Statistical Analysis Plan

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 C38072-AS-30066

NCT03052725

Approval Date: 26 June 2017

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Phase 3

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Sponsor

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

Prepared by: [redacted]

STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: **C38072-AS-30066**

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

Statistical Analysis Plan for:

- ☒ **Interim Analysis**
- ☒ **Final Analysis**
- ☐ **Integrated Summary of Efficacy**
- ☐ **Integrated Summary of Safety**

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TABLE OF CONTENTS

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LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ACQ-6	Asthma Control Questionnaire
ADA	Anti-drug Antibody
AE	Adverse Event
ALT	Alanine Aminotransferase
AM	Morning
AQLQ12+	Asthma Quality of Life Questionnaire
AST	Aspartate Aminotransferase
BLA	Biologics License Application
BP	Blood Pressure
CAE	Clinical Asthma Exacerbation
CBC	Complete Blood Count
CPK	Creatine Phosphokinase
CRF	Case Report Form
CSR	Clinical Study Report
DOR	Day of randomization
ECG	Electrocardiogram
EOT	End of Treatment
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 Second
HCU	Healthcare Utilization
HEENT	Head, Eyes, Ears, Nose, and Throat
HLGT	High Level Group Term
HLT	High Level Term
ICU	Intensive Care Unit
IMP	investigational medicinal product
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LLT	Low Level Term
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing Antibody
NHANES	National Health and Nutrition Examination Survey
OCS	Oral Corticosteroid

OL	Open Label
PCS	Potentially Clinically Significant
PD	Pharmacodynamics
PEF	Peak Expiratory Flow
PK	Pharmacokinetics
PM	Evening
PP	Per-Protocol
PT	Preferred Term
SABA	Short-Acting Beta-Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis Software
sBLA	Supplemental Biologics License Application
sc	Subcutaneous
SCS	Summary of Clinical Safety
SD	Standard Deviation
SE	Standard Error
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TB	Tuberculosis
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Teva Branded Pharmaceutical Products R&D, Inc. study C38072-AS-30066, An Open-Label (OL) Extension Study of Reslizumab 110-mg Fixed, Subcutaneous Dosing in Patients 12 Years of Age and Older with Severe Eosinophilic Asthma, and was written in accordance with SOP GBP_RD_702 (Statistical Analysis Plan).

The reader of this SAP is encouraged to read the study protocol for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for completing the participation of a patient in this study.

The SAP is intended to be in agreement with the protocol, especially with regards to the primary and all secondary endpoints and their respective analyses. However, the SAP may contain more details regarding these particular points of interest, or other types of analyses (e.g. other endpoints). When differences exist in descriptions or explanations provided in the study protocol and this Statistical Analysis Plan, the Statistical Analysis Plan prevails; the differences will be explained in the Clinical Study Report (CSR).

1. STUDY OBJECTIVES AND ENDPOINTS

1.1. Primary and Secondary Study Objectives and Endpoints

The primary objective of this study is to support the long-term safety of reslizumab 110 mg administered subcutaneous (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 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 Corticosteroid (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) 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

1.2. Exploratory/Other Objectives and Endpoints

No tertiary or other exploratory endpoints.

2. STUDY DESIGN

2.1. General Design

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), followed by an OL treatment period, an EOT visit (VEOT), a follow-up telephone call (VFU) at 12 weeks after the EOT visit, and an EOS visit (VEOS) 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 double-blind 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 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.

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 of the protocol). Patients will also be monitored for asthma exacerbations throughout the study.

Asthma control measures will be assessed as part of this 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. 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 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.

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 of the protocol (with non-substantial changes documented in any letters of clarification to the protocol).

2.2. Randomization and Blinding

This is a non-randomized OL extension study that includes patients who previously completed a Teva-sponsored double-blind, placebo-controlled study (Studies 30025 or 30027) of sc administration of reslizumab in severe eosinophilic asthma. So, no randomization or blinding will be performed.

2.3. Data Monitoring Committee

There will be no Data Monitoring Committee in this study.

2.4. Sample Size and Power Considerations

The sample size for this 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 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 study.

2.5. Sequence of Planned Analyses

2.5.1. Planned Interim Analyses

There will be a planned data cut will be produced before the supplemental Biologics License Application (sBLA) submission. For the purpose of this analysis, a data cut-off will be established in accordance with the targeted date of submission and an interim CSR will be prepared. All outputs identified in this SAP and planned for the final analysis (Section 2.5.2) will be prepared at this time. The interim CSR to support sBLA submission will be based on all data accumulated from the study start to December 2017.

An additional planned data cut will be produced before the Day 120 safety update report, following the sBLA submission. For the purpose of this analysis, a data cut-off will be established in accordance with the targeted date of submission and safety data from this study

will be integrated with safety data from the other studies within the Day 120 report (in this case, there will be no separate interim CSR). The summaries provided at the time of this data cut will be consistent with those planned for the Summary of Clinical Safety (SCS) in the sBLA.

At the time of each planned interim analysis, no individual patient's data are considered fully locked; therefore interim results are interpreted as preliminary.

