be drawn after a serious adverse event if the investigator or sponsor considers appropriate. When applicable, blood samples for ADA should be taken before drug administration. Reslizumab concentration data will be assessed from the ADA blood samples.
[f] 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. Physical examination, ECG, and vital signs (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate) should be obtained before spirometry procedures and IMP administration. If screening occurs over multiple visits, vital signs at minimum should be performed at the initial screening visit and repeated on the day of V1.
[g] Pre-bronchodilator spirometry assessments at designated clinic visits (weeks 0, 8, and 24, and EOT) should only be performed after withholding short-acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule.
[h] Investigators can reduce maintenance OCS as clinically indicated.
[i] Inquiry will include assessment of OCS dose if participants are on maintenance corticosteroids.
[j] Assessment should be made approximately 1 hour after study drug administration.

ACQ-6=Asthma Control Questionnaire; ADA=anti-drug antibody; AQLQ12+=Asthma Quality of Life Questionnaire; CBC=complete blood count; CPK=creatine phosphokinase; d=day; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; FSH= follicle stimulating hormone; FU=follow-up; HCU=healthcare utilization; HCG= human chorionic gonadotropin; IMP=investigational medicinal product; OCS=oral corticosteroid; PEF=peak expiratory flow; PI=principal investigator; ULN=upper limit of normal; V=visit; W=week

4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be randomized/enrolled are not granted by Teva (Appendix C).

Study patients will be deemed eligible only if they meet all inclusion criteria and no exclusion criteria are fulfilled. Patients who are currently enrolled in Studies 30025 and 30027 will be required to complete their respective treatment periods to be eligible for this study. In addition, adolescents (patients 12 through <18 years of age) from Study 30025 must also complete the 12-week early follow-up visit (off study drug) before transferring to this OL study.

4.1. Patient Inclusion Criteria

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

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

b. Male or female patient 12 years or older with eosinophilic asthma who was previously randomized and completed the treatment period in either of the double-blind, placebo-controlled studies (Study 30025 or 30027) for sc reslizumab and who by the assessment of the Principal Investigator can safely participate in this study.

   Adolescents from Study 30025 must also complete the early follow-up visit before being eligible for this study.

c. Unless surgically sterile or postmenopausal, female patients must have a negative urine pregnancy test at baseline. Definitions of sterile and postmenopausal are given in Appendix E.

d. Females of childbearing potential (not surgically sterile or postmenopausal) must have an exclusively same-sex partner or use a medically acceptable method of contraception and must agree to continue the use of this method for the duration of the study and for 5 months after discontinuation of the study drug. Acceptable methods of contraception include intrauterine device, steroidal contraceptive (oral, implanted, transdermal, or injected), barrier method with spermicide, abstinence, bilateral tubal occlusion, and partner vasectomy.

e. The patient must be willing and able to comply with study restrictions and willing to return to the investigational center for the follow-up procedures and assessments as specified in this protocol.

4.2. Patient Exclusion Criteria

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

a. Patient has received any iv or sc reslizumab administration in any previous clinical trial other than Studies 30025 and 30027.

b. Patient withdrew early (discontinued from treatment) from either of the placebo-controlled reslizumab studies, Studies 30025 and 30027, for any reason.

c. The patient has any clinically significant, uncontrolled medical condition (treated or untreated) that would interfere with the study schedule or procedures and interpretation of efficacy results or would compromise the patient's safety.

d. The patient has another confounding underlying lung disorder (eg, chronic obstructive pulmonary disease, interstitial lung disease, bronchiectasis eosinophilic granulomatosis with polyangiitis [also known as Churg-Strauss syndrome], or allergic bronchopulmonary aspergillosis).

e. The patient has a known/diagnosed hypereosinophilic syndrome.

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

g. The patient is a pregnant or lactating woman or intends to become pregnant during the study or within 5 months after the last dose of study drug. Administration of IMP will be discontinued for any female patient who becomes pregnant during the study.

h. The patient required treatment for an asthma exacerbation within 4 weeks of screening or during the screening. (Note: This is required only in patients who did not rollover seamlessly from Study 30025 or 30027, ie, had a gap between placebo-controlled study EOT and screening for Study 30066 [including adolescents from Study 30025 who must also complete the early follow-up visit].)

   Patients who did not rollover seamlessly from Study 30025 or 30027 may be considered for rescreening if they are excluded from study participation for not satisfying this criterion. A patient may be rescreened for this reason 1 time only. The duration between the first visit during the screening period and the rescreening must be >30 days.

i. The patient is a current smoker (ie, has smoked within the last 6 months before screening) or has a smoking history ≥10 pack-years.

j. The patient is currently using any systemic immunosuppressive or immunomodulatory biologic (eg, anti-immunoglobulin E mAb or other mAb [eg, mepolizumab, benralizumab, dupilumab] or soluble receptors) or non-biologic (eg, methotrexate or cyclosporine), except maintenance oral corticosteroids, for the treatment of asthma (up to and including 40 mg of prednisone daily or equivalent every-other-day dosing). Note: Previous use of such agents that occurred >5 half-lives from the initial screening visit may be allowed.

k. The patient participated in a clinical study other than approved Teva reslizumab studies within 30 days or 5 half-lives of the investigational drug before screening, whichever is longer.

l. The patient has a history of an immunodeficiency disorder, including human immunodeficiency virus (HIV).

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

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

o. The patient has a history of allergic reaction or hypersensitivity to any component of the study drug.

p. The patient is expected to be poorly compliant with study procedures or visits.

q. The patient is a vulnerable patient (eg, a patient who is or may be for any reason unable to take care of him or herself, unable to protect him or herself against significant harm or exploitation, or kept in detention).

4.3. Withdrawal Criteria and Procedures for the Patient

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), patients may voluntarily 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 (Section 7.2), or other reasons concerning the health or well-being of the patient or in the event of lack of cooperation.

Each patient is free to withdraw from the study at any time, without prejudice to his/her continued care. A patient must be withdrawn from the study if any of the following events occur:

1. Patient withdraws consent or requests discontinuation from the study for any reason.
2. Patient develops an illness that would interfere with his/her continued participation.
3. Patient is noncompliant with the study procedures and assessments or administration of IMPs in the opinion of the investigator.
4. Patient takes prohibited concomitant medications as defined in this protocol.
5. A female patient has a confirmation of pregnancy during the study from a positive pregnancy test.
6. The sponsor requests withdrawal of the patient.
7. Patient experiences an adverse event or other medical condition, which indicates to the investigator that continued participation is not in the best interest of the patient.

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

The reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed onto the CRF. If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event or a potentially clinically significant abnormal laboratory test result, monitoring will be continued until the event has resolved or stabilized, until the patient is referred to the care of a healthcare professional, or until a determination of a cause unrelated to the study drug or study procedure is made. The specific event or test result must be recorded on the source documentation and transcribed onto the CRF.

If a patient is found to have a positive ADA status after at least 2 doses of study drug in this OL study, the patient may be scheduled to complete an EOT visit. This testing would be done to enhance early data collection on potential washout samples.

All protocol-specific evaluations should be performed at the early withdrawal visit (Table 1). Patients who withdraw from the study will be asked to participate in a follow-up telephone assessment 12 weeks ±14 days after the early withdrawal visit. All protocol-specified evaluations should be performed during the follow up telephone assessment 12 weeks ±14 days after the early withdrawal visit (Table 1).

Patients should be treated with standard-of-care treatment after withdrawal from or withdrawal of the study, as appropriate.

For patients who are lost to follow-up (ie, patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should make every effort to re-establish contact with patient; attempts to contact the patient should be documented in the source documents. A patient should only be designated as lost to follow-up if the study center is unable to establish contact with the patient after 3 documented attempts via 2 different methods (ie, phone, text, e-mail, certified letter, etc).

See Appendix F for information regarding how the study will define and address patients who were lost to follow-up to help limit the amount and impact of missing data.

4.4. Replacement of Patients

A patient who is enrolled but does not complete the treatment period will not be replaced with another eligible patient.

4.5. Rescreening

Patients who did not rollover seamlessly from Study 30025 or 30027 may be considered for rescreening if they are excluded from study participation for required treatment for an asthma exacerbation within 4 weeks of screening or during the screening. A patient may be rescreened for this reason 1 time only. The duration between the first visit during the screening period and the rescreening must be >30 days.

There will be no rescreening of patients who do not meet the other entry criteria for this OL extension study.

4.6. Screening Failure

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Minimum information to be collected includes, but is not limited to, demography, screening failure details, eligibility criteria, and any serious adverse events.

5. TREATMENTS

5.1. Investigational Medicinal Products Used in the Study

5.1.1. Test Investigational Medicinal Product

Reslizumab will be provided as a sterile solution in a pre-filled syringe (PFS) containing 110 mg (1.0 mL) reslizumab per syringe, formulated at 110 mg/mL in [redacted] sodium acetate, with [redacted] sucrose, [redacted] polysorbate 80, and pH 5.5 buffer (Table 2). Reslizumab will be provided as a clear to slightly hazy solution.

Study drug will be administered as sc injections in the thigh, abdomen, or upper arm(s) once every 4 weeks for a total of 9 doses.

The PFS has a staked 27G 0.5-inch needle. Injections of sc study drug can be given at a 90-degree angle or at a 45-degree angle. The injection can be given at a 90-degree angle if 2 inches of skin can be grasped between the thumb and the first finger. If only 1 inch of skin can be grasped, the injection should be administered at a 45-degree angle. The sites where injections are given should be at least 1 inch away from each other. Product should be removed from the refrigerator and allowed to equilibrate at room temperature for 15 to 30 minutes before administration. Administration will be conducted by qualified study personnel.

Additional information regarding the study drug can be found in the Pharmacy Manual.

Table 2: Investigational Medicinal Products Used in the Study

IMP name	**Reslizumab**
Trade name and INN, if applicable, or company-assigned number	CINQAIR® CINQAERO® Reslizumab
Formulation	Sterile solution containing 110 mg (1.0 mL) reslizumab per syringe and formulated at 110 mg/mL in [redacted] sodium acetate, with [redacted] sucrose, [redacted] polysorbate 80, and pH 5.5 buffer
Unit dose strength(s)/dosage level(s)	110 mg (1.0 mL) reslizumab per PFS
Route of administration	Subcutaneous injection Performed by qualified study personnel
Dosing instructions	Every 4 weeks
Packaging	PFSs to study centers
Manufacturer	Teva Pharmaceuticals

IMP=investigational medicinal product; INN=International Nonproprietary Name; PFS=pre-filled syringe.

Additional details may also be found in the current version of the IB for reslizumab.
Product complaints procedures are described in Appendix S.

5.1.1.1. Starting Dose and Dose Levels

The starting dose and maximal dose administered will be 110 mg/mL sc every 4 weeks.

5.2. Preparation, Handling, Labeling, Storage, and Accountability for IMPs

5.2.1. Storage and Security

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all IMPs received and that any discrepancies are reported and resolved before use of the IMPs.

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

5.2.2. Labeling

Supplies of IMPs will be labeled according to the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) and will include any locally required statements. If necessary, labels will be translated into the local language.

5.2.3. Accountability

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

The investigator is responsible for ensuring that deliveries of IMPs and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the Code of Federal Regulations (CFR) or national and local regulations and used in accordance with this protocol.

Only patients enrolled in the study may receive IMPs, and only authorized staff at the investigational center may supply the IMP.

All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions or appropriate instructions with access limited to the investigator and authorized staff at the investigational center.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

A record of IMP accountability (ie, IMP and other study 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 IMP will be disposed of or returned to the sponsor or designee.