2.5.2. Final Analyses and Reporting

All final, planned analyses identified in this SAP will be performed after the last patient has completed the study and the database has been locked. The final study report will include all study population, efficacy, safety, and immunogenicity data as specified in the protocol and this analysis plan.

3. ANALYSIS SETS

3.1. 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 if informed consent form is obtained. The set of enrolled patients will be used for study population summaries.

3.2. 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.

3.3. Subgroup Analysis Sets

Selected efficacy and safety endpoints including clinical asthma exacerbations, FEV_1, [redacted] and adverse events will be summarized separately for seamless and non-seamless rollover patients.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include number of patients (n), mean, standard deviation (SD), standard error (SE), median, minimum, and maximum. Descriptive statistics for categorical variables include patient counts and percentages, missing categories will be presented if necessary.

4.2. Specification of Baseline Values

Baseline will be defined as the last observed value prior to the first dose of reslizumab in this study unless otherwise stated below.

4.2.1. Diary

Baseline for diary-based efficacy variables (total reliever bronchodilator medication, [redacted]) will be defined as the average of the values over the 7 days preceding the first dose of reslizumab in this study. At least 4 out of the 7 expected measurements need to be recorded for each diary variable; otherwise the baseline value for that variable will be treated as missing. This definition will exclude daily morning ambulatory FEV1 whose baseline value will be derived as outlined in Section 4.2.2.

For non-seamless rollovers, baseline will be derived from data collected in this study during 7-day run-in period prior to Visit 1. For seamless rollovers, baseline will be derived from data collected during the 7 days preceding the EOT visit of the previous study (30025 or 30027).

4.2.2. Spirometry

Pre-bronchodilator FEV_1 at pre-specified clinic visits and daily morning ambulatory FEV_1 will be measured using a handheld device that has combined spirometry and eDiary capabilities.

The baseline value for pre-bronchodilator FEV_1 measured at the clinic visits will be the last observed value prior to the first dose of reslizumab in this study. The baseline value for daily morning ambulatory FEV_1 will be defined similarly.

For non-seamless rollovers, baseline will be derived from data collected in this study on or prior to Visit 1. For seamless rollovers, baseline will be derived from data collected at the EOT visit of the previous study (30025 or 30027).

4.2.3. Patient Reported Outcomes

The baseline value for patient reported variables (ACQ-6, AQLQ +12) will be the last observed value prior to the first dose of reslizumab in this study.

For non-seamless rollovers, baseline will be derived from data collected in this study on or prior to Visit 1. For seamless rollovers, baseline will be derived from data collected on the same day as the EOT visit of the previous study (30025 or 30027).

4.2.4. Oral Corticosteroid Dose

The baseline value will be defined as the OCS dose reported on the day of first dose of reslizumab in this study.

4.2.5. Biomarkers

The baseline value for blood eosinophil levels will be the last observed value prior to the first dose of reslizumab in this study.

For non-seamless rollovers, baseline will be derived from data collected in this study on or prior to Visit 1. For seamless rollovers, baseline will be derived from data collected on the same day as the EOT visit of the previous study (30025 or 30027).

4.2.6. Safety

The baseline value for all visit-based safety assessments (eg, laboratory, vital signs, physical examination, ECG) will be the last observed value prior to the first dose of reslizumab in this study.

For non-seamless rollovers, baseline will be derived from data collected in this study on or prior to Visit 1. For seamless rollovers, baseline will be derived from data collected on the same day as the EOT visit of the previous study (30025 or 30027).

4.2.7. ADA

The baseline value for all ADA status will be the last observed value prior to the first dose of reslizumab in the previous double-blind study (30025 or 30027).

For both seamless and non-seamless rollovers, baseline will be derived from data collected on the same day as the day of randomization (DOR) visit of the previous study (30025 or 30027).

4.3. Handling Withdrawals and Missing Data

In general, missing data will not be imputed, unless otherwise specified.

4.4. Study Days and Visits

Study days will be numbered relative to the first day of study drug administration. The start of treatment (day 1) is defined as the date on which a patient takes the first dose of study drug in this study. Days will be numbered relative to study start (ie, ..., –2, –1, 1, 2, ...) with day 1 being the start of study drug and day –1 being the day before the start of study drug).

For safety-by-visit summaries, if there are multiple assessments at a post-baseline visit then the last non-missing assessment at that visit will be used for the summary. This includes assessments at the scheduled and unscheduled visits.

For efficacy by-visit summaries, only the assessments at the scheduled visit will be summarized. The assessments at unscheduled visits will only be listed. For the purpose of the efficacy analysis, assessments collected at an early termination visit will be considered as the next scheduled visit for that assessment if at least 3, but no more than 5 weeks, elapsed since the date of the last dose of study drug.

"Endpoint" for safety and efficacy analyses summaries is the time point when the last observation was obtained during the treatment period. For patients who completed treatment in this study, the treatment period will be defined from the first dose of study drug to the end of treatment (week 36) visit. For patients who prematurely discontinue treatment, the treatment period will be defined from the first dose of study drug to the last dose of study drug + 4 weeks.

For summaries of diary data and handheld spirometry data, the day used for analysis will consist of the evening assessment for the day and the morning assessment for the following day, as illustrated in Table 1. Weekly average data will be generated using 7-day window intervals derived based on these analysis days.

Table 1: Definition of Analysis Days for Diary Data

Study Period	Diary Day	Study Day[a]	Time Point
Baseline	Day -7	-7	PM
		-6	AM
	Day -6	-6	PM
		-5	AM
	Day -5	-5	PM
		-4	AM
	Day -4	-4	PM
		-3	AM
	Day -3	-3	PM
		-2	AM
	Day -2	-2	PM
		-1	AM
	Day -1	-1	PM
		1 (pre-dose)	AM
Treatment	Day 1	1	PM
		2	AM
	Day 2	2	PM
		3	AM
	…	..	PM
		..	AM
	Day 251	251	PM
		252	AM

[a]: Study Day 1 denotes the first dose of study drug; Study Day -1 is the day prior to the first dose of study drug.

5. STUDY POPULATION

5.1. General

The enrolled analysis set (Section 3.1) will be used for all study population summaries, unless otherwise specified. Summaries will be presented by double-blind treatment group in the previous studies 30025 or 30027 (placebo and reslizumab) and for all patients (ie, total), unless otherwise noted.

For continuous variables, descriptive statistics (number of patients [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.

5.2. Patient Disposition

Data from patients enrolled, patients enrolled but not treated, patients in the safety analysis set, patients who completed the treatment, patients who completed the study, patients who discontinued from treatment, and patients who withdrew from the study will be summarized using descriptive statistics. Data from patients who discontinue from the treatment and patients who withdrew from the study will also be summarized by reason for withdrawal. The previous study from which patients enrolled (30025 or 30027) will also be summarized, along with whether the patient was a seamless rollover or non-seamless rollover. This summary will include all patients enrolled into this study. The denominator for calculating the percentages will be the number of enrolled patients as appropriate.

5.3. Demographics and Baseline Characteristics

Baseline demographics and baseline characteristics, including spirometry and OCS dose, will be summarized using descriptive statistics by previous double-blind treatment group and for all patients.

Age will be calculated based on the date of birth relative to the screening visit (date of informed consent in this study). If regional data regulations prohibit collection of a full date of birth, then the patient's age should be recorded on the CRF, if possible. If only a year of birth has been collected (and age has not otherwise been reported) then the missing date of birth will be imputed as 30 June (30 June YYYY) in order to derive the patient's age at baseline.

5.4. Medical History

All medical history abnormalities will be coded using the Medical Dictionary for Regulatory Activities (MedDRA); the final version number will be indicated in the summary tables. The incidence of medical history abnormalities will be summarized by system organ class (SOC) and preferred term (PT). Patients are only counted once in each SOC and once in each PT. Summaries will be presented by previous double-blind treatment group and for all patients.

5.5. Prior Therapy and Medication

Any 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; the final version number will be indicated in the summary tables.

The incidence of prior therapies and medications will be summarized by therapeutic class using descriptive statistics by previous double-blind treatment group and for all patients. Patients are counted only once in each therapeutic class, and only once in each preferred term. Prior therapies and medications will include all medications taken and therapies administered before the first day of reslizumab administration in this study.

5.6. Electrocardiography

Electrocardiogram (ECG) findings (normal, abnormal, and missing) at baseline will be summarized using descriptive statistics by previous double-blind treatment group and for all patients.

5.7. Physical Examinations

Patients with at least 1 abnormal finding (overall) and abnormal findings for each category will be summarized at baseline by previous double-blind treatment group and for all patients.

5.8. Childbearing Potential and Methods of Contraception

For female patients, information related to childbearing potential, contraception, and menopause will be collected at screening. Information will be provided in the patient data listings.

5.9. Study Protocol Violation

Patients with at least 1 protocol violation for each category will be summarized by previous double-blind treatment group and for all patients.

6. EFFICACY ANALYSIS

6.1. General

The safety analysis set (Section 3.2) will be used for all efficacy analyses unless otherwise noted. Summaries will be presented by double-blind treatment group in the previous studies 30025 and 30027 (placebo and reslizumab) and for all patients (ie, total), unless otherwise noted.

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.

6.2. Primary Efficacy Endpoint and Analysis

There are no pre-specified primary efficacy variables and analyses in this study.

6.3. Secondary Efficacy Endpoints and Analysis

6.3.1. Clinical Asthma Exacerbations and Related Healthcare Utilization

6.3.1.1. Definition

A CAE is defined as a clinically judged deterioration in asthma control, as determined by the investigator and evidenced by new or worsening asthma signs or symptoms based on the patient history, handheld eDiary/spirometry data, 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.

6.3.1.2. Analysis

Summary statistics of frequency of CAEs and related HCU endpoints (asthma-specific hospital admissions, asthma-specific emergency department visits, school/work days missed due to asthma, and length of hospital stay and number of ICU days) will be provided by previous double-blind treatment group and for all patients. The summary will be presented for clinical asthma exacerbations recorded during the treatment period. For patients who complete treatment, the treatment period will be defined from the first dose of study drug to the end of treatment (week 36) visit. For patients who prematurely discontinue treatment, the treatment period will be defined from the first dose of study drug to the last dose of study drug + 4 weeks. All events will be included in the patient listings. The frequency of CAEs and related HCU endpoints will additionally be examined for the subgroups defined in Section 3.3.