5.3. Justification for Investigational Medicinal Products

5.3.1. Justification for Dose of Test Investigational Medicinal Product

The platform of evidence that supports the range of the reslizumab dose response is based on the observed effects on lung function and other clinical endpoints in patients with eosinophilic asthma (Studies P00290 [0.3- and 1.0-mg/kg doses], Res-5-0010 [3.0-mg/kg dose], and 3081 [0.3- and 3.0-mg/kg doses]), on eosinophil depletion in the blood in healthy subjects (Study 1102 [0.3-, 1.0-, 2.0-, and 3.0-mg/kg doses]), and in the blood and affected tissue in patients with asthma (Studies I96-350, 3081, and P00290) and eosinophilic esophagitis (Study Res-5-0002 [1.0-, 2.0-, and 3.0-mg/kg doses]). Refer to the IB for a summary and comprehensive presentation of these data. Briefly, treatment with iv reslizumab at a dose of 0.3 mg/kg produced substantially smaller and less durable reductions in the number of blood or tissue eosinophils (ie, sputum) than doses ≥1 mg/kg. In contrast, the magnitude of reductions in blood or tissue eosinophils at doses ≥1 mg/kg (ie, 1, 2, or 3 mg/kg) was similar. Improvements in patients in the reslizumab 0.3-mg/kg treatment group for FEV_1 were 0.129 L at week 16 (p=0.0481), but other efficacy endpoint results were more variable (eg, no treatment effect on forced vital capacity [FVC] and forced expiratory flow at 25% and 75% of the FVC [$FEF_{25\%-75\%}$] was observed for patients in the reslizumab 0.3-mg/kg treatment group). Therefore, iv doses of ≥1 mg/kg are anticipated to be clinically effective in most patients. Based on these clinical and eosinophil PD data, Teva has chosen reslizumab 110 mg administered once every 4 weeks as the fixed dose to study in the sc program. This approximates a 1-mg/kg iv dose for the average patient (ie, 70 kg) when adjusted to account for sc bioavailability (ie, 67%). Modeling and simulation demonstrate that the steady-state trough serum concentrations of reslizumab after administration of the proposed 110-mg sc dosing regimen are expected to fall within the range of exposures that produced meaningful effects on both blood eosinophils and FEV_1 in patients with eosinophilic asthma. Therefore, a fixed dose of 110 mg sc once every 4 weeks is anticipated to provide sufficient efficacy.

5.4. Treatment After the End of the Study

Patients will return to the care of their primary physician and/or asthma specialist after the end of this study.

5.5. Restrictions

Medications prohibited before and/or during the study are described in Section 5.6. Restrictions in regard to sexual activity and required laboratory values are provided in the inclusion and exclusion criteria.

5.6. Prior and Concomitant Medication or Therapy

Any prior or concomitant therapy, medication (including corticosteroids), or procedure a patient has had at screening up to the end of the study period, including follow-up, will be recorded on the appropriate 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 (WHO) drug dictionary.

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

For patients on maintenance OCS treatment, patients should be evaluated at each patient interaction (study visit) and their OCS dose reduced as clinically appropriate. Maintenance prednisone will not be provided by the sponsor. In an effort to standardize a patient's maintenance therapy, it is encouraged that the investigators prescribe prednisone/prednisolone as the maintenance corticosteroid preparation if deemed necessary.

With the exception maintenance OCSs for the treatment of asthma, any systemic immunosuppressive or immunomodulatory biologic (eg, anti-immunoglobulin E mAb or other mAb [eg, mepolizumab, benralizumab, dupilumab] or soluble receptors) or non-biologic (eg, methotrexate or cyclosporine) will be prohibited during this study.

5.7. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance. Drug accountability will be recorded in the CRF.

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. In such cases, the IEC/IRB should be notified.

Exposure to IMP will be assessed as required.

5.8. Randomization and Blinding

This is a nonrandomized OL extension study with no blinding.

5.8.1. Data Monitoring Committee

There will be no Data Monitoring Committee in this study.

5.9. Total Blood Volume

Blood draws will be separated by at least 2 weeks. The estimated total blood volume withdrawn over the entire study (including screening) is approximately 52 mL. To further reduce the volume of blood withdrawn, pediatric tubes will be used when possible.

Details are provided in Appendix G.

6. ASSESSMENT OF EFFICACY

6.1. Assessments of Efficacy

6.1.1. Asthma Exacerbations

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

- use of systemic corticosteroids (oral or injection) or at least a doubling from a stable maintenance oral corticosteroid dose for at least 3 days
- asthma-specific hospital admission
- asthma-specific emergency department visit

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

All asthma exacerbations (mild/moderate/severe) should be recorded on the asthma exacerbation CRF. The information on the CRF will be used to determine if an asthma exacerbation meets CAE criteria.

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

6.1.2. Spirometry

Pre-bronchodilator (on designated clinic visit days per table of procedures) and daily morning ambulatory FEV_1 will be measured using the handheld device that has combined spirometry and eDiary capabilities. The FEV_1 is the volume of air that can be forcibly exhaled from the lungs in the first second, measured in liters. The National Health and Nutrition Survey (NHANES) III reference equations will be used.

6.1.3. PEF Monitoring

PEF will be measured twice daily in the morning and evening with the use of a handheld spirometry device that has combined spirometry and eDiary capabilities. PEF is the maximum speed of exhalation.

6.1.4. Asthma Rescue Medication Use

The number of times asthma rescue medication (number of inhalations/puffs) is used will be assessed by reviewing the eDiary that will be maintained by the patient (Appendix J).
Note: SABA therapy used for exercise pretreatment should not be recorded.

6.1.5. Asthma Control Questionnaire

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

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

The AQLQ12+ is a modified version of the standardized AQLQ (AQLQ[S]), which was developed to measure functional impairments experienced by adults ≥17 years of age. The AQLQ12+ is valid for patients 12 to 70 years of age and includes 32 questions in 4 domains (symptoms, activity limitation, emotional function, and environmental stimuli) [Juniper et al 1992, Wyrwich et al 2011]. Patients will be asked to recall their experiences during the previous 2 weeks and score each of the questions on a 7-point scale, where 7=not at all limited and 1=totally limited (Appendix L).

6.1.7. Target Biomarker Measures

Eosinophil counts will be monitored throughout as a biomarker for reslizumab activity.

7. ASSESSMENT OF SAFETY

In this study, safety and tolerability of reslizumab sc administration will be assessed by qualified study personnel by evaluating the following:

- frequency of all adverse events, including serious adverse events
- clinical laboratory test results
  - hematology and chemistry results at baseline and at weeks 4 (chemistry only), 8, 24, and 36 or early withdrawal visit
- local tolerability at the injection site at approximately 1 hour after study drug administration every 4 weeks throughout the study
- vital signs measurements every 4 weeks throughout the study
- concomitant medication usage every 4 weeks throughout the study

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily require a causal relationship with this treatment.

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 reslizumab. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

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

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions
- drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- 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 or diagnostic test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)

- events associated with study procedure (eg, clinically significant adrenal insufficiency)

Asthma exacerbation is an efficacy variable for this study and should be captured on the asthma exacerbation CRF. Accordingly, asthma exacerbations should not be recorded as adverse events unless assessed as more severe than the patient's usual disease course. In this case, the investigator should determine if the adverse event is nonserious or serious based on seriousness criteria, as defined in Section 7.1.5. All asthma exacerbations should be recorded on the asthma exacerbation CRF, regardless of severity or whether it meets adverse event criteria.

7.1.2. Recording and Reporting of Adverse Events

For recording of an adverse event, the study period is defined for each patient as the time period from signature of the informed consent form to the end of the follow-up period. The follow-up period of recording of adverse events is defined as 12 weeks after the last dose of IMP. The period for reporting treatment-emergent adverse events is defined as the period after the first dose of IMP is administered and until the EOT visit.

All adverse events that occur during the defined study period must be recorded both on the source documentation and the CRF, regardless of the severity of the event or judged relationship to the test IMP. For serious adverse events, the serious adverse event form must be completed and the serious adverse event must be reported immediately (Section 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events after the defined period. Serious adverse events that occur to a patient after the end of the study should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

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; until the patient is referred for continued care to a healthcare professional; or until a determination of a cause unrelated to the test IMP or study procedure is made.

The onset and end dates, action taken regarding IMP, treatment administered, and outcome for each adverse event must be recorded both on the source documentation and the CRF. The approximate time of onset for each adverse event will also be recorded.

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

Further details are provided in the Safety Monitoring Plan.

7.1.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as one of the following:

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 Test Investigational Medicinal Product

The relationship of an adverse event to the IMP is characterized in Table 3:

Table 3: The Relationship of an Adverse Event to the Study Drug

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 IMP.	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 IMP. • 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 IMP. • It does not reappear or worsen when the IMP 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 administration of IMP 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 IMP. • 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 IMP, yet an IMP relationship clearly exists. • It follows a known pattern of response to the IMP.

IMP=investigational medicinal product.

7.1.5. Serious Adverse Events

For recording of serious adverse event, the study period is defined for each patient as that time period from signature of the informed consent form to the end of the follow-up period (follow-up telephone assessment at week 48). Serious adverse events occurring in a patient after the end of the follow-up period should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

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 a 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 that 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 study entry will not be considered serious adverse events, unless there was worsening of the pre-existing condition during the patient's participation in this study. Note: Hospitalizations due to asthma exacerbation will be reported as serious adverse events if the presentation or outcome is more severe than the patient's known course of asthma.
- 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
- is an important medical event that may not result in death, may not be life-threatening, or may not 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.

All occurrences of possible drug-induced liver injury that meet Hy's law criteria, defined as **all** of the below occurring together, must be reported by the investigator to the sponsor as a serious adverse event:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase of >3× the upper limit of normal (ULN)
- total bilirubin increase of >2× ULN

- absence of initial findings of cholestasis (ie, no substantial increase of alkaline phosphatase [ALP])

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 may be found in the IB. For the purpose of suspected unexpected serious adverse reaction (SUSAR) reporting, the version of the IB at the time of occurrence of the SUSAR applies. All serious adverse events will be evaluated for expectedness by the sponsor's Global Patient Safety and Pharmacovigilance (GPSP) department.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of judged relationship to administration of the test IMP, 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 last administration of IMP 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 designee (a contract research organization [CRO] in a country without a sponsor LSO) [contact information is in the Clinical Study Personnel Contact Information section]; the LSO will forward the report to the sponsor's GPSP. Further details regarding this process can be found in the Safety Monitoring Plan.

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 test IMP (no reasonable possibility, reasonable possibility)

Additional information includes the following:

- age and sex of patient
- date of first dose of IMP

- date and amount of last administered dose of IMP
- 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 IMP)
  - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the test IMP, 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 GPSP will distribute the Council for International Organizations of Medical Sciences form/Extensible Markup Language file to the LSO/CRO for submission to the competent authorities, IEC/IRBs, and investigators, according to regulations. The investigator must ensure that the IRB is also informed of the event, in accordance with national and local regulations.

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 (Section 7.2).

7.1.5.3.2. Sponsor Responsibility

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

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

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- 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 of Special Interest

For the purposes of this protocol, the following are considered protocol-defined adverse events of special interest to be sent to the sponsor's GPSP for evaluation:

- systemic reactions, including anaphylaxis
- administration site reactions
- newly diagnosed malignancy
- infections, including parasitic helminth infection and opportunistic infections

A list of potential opportunistic infections is found in Appendix M.

Information on data collection for all suspected anaphylaxis events is discussed in Section 7.1.6.1.1.

The process for reporting a protocol-defined adverse event of interest is the same as that for reporting a serious adverse event (Section 7.1.5.3). An adverse event of special interest does not necessarily need to be defined as a serious adverse event. Protocol-defined adverse events of special interest to be reported to GPSP can be either serious or nonserious, according to the criteria outlined in Section 7.1.5.1.

7.1.6.1. Specific Adverse Event Case Report Form Capturing

Additionally, the following specific adverse events will have specific CRFs for capturing the events.

7.1.6.1.1. 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 N). 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. These events can be either serious or nonserious, according to the criteria outlined in Section 7.1.5.1.

7.1.6.1.2. 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 CRF. 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").

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

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

7.1.7. Withdrawal Due to an Adverse Event

Any patient who will experience an adverse event may be withdrawn from the study 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 the 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 healthcare professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The investigator must inform the medical monitor as soon as possible of all patients who are being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

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

7.1.8. Overdose of Study Drug

Any dose of study drug, whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor. Medication errors will be captured as protocol violations or deviations depending on the error.