6.3.2. Spirometry

6.3.2.1. Definition

Pre-bronchodilator (on designated clinic visit days per Table 1 of the protocol; Screening/Baseline and week 8, 24, and 36 or early withdrawal visit) and daily morning ambulatory FEV1 will be measured using the handheld device that has combined spirometry and eDiary capabilities. The FEV1 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.

6.3.2.2. Analysis

Summary statistics of actual values and changes from baseline to each scheduled visit in pre-bronchodilator FEV1 measured using spirometry will be provided by previous double-blind treatment group and for all patients. A line graph presenting the mean change from baseline over time (at each visit) will be provided for prebronchodilator FEV1 by previous double-blind treatment group.

A weekly average of daily morning ambulatory FEV1 (measured by the handheld spirometry device) will be derived using 7-day window intervals based on these analysis days (see Table 1 for the definition of analysis days for diary data). The average will be calculated as the sum of all values divided by the number of non-missing assessments. There will be no imputation of missing data. At least 4 of the 7 measurements need to be recorded for a week to be included in the analysis; otherwise the week will be treated as missing.

Summary statistics of actual values and changes from baseline in weekly average of daily morning ambulatory FEV1 (measured by the handheld spirometry device) at each week through week 36 will be provided by previous double-blind treatment group and for all patients.

FEV1 will additionally be examined for the subgroups defined in Section 3.3.

6.3.3. Daily oral corticosteroids dose

6.3.3.1. Definition

OCS dose information is collected in Concomitant Medication CRF page. Doses at Week 20 and 36 will be derived based on the study drug administration visit schedule by comparing OCS medication dates with the start date and end date of each visit (Table 2). Daily OCS dose is defined as total OCS dose in a day (accounting for reported dose and dose frequency) and converting the total daily dose to a prednisone-equivalent dose (Table 3).

For patients on maintenance OCS treatment at baseline, the week 20 and 36 OCS dose and corresponding values for absolute and percent change from baseline will be calculated as follows:

- **Baseline dose** = the prescribed OCS dose on the day of first dose of study drug in this study (Table 2).
- **Dose at week 20 (or 36)** = mean of all daily OCS doses during the period from week 16 to week 20 (or from week 32 to week 36) (Table 2).
- **Absolute change** = maintenance dose – baseline dose
- **Percent change** = 100 x (absolute change / baseline dose)

Table 2: Definition of Observed Days for OCS Dose

Visit period	Start day	Stop day
Baseline Dose	Day of first dose of study drug	N/A
Week 16 to Week 20	Day of W16 Visit + 1 day	Day of W20 Visit
Week 32 to Week 36	Day of W28 Visit + 1 day	Day of W36 Visit

Table 3: Conversion of ICS to Fluticasone-Equivalent Doses

Inhaled corticosteroid (mcg)	Conversion factor
Fluticasone	1
Fluticasone furoate	2
Mometasone	1.14
Budesonide	0.625
Ciclesonide	1.56
Beclomethasone	1.25
Triamcinolone	0.25

6.3.3.2. Analysis

Summary statistics of absolute and percent change in the daily OCS dose at weeks 20 and 36 as compared with the dose at baseline (for patients on daily OCS at baseline) will be provided by previous double-blind treatment group and for all patients.

6.3.4. Total reliever bronchodilator medication

6.3.4.1. Definition

Total reliever bronchodilator medication use (inhalations/puffs) will be assessed by reviewing the eDiary that will be maintained by the patient daily, once in the morning and once in the evening. Total reliever use will be derived as the sum of the morning and evening counts.

6.3.4.2. Analysis

A weekly average of total reliever use will be derived (see Table 1 for the definition of analysis days for diary data). The average will be calculated as the sum of all values divided by the number of non-missing assessments. There will be no imputation of missing data. At least 4 of the 7 measurements need to be recorded for a week to be included in the analysis; otherwise the week will be treated as missing.

Summary statistics of actual values and change from baseline in total inhalations of reliever bronchodilator medication measured using weekly averages to each week through week 36 will be provided by previous double-blind treatment group and for all patients.

6.3.5. Asthma Control Questionnaire

6.3.5.1. Definition

The ACQ-6 is a validated asthma assessment tool that has been widely used. There are 6 self-assessment questions. Each item on the ACQ-6 has a possible score ranging from 0 to 6 (higher scores are an indication of poorer asthma control), and the total score is the mean of all responses. At weeks 0, 8, 24, and 36 (or early withdrawal), the patient answers each of the 6 questions, identifying the response that best describes how the patient has been during the past week.

6.3.5.1.1. Missing data handling and total score calculation

The overall score of the ACQ-6 is derived as the average of the individual item scores; the analysis will be based on the available data.

For incomplete data, the following rules will apply:

1. Total score for the visit will not be calculated if Question 1 is left blank, irrespective of the completion of the remaining questions.
2. A missing score on post screening questionnaire for Questions 2-6 will be imputed based on the total scores from the previous visit, as long as at least 3 out of the 5 questions have responses for the current visit (ie, at least half of the remaining questions are answered).

The formula is: (total sum of non-missing scores for the current visit / total sum of scores for the previous visit for questions answered for the current visit) * (score for the missing question on the previous visit)

3. Total score at screening will not be calculated if Question 1 or two or more among Questions 2-6 is left blank. A missing score for Questions 2-6 at screening will be replaced by an average of the available scores.

6.3.5.2. Analysis

Summary statistics of actual values and changes from baseline to each scheduled visit in ACQ-6 score will be provided by previous double-blind treatment group and for all patients. A line graph presenting the mean change from baseline over time (at each visit) will be provided for the overall score by previous double-blind treatment group.

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

6.3.6.1. Definition

The AQLQ +12 is a modified version of the standardized AQLQ (AQLQ[S]), which was developed to measure functional impairments experienced by adults ≥17 years of age. The AQLQ +12 is valid for patients 12 to 70 years of age and includes 32 questions in 4 domains (symptoms, activity limitation, emotional function, and environmental stimuli). 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

The 32 questions (items) in the AQLQ +12 are divided into 4 domains:

- Activity limitations: Items 1-5, 11, 19, 25, 28, 31, 32
- Symptoms: Items 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
- Emotional function: Items 7, 13, 15, 21, 27
- Environmental stimuli: Items 9, 17, 23, 26

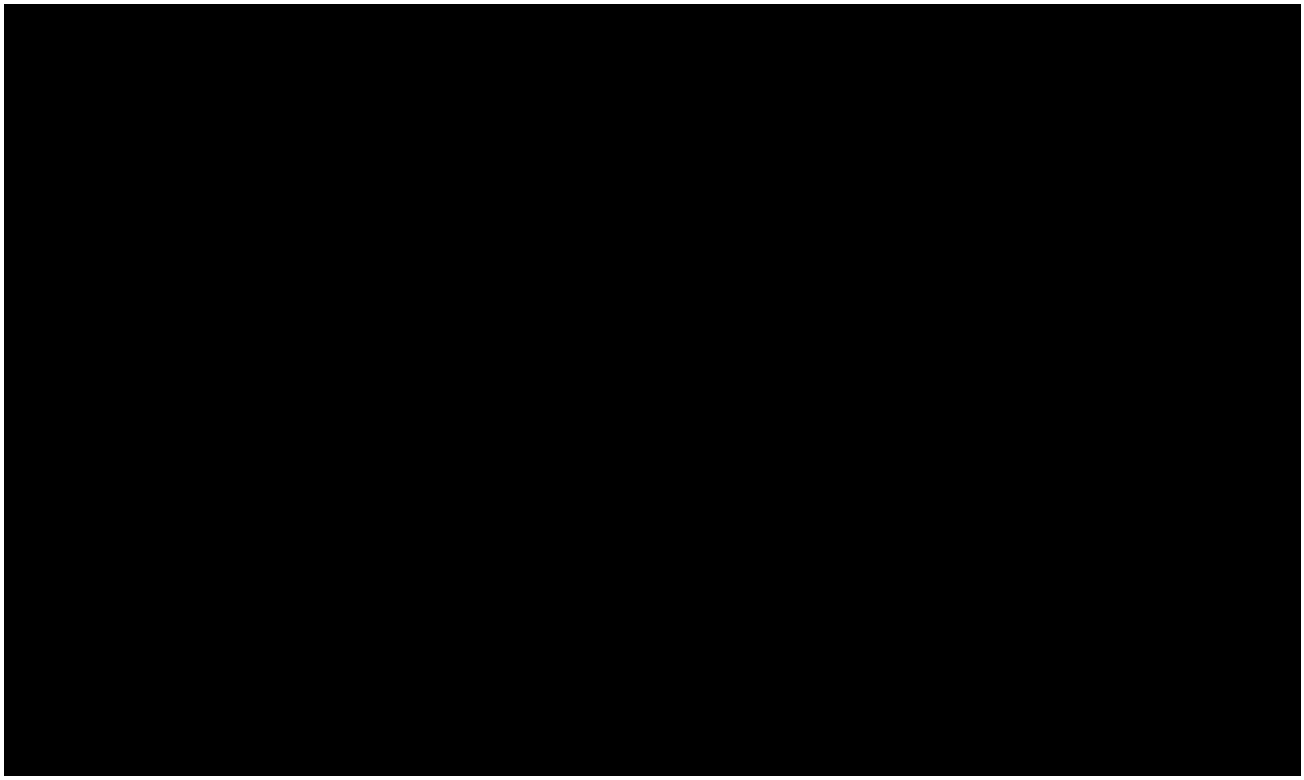
6.3.6.1.1. Missing data handling and total score calculation

The overall and domain scores of the AQLQ +12 are derived as the average of the corresponding items; the analysis will be based on the available data.

For incomplete data, the overall AQLQ +12 score for a particular visit will not be calculated if 3 or more responses are missing with no more than 1 per domain. For the symptom and activity domain total scores, calculation will require no more than 1 missing item. Total scores for the other 2 domains will be regarded as missing if 1 or more item is missing.