7.1.9. 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

Administration of IMP will be discontinued for any female patient who becomes pregnant during the study.

All pregnancies of women participating in the study that occur during the study, or within at least 5 months after the last IMP injection, 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/CRO) 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, one 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 Related to the Investigational Medicinal Products

Any administration of IMP 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

(Appendix C), or as a deviation in the patient's source documents, regardless of whether or not an adverse event occurs as a result. When meeting protocol violation criteria, all instances of incorrect IMP administration should be categorized on the CRF as "Noncompliance to investigational medicinal product (IMP)."

The following are 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. Any dose of IMP, whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.
3. Misuse: Situations where the IMP is intentionally and inappropriately used (not in accordance with the authorized product information).
4. Abuse: Persistent or sporadic, intentional excessive use of IMP that is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information.
6. Occupational exposure: Exposure to an IMP, as a result of one's professional or nonprofessional occupation.
7. Breastfeeding: Suspected adverse reactions that occur in infants after exposure to a medicinal product from breast milk.

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 is judged by the investigator as clinically significant will be recorded both on the source documentation and on the CRF as an adverse event and will be monitored as described in Section 7.1.2. An event may include a laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the patient from the study, the temporary or permanent withdrawal of IMP or medical treatment, or further diagnostic workup. (Note: Abnormal laboratory or diagnostic test results at the screening visit that preclude a patient from entering the study or receiving IMP are not considered adverse events.)

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

7.4.1. Serum Chemistry and Hematology

Clinical laboratory tests (serum chemistry and hematology) will be performed before IMP administration at the time points detailed in Table 1. Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are provided below and in Appendix H.

7.4.1.1. Serum Chemistry

The following serum chemistry tests will be performed:

- calcium
- phosphorus
- sodium
- potassium
- chloride
- CPK (at scheduled visits as noted in Table 1)
- bicarbonate or carbon dioxide
- glucose
- BUN
- creatinine
- ALT
- AST
- ALP
- total protein
- albumin
- total bilirubin
- direct bilirubin
- indirect bilirubin
- follicle stimulating hormone (FSH) level, as required

7.4.1.2. Hematology

The following hematology tests will be performed:

- hemoglobin
- hematocrit
- platelet count
- absolute neutrophil count

- WBC count and differential count
  - polymorphonuclear leukocytes (neutrophils)
  - lymphocytes
  - eosinophils (absolute values)
  - monocytes
  - basophils

7.4.2. Other Clinical Laboratory Tests

There will be no other clinical laboratory tests.

7.4.2.1. Human Chorionic Gonadotropin Tests

Human chorionic gonadotropin tests in serum will be performed for all women who did not seamlessly rollover to the OL extension. This will be performed at screening visit 0. Urine pregnancy tests will be performed at baseline, before study drug injection at each administration visit, at EOT or early withdrawal, and at home for the follow-up telephone assessment. Administration of IMP will be discontinued for any female patient who becomes pregnant during the study. Procedures for reporting the pregnancy are provided in Section 7.2.

7.5. Electrocardiography

A 12-lead ECG will be conducted at screening (visit 0), visit 1, and EOT or early withdrawal visit. ECGs should be obtained before other assessments (eg, blood draw and pulmonary function testing) and study drug administration. Standard ECG parameters will be recorded using the site's equipment, and the ECG will be interpreted locally by the Principal Investigator (or qualified physician) as normal or abnormal. If the ECG is read as abnormal, the Principal Investigator will indicate whether or not the abnormality is clinically significant (yes or no) and write in the detailed interpretation/diagnosis. Clinically significant abnormal ECG findings at baseline and screening should be recorded as part of the medical history. Any ECG finding that is judged by the investigator as a clinically significant change compared with a baseline value will be considered an adverse event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.

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

7.6. Physical Examinations

Physical examinations, including height and weight, will be performed at the time points detailed in Table 1. Any physical examination finding that is judged by the investigator as clinically significant (except at the screening visit) will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

A full physical examination (performed before spirometry) will include at a minimum the following organ systems: general appearance; head, eyes, ears, nose, and throat (HEENT); chest and lung; heart; abdomen; musculoskeletal; skin; lymph nodes; and neurological.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.7. Vital Signs

Vital signs (blood pressure [systolic/diastolic], respiratory rate, body temperature, and pulse) will be measured at the time points detailed in Table 1. 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 rest in a supine or semi-erect/seated position 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 value, 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 both on the source documentation and the CRF as an adverse event and will be monitored as described in Section 7.1.2.

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

7.8. Assessment of Local Tolerability and Pain

Local tolerability at the injection site (eg, pain, erythema, and swelling) will be evaluated.

The following procedures/assessments will be performed during and after administration of study drug:

- Patients will be observed for 1 hour after study injection.
- Evaluation of injection site for reaction will be performed at approximately 1 hour after dosing using the injection site CRF. Clinically significant injection site reactions should be recorded as an adverse event.

8. OTHER ASSESSMENTS

8.1. Immunogenicity Testing

Immunogenicity of reslizumab sc administration will be assessed by qualified study personnel by evaluating the following:

- ADA measurement at baseline and at weeks 8, 24, and 36 or early withdrawal visit to evaluate the long-term immunogenicity of sc reslizumab
- ADA measurement at EOS visit (19 weeks after final dose) to evaluate immunogenicity after study drug washout

Blood samples (5 mL) for the assessment of ADA response will be taken before dosing at the time points indicated in Table 1. A blood sample will also be collected in the event of withdrawal from the study or upon observation of any severe hypersensitivity reaction (eg, anaphylaxis). An unscheduled sample can also be drawn after a serious adverse event if the investigator or sponsor considers appropriate. Drug levels may be measured in the serum samples collected for ADAs to help inform ADA analysis.

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, custom identification (ID), and nominal visit. Blood samples will be left standing upright at room temperature (20°C to 25°C) to clot for approximately 30 to 60 minutes. Samples should then be centrifuged at a minimum of 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 maintain ambient temperature during centrifugation.

Separated serum will be transferred, in approximately equal portions, into 2 labeled cryovial tubes (primary Aliquot A and back-up Aliquot B) and stored in an ultra-low freezer at –65°C or lower until they are shipped to a central or bioanalytical laboratory with temperature monitoring. Sample labels should include patient number, custom ID, study number, nominal visit or week, and indication that it is an ADA sample aliquot (A or B). Storage at –15°C to –20°C should not exceed 60 days if a freezer with a temperature of –65°C or lower is not available. The listed temperatures must be maintained. The actual times and dates of sampling will be recorded on the CRF.

8.1.1. Shipment and Analysis of Samples

Serum samples for immunogenicity assessments for all patients will be shipped from the investigational center to the central laboratory, where they will be stored until shipped to the sponsor or its designee for analysis. Samples will be stored in an upright position at ≤–65°C 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. Aliquot 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.

Aliquot set B samples will either be sent to the same laboratory as that for aliquot 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 for ADA using appropriately validated methods. The ADA serum samples may be used to measure serum drug concentration if necessary to help ADA analysis. 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 ADAs are provided in the investigator laboratory manual and its associated specimen collection summary. Further details can be found in Appendix P.

8.2. Pharmacokinetic Assessment

Pharmacokinetic parameters will be assessed in the context of ADA samples in this study.

8.3. Pharmacodynamics Assessment

See below in “Assessment of Biomarker” section.

8.4. Assessment of Biomarkers

Biomarker measures will include blood eosinophil data, measured at the time points indicated in Table 1. Details of blood sampling and preparation are described in the Laboratory Manual provided in the study file documents. Summaries will be provided, if appropriate.

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

The sample size for this OL extension study is not based on power considerations. The sample size is determined by the number of patients anticipated to rollover from the 2 double-blind, placebo-controlled, Phase 3 studies of reslizumab sc (Studies 30025 and 30027).

Approximately 360 patients will be enrolled in this OL extension study. The objective of this study is primarily safety oriented; therefore, no formal hypothesis testing is planned. Patients completing at least the full treatment periods of Studies 30025 and 30027 (or through at least the early follow-up visit for adolescents from Study 30025) and meeting the protocol's inclusion criteria and none of the exclusion criteria are eligible for enrollment in this study. It is estimated that the majority of patients enrolled in eligible reslizumab safety and efficacy studies will rollover to this OL extension study.

9.2. Analysis Sets

9.2.1. Enrolled Analysis Set

The enrolled analysis set will include all enrolled patients, regardless of whether or not a patient took any dose of reslizumab. A patient is considered enrolled according to the status reported in the database. The set of enrolled patients will be used for study population summaries.

9.2.2. Safety Analysis Set

The safety analysis set will include all patients who received at least 1 dose of reslizumab in this study. The primary analysis population for both safety and efficacy summaries will be the safety analysis set.

9.3. Data Handling Conventions

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

9.3.1. Handling Withdrawals and Missing Data

Missing data will not be imputed, unless otherwise specified.

9.4. Study Population

The enrolled analysis set (Section 9.2.1) will be used for all study population summaries, unless otherwise specified. Summaries will be presented for all patients. For continuous variables,

descriptive statistics (number [n], mean, standard deviation [SD], standard error [SE], median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

9.4.1. Patient Disposition

Data from patients screened, from patients screened but not treated, from patients in the safety analysis set, from patients who completed the study, and from patients who withdrew from the study will be summarized using descriptive statistics. Data from patients who withdrew from the study will also be summarized by reason for withdrawal.

9.4.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, comorbidities, and prior and concomitant medications, will be summarized using descriptive statistics.

9.5. Efficacy Analysis

The safety analysis set (Section 9.2.2) will be used for all efficacy analyses unless otherwise noted. Summaries will be presented for all patients. For continuous variables, descriptive statistics (n, mean, SD, SE, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

9.5.1. Efficacy Endpoints

The secondary objective of this study and the secondary endpoints are listed in Section 2.1.

9.5.2. Planned Method of Analysis

All analyses will be descriptive. No inferential statistics are planned. Efficacy assessments will be summarized by time point using descriptive statistics. Baseline for clinic-based efficacy variables measured and summarized over time will be defined as the last observation recorded before administration of the first dose of reslizumab in this OL extension study. Baseline for diary-based efficacy variables will be defined as the average of the values over the 7 days preceding the first dose of reslizumab in this OL extension study.

9.6. Safety Analysis

Safety analyses will be performed on the safety analysis set (see Section 9.2.2).

Safety assessments and time points are provided in Table 1. For all clinic-based safety variables measured and summarized over time, baseline will be defined as the last observation recorded before administration of the first dose of reslizumab in the OL extension study.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to test IMP (ie, reasonable possibility; see Section 7.1.4) (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from

the study. Summaries will be presented for all patients. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

For continuous variables of safety measures, descriptive statistics (n, mean, SD, 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.

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 reslizumab.

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.

9.7. Immunogenicity Analysis

The immunogenicity assessments for this study include the following:

- ADA measurement at baseline and at weeks 8, 24, and 36 or early withdrawal visit to evaluate the long-term immunogenicity of sc reslizumab
- ADA measurement at EOS visit (19 weeks after the final dose) to evaluate immunogenicity after study drug washout

ADA status will be listed. ADA status will be correlated with variables of safety, if appropriate.

9.8. Pharmacokinetic Analysis

Pharmacokinetic parameters will be assessed in the context of ADA samples in this study.

9.9. Pharmacodynamics Analysis

See below in “Biomarker Analysis” section.

9.10. Biomarker Analysis

Biomarker results (eosinophil counts) will be summarized using descriptive statistics.

9.11. Planned Interim Analysis

There will be a planned data cut with statistical output produced before the supplemental Biologics License Application submission.

9.12. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in the 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. QUALITY CONTROL AND QUALITY ASSURANCE

Refer to Appendix C for information regarding quality control and quality assurance. This includes information about protocol amendments, deviations and violations, responsibilities of the investigator to study personnel, study monitoring, and audit and inspection.

11. COMPLIANCE STATEMENT

This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline for 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 GCP in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

The investigator is responsible for performing the 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 by 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 IMP as described in the IB or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the clinical study at that investigational center and for contacts with study management, with the IEC/IRB, and with competent authorities.