6.3.6.2. Analysis

Summary statistics of actual values and change from baseline to each scheduled visit in the overall and domain scores of AQLQ + 12 will be provided by previous double-blind treatment group and for all patients. A line graph presenting the mean change from baseline over time (at each visit) will be provided for the overall score by previous double-blind treatment group.



7. MULTIPLE COMPARISONS AND MULTIPLICITY

There are no pre-specified adjustments for multiplicity applied to this study.

8. SAFETY ANALYSIS

8.1. General

The safety analysis set (Section 3.2) will be used for all safety analyses unless otherwise noted. Summaries will be presented by double-blind treatment group in the previous studies 30025 and 30027 (placebo and reslizumab) and for all patients (ie, total), unless otherwise noted.

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.

8.2. Study Drug Administration

The exposure to study drug will be characterized by duration of treatment and by the number of patients receiving at least 1, 2, 3, etc. injections. Total patient years will also be summarized. The summaries will be provided by previous double-blind treatment group and for all patients.

Duration of treatment period is defined separately for patients who completed/discontinued treatment.

- Completed: End of treatment (week 36) visit date – first dose date + 1
- Discontinued: Last dose date – first dose date + 29

For non-seamless rollovers, the length of the "gap" between the end of study drug administration from the previous double-blind study to the start of study drug administration in this study will also be summarized.

8.3. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA); the final version number will be indicated in the summary tables.

On-treatment adverse event summaries will be presented by previous double-blind treatment group and for all patients, based on events with onset during the treatment period. If the AE start date is missing or partial, the event will be considered on-treatment unless there is evidence to the contrary (eg, month and year of AE start is present and is less than the month and year of the first dose of study drug). Post-treatment adverse events with onset during the follow-up period (ie, AE start date greater than the upper bound of the treatment period, as described in Section 4.4 previously) will be summarized separately.

Summaries will be presented by SOC and/or PT for all adverse events (overall and by severity), adverse events determined by the investigator to be related to study treatment (overall and by severity), serious adverse events, adverse events causing discontinuation from study treatment, and non-serious adverse events. Treatment related adverse event summaries will include events with missing relationship to study drug. For summaries by severity, patients will be counted at the greatest reported severity. Adverse events missing the flag indicating a serious adverse event will be excluded from the summary of serious adverse events, but included in the summary of non-serious adverse events.

In addition, adverse events that begin within 24 hours after study drug injection and injection-site adverse events (as recorded on the CRF) will each be summarized separately.

A summary for the most common adverse events (incidence ≥2% for all patients) will also be presented. Adverse events will additionally be presented for subgroups defined in Section 3.3.

All adverse events, including events with onset prior to the first dose of reslizumab in this study, will be included in the patient listings. The mapping of MedDRA dictionary terms for adverse event descriptions will also be provided.

8.3.1. Adverse Events of Special Interest

8.3.1.1. Administration Site Reactions

Administration site reactions will be defined based on:

- MedDRA High Level Group Term (HLGT): Administration Site Reactions

Summaries will be presented by high level term (HLT), preferred term, and previous double-blind treatment group. Patients will further be assessed on a 4-point Likert scale (none, mild, moderate, severe) for several domains of localized injection site tolerability including pain, tenderness, erythema, warmth, and swelling. The number and percentage of patients reported for each of the levels will be summarized descriptively for each domain by visit.

8.3.1.2. Anaphylaxis and Hypersensitivity

Anaphylaxis and hypersensitivity events will be defined based on:

- MedDRA SMQ: Anaphylactic Reaction
- MedDRA SMQ: Hypersensitivity

Summaries will be presented separately for both the broad (broad+narrow) and narrow preferred terms by previous double-blind treatment group.

Adverse events suspected by the investigator to be anaphylaxis events will be summarized by preferred term and double-blind treatment group. Supplemental information related to the relative timing, clinical manifestation, and treatment of these suspected events will be collected in a dedicated CRF and reported in the patient listings.

8.3.1.3. Malignancies

Malignancies will be defined based on:

- MedDRA SMQ: Malignant Tumors

Summaries will be presented by preferred term and previous double-blind treatment group.

8.3.1.4. Helminth infections

Helminth infections will be defined based on:

- MedDRA HLGT: Helminthic Disorders

Summaries will be presented by HLT, preferred term, and previous double-blind treatment group.

8.3.1.5. Muscle Disorders

Muscle disorders will be defined based on:

- MedDRA HLGT: Muscle Disorder
- MedDRA PT: Blood Creatine Phosphokinase Increased

Summaries will be presented by HLT, preferred term, and previous double-blind treatment group.

8.3.1.6. Opportunistic Infections

Opportunistic infections will be defined based on the following list of terms, derived from the preferred term (PT) or low level term (LLT) summarized in Table 4. Food and Drug Administration (FDA) terms provided are from the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents.

Summaries will be presented by preferred term and previous double-blind treatment group.

Table 4: List of Terms for Opportunistic Infections

Term	Code	Level	List from Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents	If LLT- under which PT
Acinetobacter infection	10051894	PT	Acinetobacter infection	
Acinetobacter bacteraemia	10064965	PT	Acinetobacter infection	
Aspergillus infections	10003486	HLT	Aspergillosis	
Blastomycosis	10005098	PT	Blastomycosis, extrapulmonary	
Epididymitis blastomyces	10015001	PT	Blastomycosis, extrapulmonary	
Osteomyelitis blastomyces	10031255	PT	Blastomycosis, extrapulmonary	
Burkitt's lymphomas	10006596	HLT	Burkitt's lymphoma	
Oesophageal candidiasis	10030154	PT	Candidiasis of esophagus	
Cerebral toxoplasmosis	10057854	PT	Toxoplasmosis of brain	
Meningitis toxoplasmal	10048848	PT	Toxoplasmosis of brain	
Cervix carcinoma	10008342	PT	Cervical cancer invasive	
Cervix carcinoma stage II	10008346	PT	Cervical cancer invasive	
Cervix carcinoma stage III	10008347	PT	Cervical cancer invasive	

Term	Code	Level	List from Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents	If LLT- under which PT
Cervix carcinoma stage IV	10008348	PT	Cervical cancer invasive	
Coccidioides infections	10009824	HLT	Coccidioidomycosis, dissemintaed or extrapulmonary	
Cryptococcosis	10011490	PT	Cryptococcosis, extrapulmonary	
Cryptococcal fungaemia	10067112	PT	Cryptococcosis, extrapulmonary	
Cryptococcal cutaneous infection	10054216	PT	Cryptococcosis, extrapulmonary	
Disseminated cryptococcosis	10013439	PT	Cryptococcosis, extrapulmonary	
Gastroenteritis cryptococcal	10011485	PT	Cryptococcosis, extrapulmonary	
Meningitis cryptococcal	10027209	PT	Cryptococcosis, extrapulmonary	
Neurocryptococcosis	10068368	PT	Cryptococcosis, extrapulmonary	
Cryptosporidia infections	10011499	HLT	Cryptosporidiosis infection, chronic intestinal (> 1 month duration)	
Cytomegalovirus chorioretinitis	10048843	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus colitis	10048983	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus duodenitis	10049014	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus enteritis	10049074	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus enterocolitis	10049015	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus gastritis	10049016	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus gastroenteritis	10051349	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus gastrointestinal infection	10052817	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus gastrointestinal ulcer	10075619	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus nephritis	10079095	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	

Term	Code	Level	List from Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents	If LLT- under which PT
Cytomegalovirus mucocutaneous ulcer	10065036	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus myelomeningoradiculitis	10065621	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus myocarditis	10056261	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus oesophagitis	10049018	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus pancreatitis	10049566	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus pericarditis	10056721	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus urinary tract infection	10051350	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Disseminated cytomegaloviral infection	10049075	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Encephalitis cytomegalovirus	10014586	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Pneumonia cytomegaloviral	10035676	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Hepatitis B	10019731	PT	Hepatitis B	
Acute hepatitis B	10059193	PT	Hepatitis B	
Chronic hepatitis B	10008910	PT	Hepatitis B	
Hepatitis C	10019744	PT	Hepatitis C	
Acute hepatitis C	10065051	PT	Hepatitis C	
Chronic hepatitis C	10008912	PT	Hepatitis C	
Herpes simplex skin chronic ulcers	10058426	LLT	Herpes simplex ulcers chronic (>1mo)	Under "Herpes dermatitis" PT
Lower respiratory tract herpes infection	10019948	PT	Herpes simplex bronchitis	
Herpes simplex pneumonia	10065046	PT	Herpes simplex pneumonitis	
Pneumonia herpes viral	10035703	PT	Herpes simplex pneumonitis	

Term	Code	Level	List from Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents	If LLT- under which PT
Herpes simplex oesophagitis	10074242	PT	Herpes simplex oesophagitis	
Herpes oesophagitis	10052330	PT	Herpes simplex oesophagitis	
Shingles	10040555	LLT	Shingles when 2 distinct episodes or more than 1 dermatome	Under "Herpes zoster" PT
Herpes zoster cutaneous disseminated	10074297	PT	Shingles when 2 distinct episodes or more than 1 dermatome	
Herpes zoster disseminated	10065038	PT	Shingles when 2 distinct episodes or more than 1 dermatome	
Histoplasmosis	10020141	PT	Histoplasmosis extrapulmonary	
Histoplasmosis disseminated	10020144	PT	Histoplasmosis disseminated	
Endocarditis histoplasma	10014676	PT	Histoplasmosis disseminated	
Histoplasmosis cutaneous	10049142	PT	Histoplasmosis disseminated	
Meningitis histoplasma	10027243	PT	Histoplasmosis disseminated	
Pericarditis histoplasma	10034489	PT	Histoplasmosis disseminated	
Presumed ocular histoplasmosis syndrome	10063664	PT	Histoplasmosis disseminated	
Retinitis histoplasma	10038912	PT	Histoplasmosis disseminated	
HIV wasting syndrome	10050309	PT	Wasting secondary to HIV	
Human polyomavirus infection	10057366	PT	Human polyomavirus infection	
Immunoblastic lymphoma	10053574	PT	Lymphoma immunoblastic	
Isosporiasis	10023076	PT	Isosporiasis, chronic intestinal (> 1 month’s duration)	
Kaposi's sarcomas	10023285	HLT	Kaposi’s sarcoma	
Lymphoid interstitial pneumonia	10062997	LLT	Lymphoid interstitial pneumonia	Under " Idiopathic interstitial pneumonia " PT
Listeria infections	10024639	HLT	Listeriosis	
Atypical mycobacterial infections	10003754	HLT	Mycobacterium infections, other species or unidentified species, disseminated or extrapulmonary (eg, M. haemophilium, M. fortuitum, or M. marinum)	
Nocardia infections	10029443	HLT	Nocardiosis	