See Appendix D for the ethics expectations of informed consent or assent, competent authorities and IEC and IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.

12. DATA MANAGEMENT AND RECORD KEEPING

See Appendix T for information regarding data management and record keeping. This includes direct access to source data and documents, data collection, data quality control, and archiving of CRFs and source documents.

13. 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 IMP is delivered.

The patients in this clinical study are 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, inter alia, are 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 (21CFR54), the investigator will provide the sponsor with financial information required to complete the FDA Form 3454. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

14. PUBLICATION POLICY

See Appendix U for information regarding the publication policy.

15. REFERENCES

Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al; SIRIUS Investigators. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014;371(13):1189-97.

Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized Phase 3 study. Chest 2016;150(4):789-98.

Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med 2011;184(10):1125-32.

Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, Phase 3 trials. Lancet 2015;3(5):355-66.

Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. Chest 2016;150(4):799-810.

Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma—Summary Report 2007. National Asthma Education and Prevention Program. National Institutes of Health, Washington (DC).

Foster PS, Hogan SP, Ramsay AJ, Matthaei KI, Young IG. Interleukin 5 deficiency abolishes eosinophilia, airways hyperreactivity, and lung damage in a mouse asthma model. J Exp Med 1996;183(1):195-201.

The Global Asthma Report 2014. Auckland, New Zealand: Global Asthma Network, 2014.

Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2016. Available at: http://www.ginasthma.org. Accessed 06 June 2016.

Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 2009;360(10):973-84.

Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax 1992;47(2):76-83.

Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14(4):902-7.

Molfino NA, Nowak R, Silverman RA, Rowe BH, Smithline H, Khan F, et al. Reduction in the number and severity of exacerbations following acute severe asthma: results of a placebo-controlled, randomized clinical trial with benralizumab. Am J Respir Crit Care Med 2012;185:A2753.

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

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

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

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

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

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

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

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

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

Zeiger RS, Schatz M, Li Q, Solari PG, Zazzali JL, Chen W. Real-time asthma outreach reduces excessive short-acting β2-agonist use: a randomized study. J Allergy Clin Immunol Pract 2014;2(4):445-56.

Appendix A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted] Teva Branded Pharmaceutical Products R&D, Inc Tel: [redacted]
Legal Representative of the Sponsor in the European Union	[redacted] Teva GmbH Graf-Arco-Str. 3, Ulm. 89079. Germany Tel: [redacted]
Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study	[redacted] Tel: [redacted] (24-hour access)
Study Principal Investigator	[redacted] France Tel: [redacted]
Sponsor's Representative of Global Patient Safety and Pharmacovigilance For **serious adverse events:** Send by email to the local safety officer/contract research organization (LSO/CRO). The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.	[redacted] Teva Branded Pharmaceutical Products R&D, Inc Tel: [redacted]
Contract Research Organization	[redacted]

Central Clinical Laboratory	[redacted]
Central Institutional Review Board (IRB)	[redacted]
Electronic Data Capture	[redacted]
Bioanalytical Pharmacokinetics Evaluation	Teva Pharmaceuticals Biologics Assays and Technology West Chester, PA 19380
Bioanalytical Immunogenicity Evaluation	Teva Pharmaceuticals Biologics Assays and Technology West Chester, PA 19380
Randomization and Trial Supply Management (RTSM) vendor	[redacted]
Handheld Device & eDiary	[redacted]

APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

1. **Procedures at Screening (Visit 0, Week -2 to Week -1) – Patients with a gap between Study 30025 or 30027 and Study 30066**

NOTE: seamless rollover patients are those who have their screening/baseline visit for Study 30066 conducted on the same day as the end-of-treatment (EOT, week 52 or week 24, respectively) visit for either Study 30025 or 30027.

Patients who **did not** rollover seamlessly from Study 30025 or 30027 (had a gap between placebo-controlled study EOT and screening for Study 30066 [including adolescents from Study 30025 who must also complete the early follow-up visit before they are eligible to rollover to Study 30066]) will be seen first at an earlier screening visit (visit 0, week -2 to week -1) in order to complete informed consent and eligibility criteria procedures before completing all other procedures and investigational medicinal products (IMPs) administration at visit 1. Adolescents (a patient 12 through <18 years of age) from Study 30025 can complete the V0 screening visit of Study 30066 the same day as the 12-week early follow-up visit for Study 30025. Additionally, any patient who did not rollover seamlessly from Study 30025 or 30027 will participate in a 7-day run-in period where baseline measures for asthma control and spirometry will be established. The screening period (including run-in) will be up to a maximum of 14 days.

Any blood tests completed by adolescents at the 12-week early follow-up visit for Study 30025 can be used for the V0 screening visit of Study 30066 and do not need to be repeated.

The following procedures will be performed at visit 0, week -2:

- Obtain written informed assent/consent before any other study-related procedures are performed.
- Review medication history.
- Review inclusion/exclusion criteria.
- Perform human chorionic gonadotropin tests in serum (for female patients who are not postmenopausal or surgically sterile only).
- Perform hematology tests.
- Perform serum chemistry tests with creatine phosphokinase (CPK).
- Perform full physical examination (should include the following organ systems: general appearance; head, eyes, ears, nose, and throat (HEENT); chest and lung; heart; abdomen; musculoskeletal; skin; lymph nodes; and neurological).
- Perform electrocardiogram (ECG).
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Measure height and weight.

- Assess asthma exacerbations and related healthcare utilization (HCU).
- Perform adverse event inquiry.
- Perform concomitant medication inquiry (includes assessment of oral corticosteroid (OCS) dose if participants are on maintenance corticosteroids).
- Provide handheld electronic diary (eDiary)/spirometry device.

The following procedures will be performed from day -7 through day 0 (run-in period):

- Patients will use the handheld eDiary/spirometry device daily to obtain obtain peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV_1) measurements, and record rescue inhaler use. (This will provide those patients with a gap in study drug administration baseline measures for asthma control and spirometry assessments.)

2. **Procedures at Screening/Baseline (Visit 1, Week 0)**

All patients will be required to attend visit 1 at week 0. The following procedures will be performed at visit 1 at week 0 (or as part of the EOT visit of the preceding Teva-sponsored double-blind study of reslizumab for patients who seamlessly rollover) for all patients:

Patients who complete the screening assessments of informed assent/consent, medication history, and inclusion and exclusion criteria at V0 (standalone screening visit) do not need to repeat them at V1 (screening/baseline visit). Any assessments that are performed at V0 do not need to be repeated at V1 if completed within the previous 14 days.

NOTE: the assessments noted with ***** may have been done as part of the EOT visit of Study 30025 or 30027 if a patient seamlessly enters this open-label study.

- Obtain written informed assent/consent before any other study-related procedures are performed.
- Review medication history.
- Review inclusion/exclusion criteria.
- Perform urine pregnancy testing (for female patients who are not postmenopausal or surgically sterile only).*****
- Perform hematology tests.*****
- Perform serum chemistry tests with CPK and follicle stimulating hormone (FSH) (Note: FSH only as required to assess postmenopausal status).*****
- Collect blood sample for immunogenicity (anti-drug antibody [ADA]) assessment. *****
- Perform full physical examination (should include the following organ systems: general appearance, HEENT, chest and lung, heart, abdomen, musculoskeletal, skin, lymph nodes, and neurological).*****
- Perform ECG.*****

- Perform vital sign measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate). *****
- Provide handheld eDiary/spirometry device (if not provided at V0).
- Perform pre-bronchodilator spirometry (FEV_1). Patients will perform spirometry using the centralized spirometry if rolling over seamlessly from the previous double-blinded studies (Studies 30025 or 30027). If there is a gap between the EOT visit of Studies 30025 or 30027 and Visit 1 of this study, the spirometry will be performed using the handheld spirometry device. *****
    - Pre-bronchodilator spirometry assessments should only be performed after withholding short-acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule.
- Reinforce eDiary, PEF/spirometry compliance, and rescue medication use.
- Complete asthma-specific tests (Asthma Control Questionnaire [ACQ-6] and Asthma Quality of Life Questionnaire [AQLQ12+]).*****
- Assess asthma exacerbations and related HCU. *****
- Perform adverse event inquiry. *****
- Perform concomitant medication inquiry (includes assessment of OCS dose if participants are on maintenance corticosteroids). *****
- Perform IMP administration.
- Observation at the study center for 1 hour after IMP administration
- Vital sign assessment for any reported symptoms during 1-hour observation.
- Assessment of injection site by study personnel approximately 1 hour after IMP administration.

Additionally, patients will complete a question regarding new symptoms on the handheld eDiary/spirometry device the evening after the IMP administration and the following morning as well as obtain PEF and FEV_1 measurements, and record rescue inhaler use.

3. **Procedures During Administration of Investigational Medicinal Product (Open-Label Treatment Period, Visit 2 through Visit 9)**

During the OL treatment period, patients will return to the study center once every 4 weeks (±7 days) and thereafter (relative to baseline) for administration of study drug and assessments until week 32 or early withdrawal.

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

- Perform urine pregnancy testing (for female patients who are not postmenopausal or surgically sterile only).
- Perform hematology tests (weeks 8 and 24).
- Perform serum chemistry tests with CPK (weeks 4, 8, and 24).
- Collect blood sample for immunogenicity (ADA) assessment (week 8 and 24).
- Perform vital sign measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform pre-bronchodilator spirometry, including FEV_1 (week 8 and 24), using the handheld spirometry device.
    - Pre-bronchodilator spirometry assessments should only be performed after withholding short-acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule.
- Complete asthma-specific tests (ACQ-6 and AQLQ12+) (week 8 and 24 only).
- Assess asthma exacerbations and related HCU.
- Reinforce eDiary, PEF/spirometry compliance, and rescue medication use.
- Perform adverse event inquiry.
- Perform concomitant medication inquiry (includes assessment of OCS dose if participants are on maintenance corticosteroids).
- Perform IMP administration.
- Observation at the study center for 1 hour after IMP administration
- Vital sign assessment for any reported symptoms during 1-hour observation.
- Assessment of injection site by study personnel approximately 1 hour after IMP administration.

Additionally, patients will complete a question regarding new symptoms on the handheld eDiary/spirometry device the evening after the IMP administration and the following morning as well as obtain PEF and FEV_1 measurements, and record rescue inhaler use.

4. **Procedures at End of Treatment or Early Withdrawal (V_{EOT}, Week 36)**

An EOT visit (week 36 ±7 days, [V_{EOT}]) will occur 4 weeks after the final administration of study drug or at the time of early withdrawal of the patient. The following procedures/assessments will be performed at this visit:

- Perform urine pregnancy testing (for female patients who are not postmenopausal or surgically sterile only).

- Perform hematology tests.
- Perform serum chemistry tests with CPK.
- Collect blood sample for immunogenicity (ADA) assessment.
- Perform full physical examination (should include the following organ systems: general appearance, HEENT, chest, lung, and heart, abdomen, musculoskeletal, skin, lymph nodes, and neurological).
- Perform ECG.
- Perform vital signs measurements.
- Measure height and weight.
- Perform pre-bronchodilator spirometry (FEV_1) using the handheld spirometry device.
  - Pre-bronchodilator spirometry assessments should only be performed after withholding short-acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule.
- Complete asthma-specific tests (ACQ-6 and AQLQ12+).
- Assess asthma exacerbations and related HCU.
- Collect handheld eDiary/spirometry device.
- Perform adverse event inquiry.
- Perform concomitant medication inquiry (includes assessment of OCS dose if participants are on maintenance corticosteroids).
- Provide urine pregnancy test for use on date of telephone follow-up assessment (V_{FU}, week 48)

5. **Procedures at Follow-up Telephone Assessment (V_{FU}, Week 48)**

The following procedures/assessments will be performed at the follow-up telephone assessment (EOT + 12 weeks ±14 days [V_{FU}]):

- Perform home urine pregnancy testing (for female patients who are not postmenopausal or surgically sterile only).
- Perform adverse event inquiry.
- Perform concomitant medication inquiry (includes assessment of OCS dose if participants are on maintenance corticosteroids).

6. **Procedures at End of Study Visit (V_{EOS}, Week 51)**

The following procedures/assessments will be performed at the end of study visit (visit 9 + 19 weeks ±14 days [V_{EOS}]):

- Collect blood sample for immunogenicity (ADA) assessment (reslizumab concentration data will be assessed from the ADA blood samples).

7. **Unscheduled Visits**

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

Procedures performed during unscheduled visits include the following:

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

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

Unscheduled blood samples for ADA assessment will also be obtained from all patients (inside and outside of the United States) experiencing a serious adverse event, an adverse event leading to withdrawal, an observation of any severe hypersensitivity reaction (eg, anaphylaxis), or an exacerbation of asthma symptoms.

If a potentially clinically significant CPK level (≥3.1× upper limit of normal [ULN]) occurs, the patient should attend an unscheduled visit for a physical examination, as well as additional testing, if indicated per investigator judgement.

APPENDIX C. QUALITY CONTROL AND QUALITY ASSURANCE

Protocol Amendments and Protocol Deviations and Violations

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 independent ethics committee/institutional review board (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.

Protocol Violations

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the patients in 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 Good Clinical Practice (GCP) guidelines; noncompliance to investigational medicinal product (IMP) administration; use of prohibited medications. Protocol violations will be identified and recorded by investigational center personnel in the case report form (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.

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.

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 Standard Operating Procedures (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 monitors 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 monitors will contact the investigator and visit the investigational center according to the monitoring plan. The study monitor will be permitted to review and verify the various records (CRFs and other pertinent source data records, including specific electronic source document relating to the study) to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

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 during the course of these monitoring visits or provided in follow-up written communication.

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 Specialty 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.

APPENDIX D. ETHICS

Informed Consent/Assent

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. 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.

The investigator, or a qualified person designated by the investigator, should fully inform the patient and <each> parent/legally acceptable representative 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 <each> parent/legally acceptable representative and the patient. The patient and <each> parent/legally acceptable representative should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.

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

Competent Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to the national competent authority and to the respective IEC/IRB for review. As required, the study will not start at a given investigational center before the IEC/IRB and competent authority (as applicable) for the investigational center give written approval or a favorable opinion.

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 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.

Registration of the Clinical Study

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

APPENDIX E. WOMEN OF CHILDBEARING POTENTIAL AND BIRTH CONTROL METHODS

The following is standard in current Teva protocols:

Contraception recommendations and pregnancy testing should encompass all investigational medicinal products (IMP)s as well as non-IMPs, eg, background therapy, and the measures to be followed should be based on the medicinal product with highest risk.

Assessment of likelihood of possible interaction between IMP or concomitant medications and hormonal contraception should be conducted. Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method, eg, CYP 4A inducers. In case of suspected interaction, hormonal contraceptive alone may not be sufficient. In the absence of clinical pharmacokinetic (PK) interaction study data in IMPs with demonstrated or suspected human teratogenicity/fetotoxicity, recommendation for use of hormonal contraceptives should be thoroughly justified by the sponsor. Additional contraceptive methods, including supplementary barrier methods, may be considered.

Women/Girls of childbearing potential are defined as:

- not surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile
- not postmenopausal

Postmenopausal women:

- 1 year postmenopausal (no menses for 12 months without an alternative medical cause plus an increased concentration of follicle stimulating hormone of more than 35 U/L) in women not using hormonal contraception or hormonal replacement therapy

Recommendations for application of birth control methods:

- IMPs with Marketing Authorisation (MA)
  - Summary of Product Characteristics (SmPC): in case of no contraception recommendations, the principles of IMPs without MA should be applied
- IMPs without MA
  - All female reproduction toxicity studies and standard battery of genotoxicity tests should be completed before the inclusion, in any clinical trial, of women of childbearing potential (WOCBP) not using highly effective birth control or whose pregnancy status is unknown (in compliance with International Counsil for Harmonisation module 2 [ICH M2])
  - Unavailable or insufficient nonclinical data should be considered as “effects detected” and the highest risk category assumed.
- IMP with demonstrated or suspected human teratogenicity/fetotoxicity
  - Highly effective contraception using methods with low user dependency

  - Contraception during treatment and until the end of relevant systemic exposure. This period should be extended by 30 days in case of genotoxicity.
  - Monthly pregnancy testing to be maintained until end of relevant systemic exposure – should be extended by 30 days in case of genotoxicity. Shorter testing intervals are to be considered depending on drug dosing schedule.
- IMP with possible human teratogenicity/fetotoxicity
  - Highly effective method of contraception
  - Contraception during treatment and until the end of relevant systemic exposure
  - Additional pregnancy testing to be considered; as a minimum, at the end of relevant systemic exposure
  - In each case of delayed menstrual period (over 1 month between menstruations) confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycles.
- IMP with unlikely risk of human teratogenicity/fetotoxicity, for which assessment of the completed necessary nonclinical studies does not indicate teratogenicity/fetotoxicity, in early pregnancy and human data are not available or do not contradict these findings or there is already sufficient evidence for lack of risk based on human data
  - An acceptable effective method of contraception unless an absence of risk of human teratogenicity/fetotoxicity in early pregnancy can be justified
  - As a minimum, contraception until treatment discontinuation

Highly effective birth control methods:

Highly effective birth control methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered. Such methods include:

- Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 7 days (for IMPs without suspected teratogenicity/genotoxicity) and 1 month (for IMPs potentially teratogenic/genotoxic) before the first dose of IMP
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 7 days (for IMPs without suspected teratogenicity/genotoxicity) and 1 month (for IMPs potentially teratogenic/genotoxic) before the first dose of IMP
- Intrauterine device and intrauterine hormone-releasing system need to be in place at least 2 months before screening
- Bilateral tubal occlusion and vasectomized partner provided he is the sole sexual partner and has received medical assessment of the surgical process

- Sexual abstinence is **only** considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.
- Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are **not** acceptable methods of contraception (according to Medicines and Healthcare Products Regulatory Agency).

Acceptable birth control methods:

Acceptable birth control methods that result in a failure rate of more than 1% per year include: progestogen-only oral hormonal contraception for which the inhibition of ovulation is not the primary mode of action; male or female condom with or without spermicide; cap, diaphragm, or sponge with spermicide. The combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable but not highly effective methods of birth control.

Unacceptable birth control methods:

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

Male contraception:

Male patients must always use a condom, except in cases of no genotoxicity or demonstrated or suspected human teratogenicity/fetotoxicity.

Vasectomy:

Use of contraceptive methods applies also to vasectomized men, because of the risk associated with transfer of a drug via seminal fluid.

Contraception for female partners of male study participants:

Female partners of male study participants must use contraception for non-pregnant WOCBP partner until the end of relevant systemic exposure in case of IMPs with genotoxicity or IMPs with no genotoxicity but demonstrated or suspected human teratogenicity/fetotoxicity.

Pregnancy tests in women of childbearing potential:

1. Conduct monthly pregnancy testing from first dose of IMP until last dose of IMP and additional 30 days in case the IMP does not have a marketing authorization and has suspected human teratogenicity/genotoxicity/fetotoxicity. Conduct monthly pregnancy testing and in case the IMP has a marketing authorization, if the IMP has a demonstrated or suspected human teratogenicity/genotoxicity/fetotoxicity according to SmPC. Shorter testing intervals are to be considered depending on drug dosing schedule.
1. Consider additional pregnancy testing, but at least at the end of relevant systemic exposure, in case of possible human teratogenicity/fetotoxicity. This refers to IMPs, for which human data on pregnancies is limited or not available, there is no suspicion of human teratogenicity based on class effects or genotoxic potential, and nonclinical

reproductive toxicity studies of relevance for early human pregnancy show positive findings that do not generate a strong suspicion of human teratogenicity/ fetotoxicity.

2. For IMPs with unlikely risk of human teratogenicity/fetotoxicity, additional pregnancy testing is generally not necessary. This refers to IMPs for which assessment of the completed necessary nonclinical studies does not indicate teratogenicity/ fetotoxicity in early pregnancy and human data are not available or do not contradict these findings or there is already sufficient evidence for lack of risk based on human data.

APPENDIX F. LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the investigational center.

The following actions must be taken if a patient fails to return to the investigational center for a required study visit:

- The investigational center must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up'.

APPENDIX G. TOTAL BLOOD VOLUME

The total blood volume to be collected for each patient in this study is approximately 52 mL.

Total Blood Volumes

Type of samples	Volume per sample (mL)	Total number of samples	Total volume (mL)
Hematology (CBC with differential)	2 mL	5	10 mL
Serum chemistry tests with CPK	2 mL	6	12 mL
ADA	5 mL	5	25 mL
ADA Unscheduled	5 mL	1	5 mL
Total 1			**52 mL**

ADA= anti-drug antibody; CBC=complete blood count; CPK=creatine phosphokinase; mL=milliliters.

APPENDIX H. CLINICAL LABORATORY TESTS

Clinical Laboratory Tests

Serum Chemistry	Hematology and Coagulation	Urinalysis
calcium phosphorus sodium potassium chloride creatine phosphokinase (CPK) bicarbonate or carbon dioxide glucose blood urea nitrogen (BUN) creatinine alanine aminotransferase (ALT) aspartate aminotransferase (AST) alkaline phosphatase (ALP) total protein albumin total bilirubin direct bilirubin indirect bilirubin follicle stimulating hormone (FSH), as required	hemoglobin hematocrit platelet count absolute neutrophil count WBC count and differential count -polymorphonuclear leukocytes (neutrophils) -lymphocytes -eosinophils (absolute values) -monocytes -basophils Human chorionic gonadotropin (HCG)	None

APPENDIX I. GLOBAL INITIATIVE FOR ASTHMA ICS CLINICAL COMPARABILITY TABLE

Post-Text Table 1: Rationale Medium or Higher Daily Doses of Inhaled Corticosteroids in Patients 12 Years and Older

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

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

APPENDIX J. ASTHMA CONTROL DIARY (ELECTRONIC DIARY)

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

Handheld Spirometer

- You will need to perform your forced expiratory volume in 1 second (FEV_1) and peak expiratory flow (PEF) reading every morning using the handheld spirometer.
- You will need to perform your PEF every evening using the handheld spirometer.
- Blow into your handheld spirometer 3 times in the morning and 3 times in the evening.

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

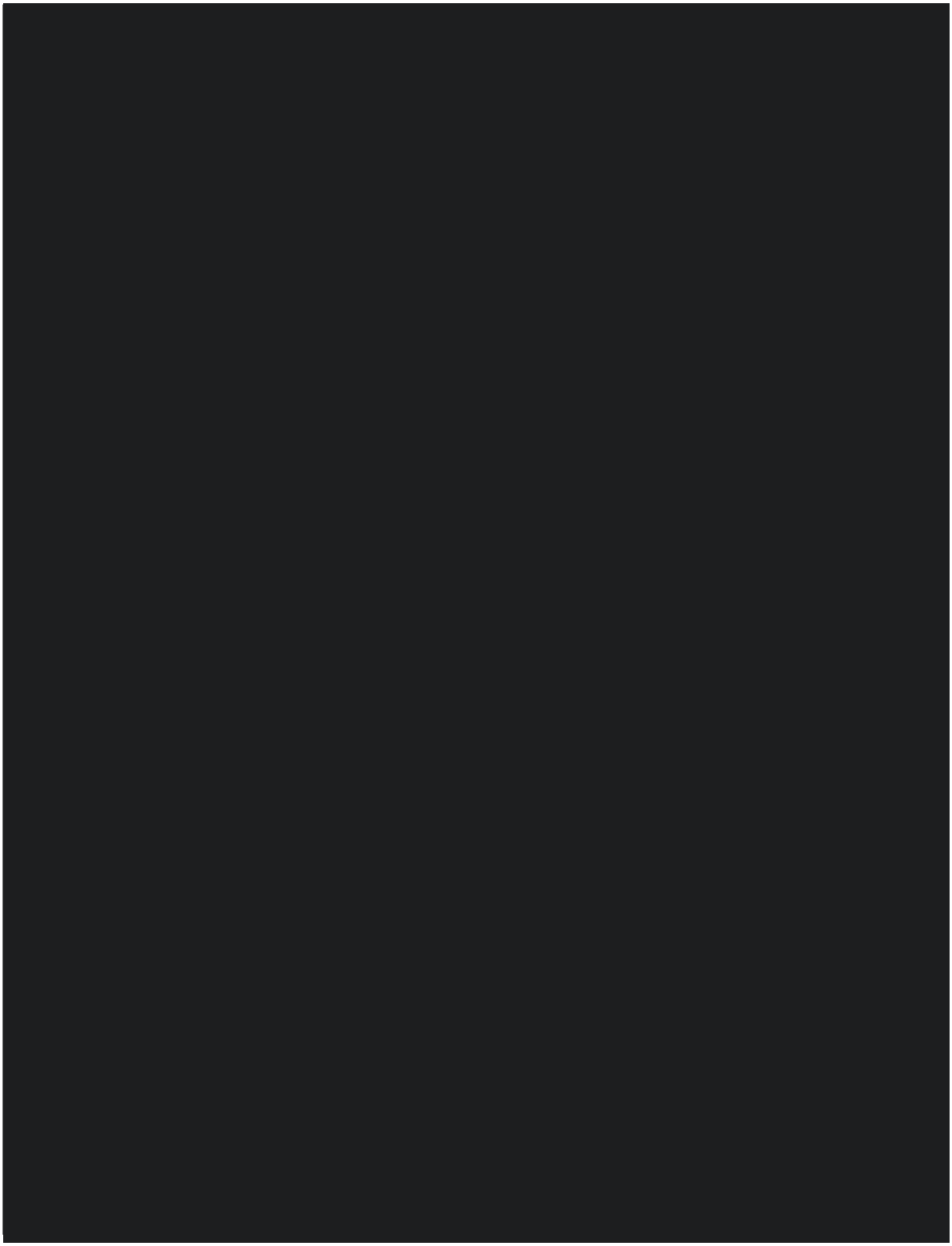
Total number of puffs (daily):

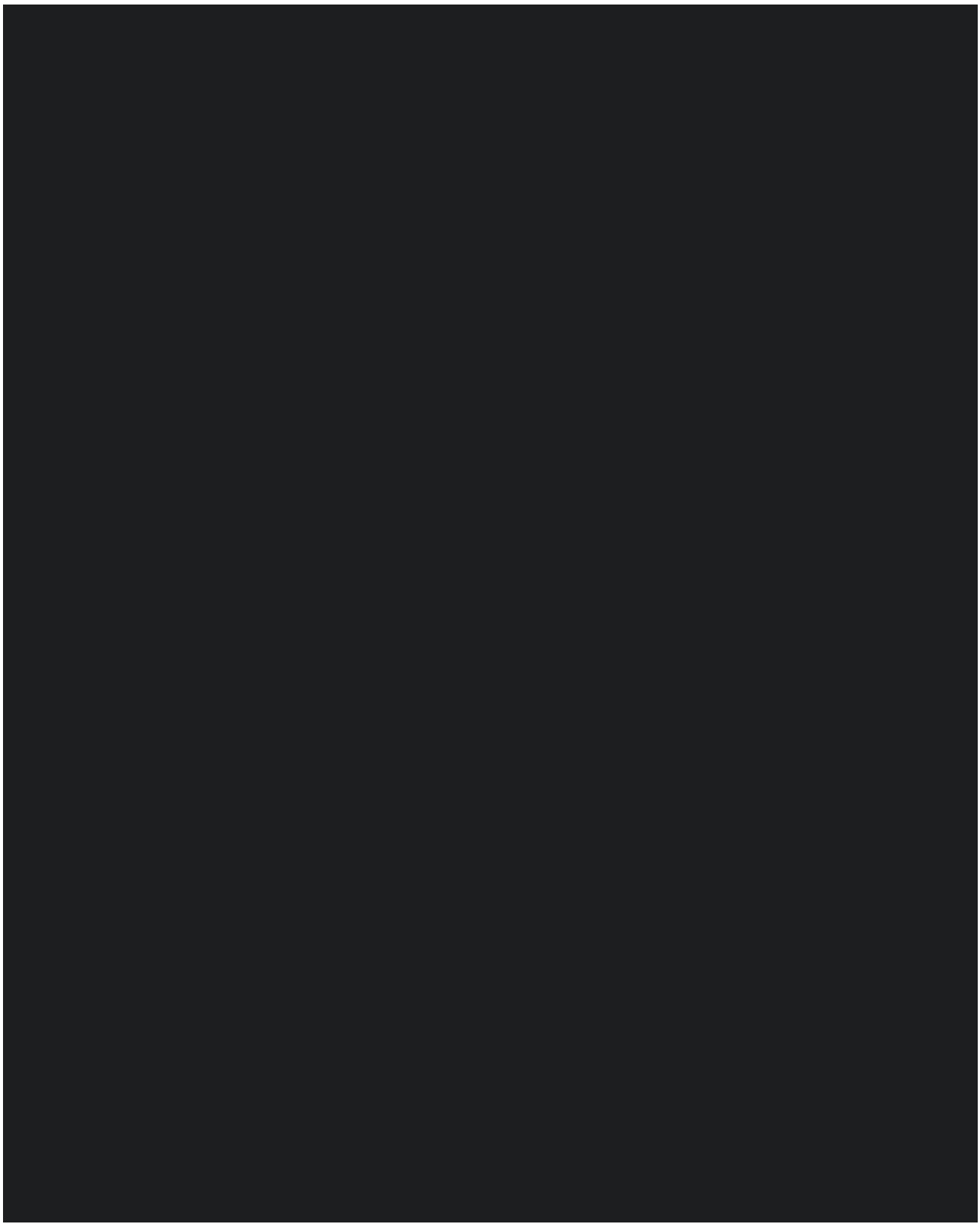
Symptoms Post-injection:

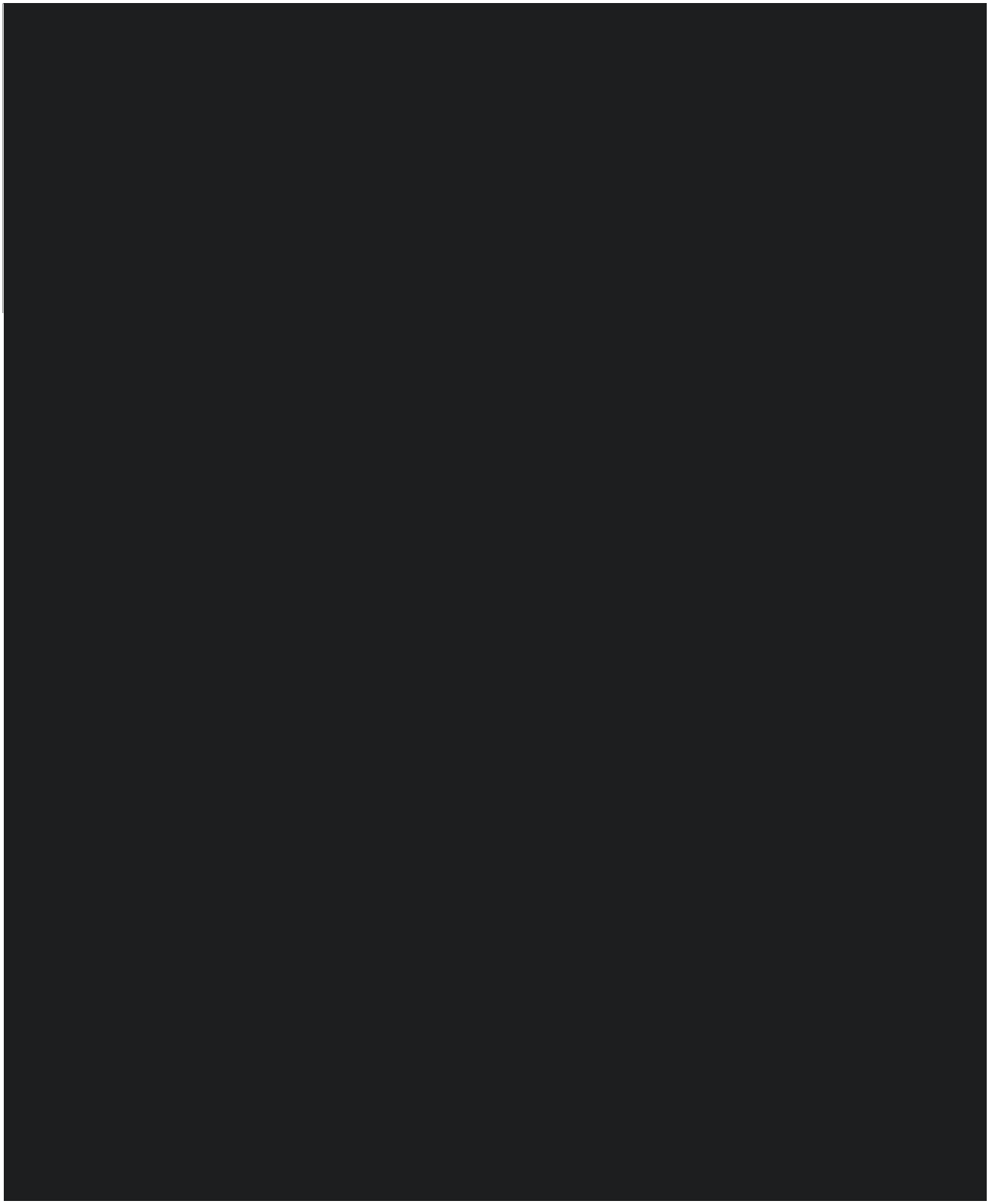
- Have you received a study medication injection within the last 24 hours?
- Have you experienced any new symptoms since the study drug injection?

APPENDIX K. ASTHMA CONTROL QUESTIONNAIRE

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

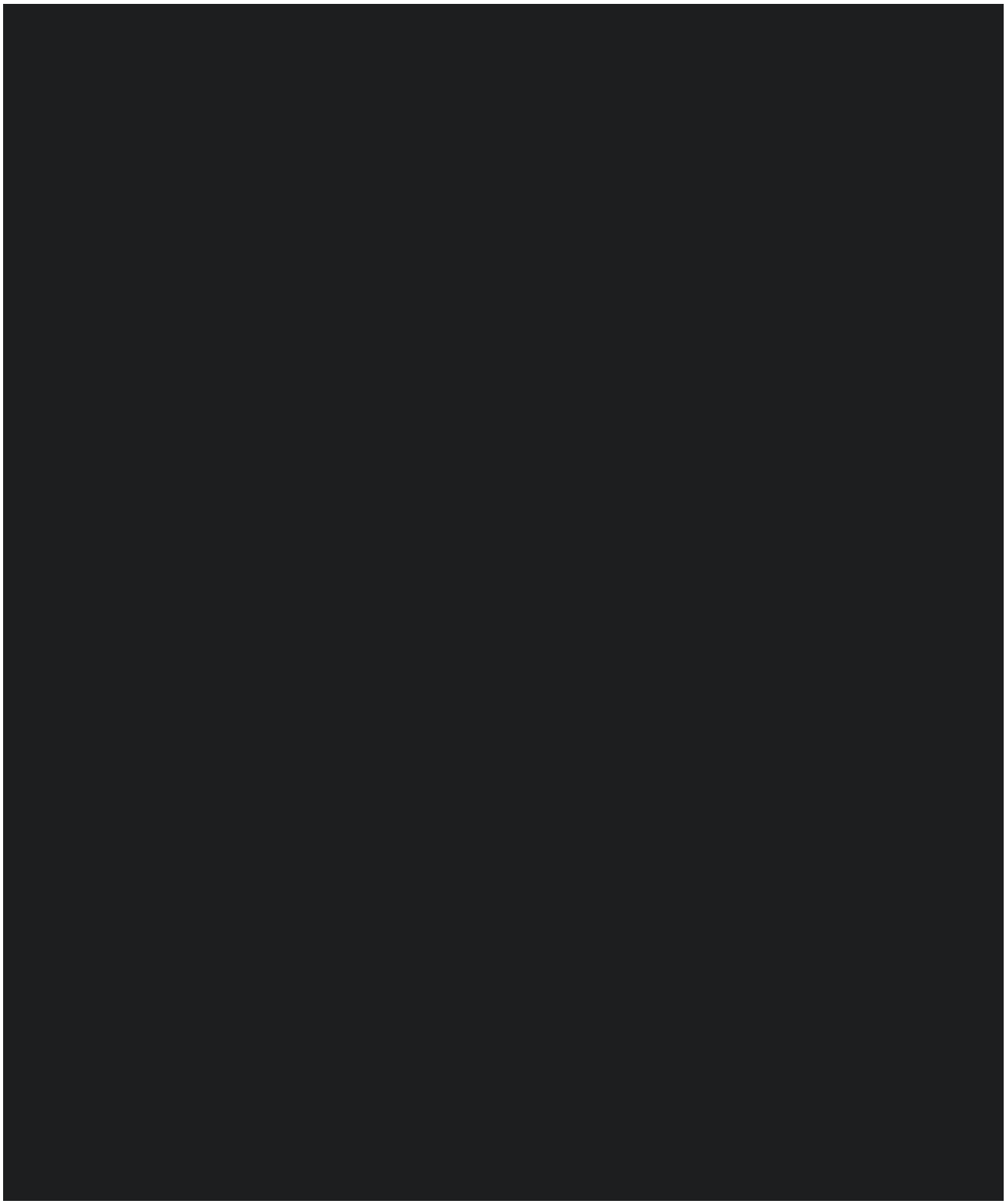


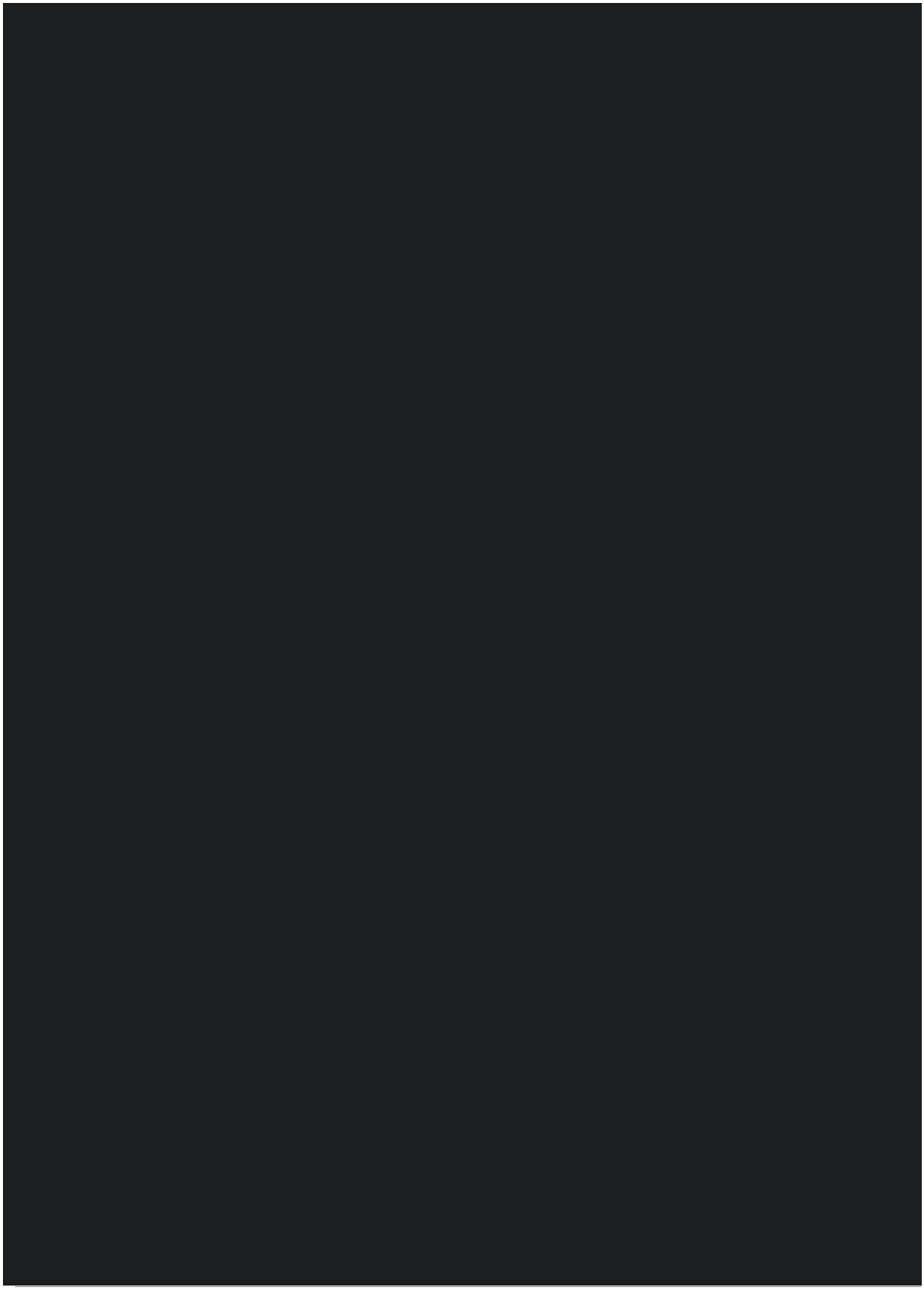


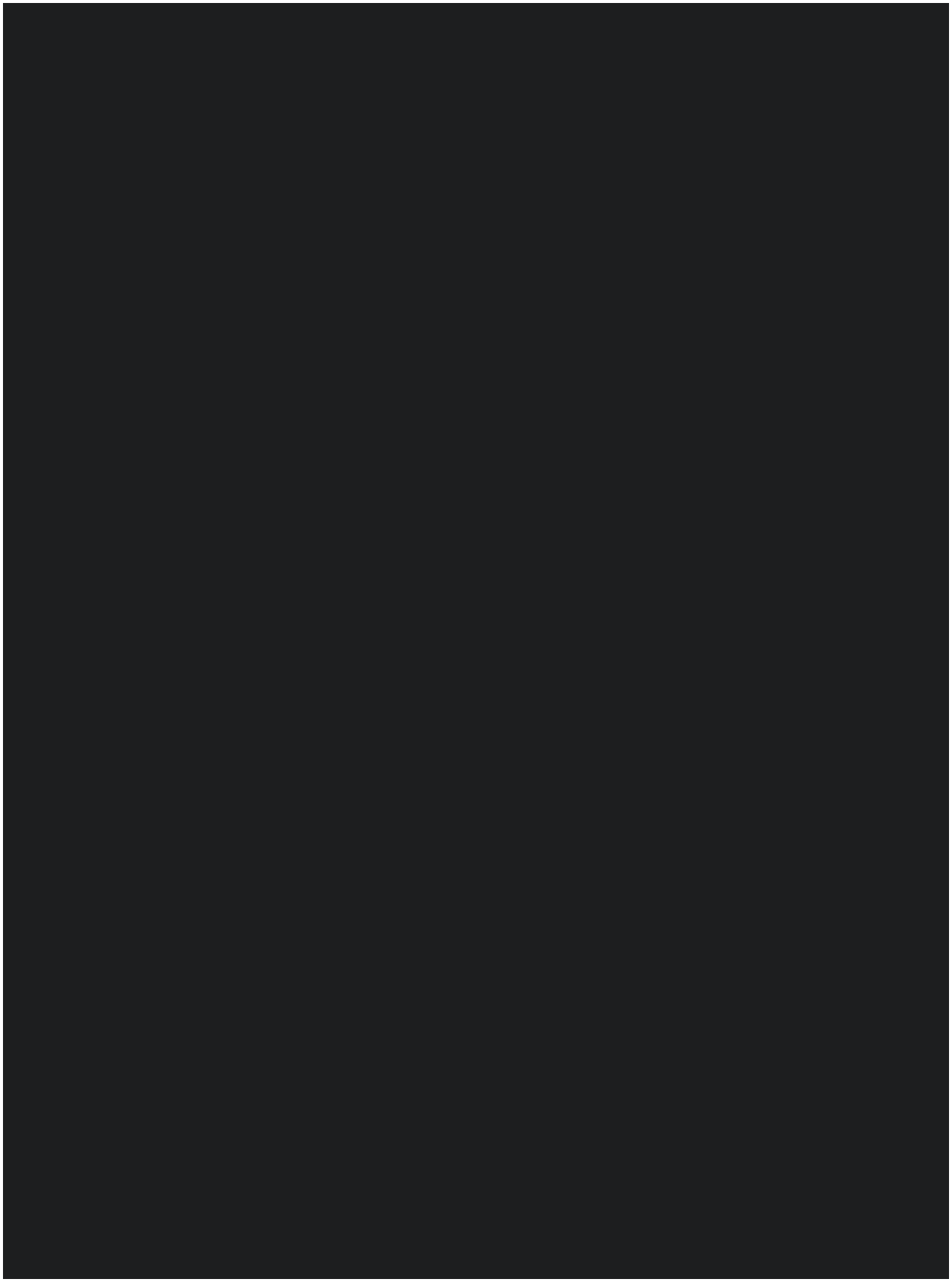


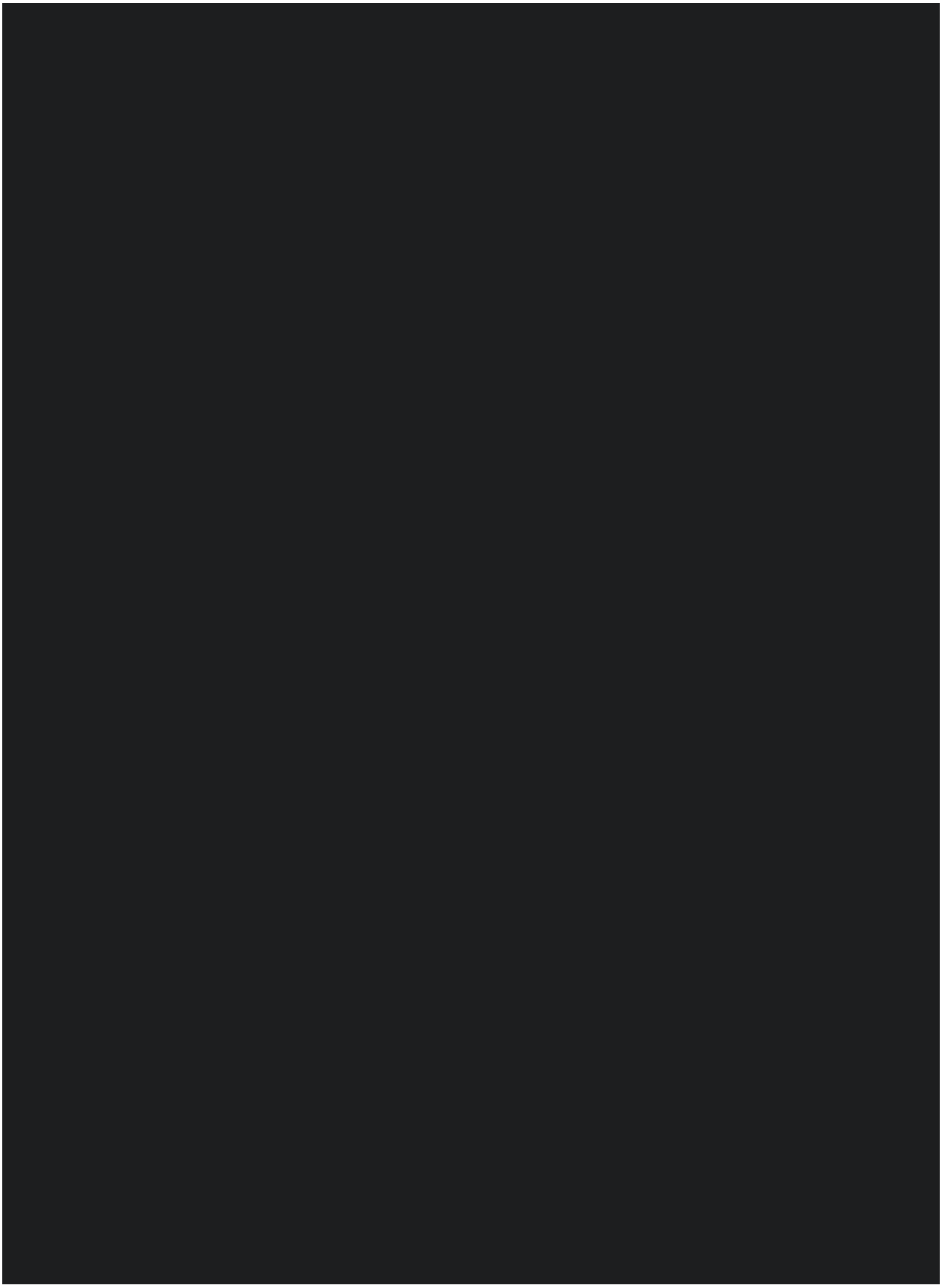
APPENDIX L. ASTHMA QUALITY OF LIFE QUESTIONNAIRE

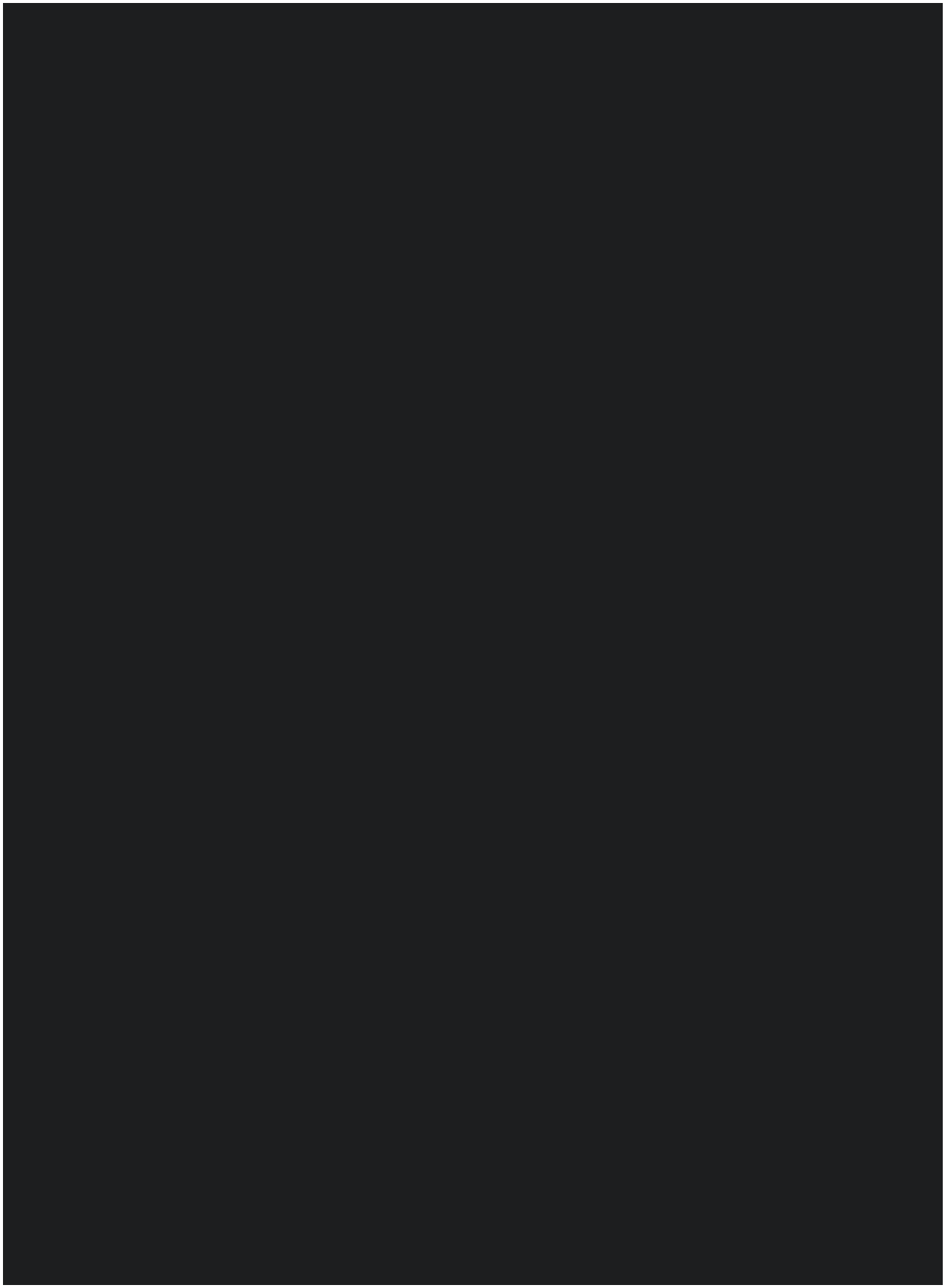
(Sample provided in this appendix is for reference only.)

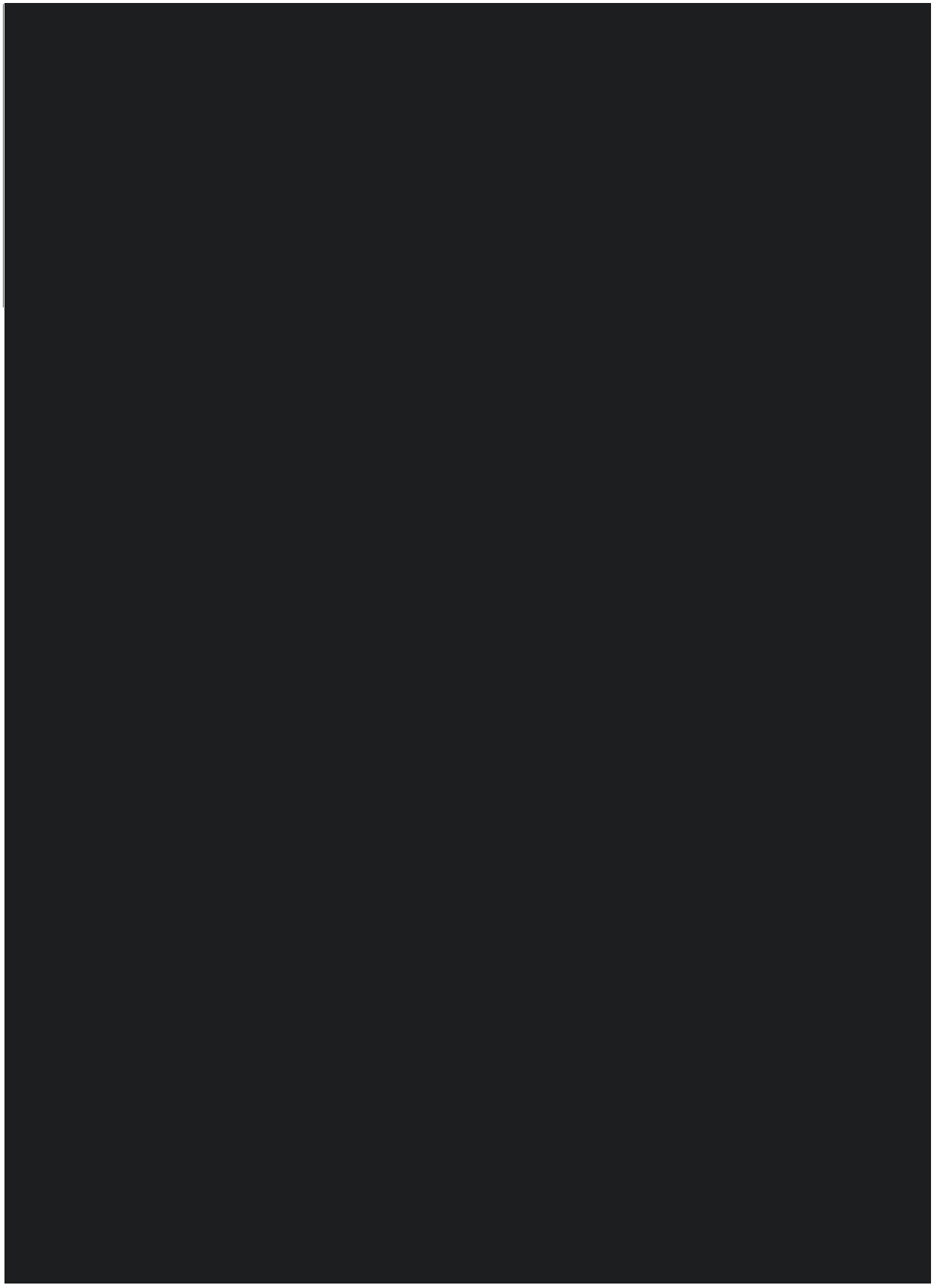












APPENDIX M. OPPORTUNISTIC INFECTIONS

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

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

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

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

APPENDIX N. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

Anaphylaxis is highly likely when any 1 of the following 3 criteria are fulfilled:

a. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips, tongue, or uvula) AND AT LEAST 1 OF THE FOLLOWING
   - Respiratory compromise (eg, dyspnea, wheeze, bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
   - Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

b. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   - Involvement of the skin/mucosal tissue (eg, generalized hives, itch, flush, swollen lips, tongue, or uvula)
   - Respiratory compromise (eg, dyspnea, wheeze, bronchospasm, stridor, reduced PEF, hypoxemia)
   - Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   - Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

c. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   - Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

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

APPENDIX O. PHARMACODYNAMICS SAMPLES

Pharmacodynamics is not evaluated in this study.

APPENDIX P. IMMUNOGENICITY SAMPLES

Immunogenicity procedures are discussed in Protocol Section 8.1. Additional information is available in the clinical laboratory manual.

APPENDIX Q. EXPLORATORY BIOMARKERS SAMPLES

Exploratory biomarkers are not evaluated in this study.

APPENDIX R. PHARMACOGENETIC ASSESSMENTS

Pharmacogenomics is not evaluated in this study.

APPENDIX S. PRODUCT COMPLAINTS

Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical IMP supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product 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 complaint by completing the product complaint form provided by Teva and emailing it to [redacted] within 48 hours of becoming aware of the issue.

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

1. **Product Complaint Information Needed from the Investigational Center**

In the event that the product complaint form cannot be completed, the investigator will provide the following information, as available:

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

- description or nature of complaint
- associated serious adverse event Yes/No
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

Note: Reporting a product 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 obtain any outstanding information.

2. **Handling of Investigational Medicinal Product(s) at the Investigational Center(s)**

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 IMP.

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

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).

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.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

APPENDIX T. DATA MANAGEMENT AND RECORD KEEPING

Direct Access to Source Data and Documents

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 by other 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 but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management).

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. The investigator must maintain a confidential patient identification list that allows the unambiguous identification of each patient.

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 (USA) and documents of other concerned competent authorities. Before using the CDMS, it will be fully validated and 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.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data, electronic patient-reported outcome [ePRO] tablet), these data will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management). 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.

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.

Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. 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.

Data will be verified by the study monitor using the data source, and reviewed by Data Management using both automated logical checks and manual review. Data identified as erroneous, or data that are missing, will be referred to the investigational center for resolution through data queries. 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 and any discrepancies will be queried.

Applicable terms will be coded according to the coding conventions for this study.

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. 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.

Archiving of Case Report Forms and Source Documents

Sponsor Responsibilities

The original CRFs will be archived by the sponsor. Investigational center-specific CRFs will be provided to the respective investigational centers for archiving.

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, handheld eDiary/spirometry device)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the IMPs
- 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.

APPENDIX U. PUBLICATION POLICY

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 results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results: "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. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual investigational center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements:

- 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.

Citation: International Committee of Medical Journal Editors (ICMJE). Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Available at: http://www.icmje.org/recommendations/. Accessed 02 July 2014.