Term	Code	Level	List from Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents	If LLT- under which PT
Pneumocystis jirovecii infection	10073756	PT	Pneumocystis jirovecii infection	
Pneumocystis jirovecii pneumonia	10073755	PT	Pneumocystis jirovecii infection	
Pneumonia recurrent	10066727	LLT	Pneumonia recurrent	Under "Pneumonia" PT
Polyomavirus-associated nephropathy	10065381	PT	Polyomavirus (JC virus or BK virus)-associated nephropathy (including progressive multifocal leukoencephalopathy)	
JC virus granule cell neuronopathy	10074361	PT	Polyomavirus (JC virus or BK virus)-associated nephropathy (including progressive multifocal leukoencephalopathy)	
Progressive multifocal leukoencephalopathy	10036807	PT	Polyomavirus (JC virus or BK virus)-associated nephropathy (including progressive multifocal leukoencephalopathy)	
Central nervous system lymphoma	10007953	PT	Lymphoma primary of brain	
Respiratory moniliasis	10038705	PT	Candidiasis of bronchi	
Candidiasis of trachea	10064459	PT	Candidiasis of trachea	
Candida pneumonia	10053158	PT	Candidiasis of lungs	
Salmonella sepsis	10058878	PT	Salmonella sepsis	
Salmonella septicemia	10039445	LLT	Salmonella septicemia, recurrent	Under "Salmonella sepsis" PT
Salmonella sepsis recurrent	10066745	LLT	Salmonella sepsis if recurrent	Under "Salmonella sepsis" PT
Tuberculous infections	10044756	HLT	Any active TB Mycobacterium tuberculosis, any site, latent or active	

8.4. Deaths

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.

8.5. Clinical Laboratory Tests

Clinical laboratory tests (serum chemistry and hematology) will be performed prior to reslizumab administration at the time points detailed in Table 1 of the protocol. Clinical

laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are provided in protocol section 7.4.1.

Summary statistics for laboratory tests will be presented at each scheduled visit. Actual values and changes from baseline to each visit will be summarized using descriptive statistics. Shifts (below, within, and above the normal range) from baseline to each visit will be summarized using patient counts and percentages. Shifts from baseline (Grade 0-4) will be provided for creatine phosphokinase (CPK) at each visit, based on the following grading scale:

- **Grade 0**: <1.25 x ULN
- **Grade 1**: 1.25 to 1.5 x ULN
- **Grade 2**: 1.6 to 3 x ULN
- **Grade 3**: 3.1 to 10 x ULN
- **Grade 4**: >10 x ULN

For CPK values ≥3.1xULN (Grade 3-4), investigators will collect additional information promptly from the patient related to symptoms associated with the elevation and any potential alternate causes. This supplemental data will be reported in the patient listings.

The incidence of potentially clinically significant abnormal values will be summarized for laboratory data using descriptive statistics with the criteria specified in Table 5; criteria have been provided for adults and adolescents separately.

Summaries of potentially clinically significant laboratory values will include all relevant post-baseline values (including scheduled, unscheduled, and early termination visits). A post-baseline laboratory value will be considered potentially clinically significant only if it satisfies the specified criteria and is more extreme (farther from the limit) than the baseline value. Listings for potentially clinically significant laboratory data will be presented. If any patient has a positive pregnancy test, relevant information will be supplied in data listings.

A scatter plot will be provided for the baseline and maximum value for CPK.

Table 5: Criteria for Potentially Clinically Significant Laboratory Values

		Adults (≥18 years)		Adolescents (12 to <18 Years)	
Test		**Criterion value**	**Change from baseline**	**Criterion value**	**Change from baseline**
Serum chemistry					
Alanine aminotransferase		≥3xULN	Increase >0	≥3xULN	Increase >0
Aspartate aminotransferase		≥3xULN	Increase >0	≥3xULN	Increase >0
Alkaline phosphatase		≥3xULN	Increase >0	≥3xULN	Increase >0
Gamma-glutamyl transpeptidase		≥3xULN	Increase >0	≥3xULN	Increase >0
Lactate dehydrogenase		≥3xULN	Increase >0	≥3xULN	Increase >0
Blood urea nitrogen		≥10.71 mmol/L	Increase >0	≥10.71 mmol/L	Increase >0
Creatinine		≥177 µmol/L	Increase >0	≥177 µmol/L	Increase >0
Uric acid:	Men	≥625 µmol/L	Increase >0	≥625 µmol/L	Increase >0
	Women	≥506 µmol/L	Increase >0	≥506 µmol/L	Increase >0
Bilirubin (total)		≥34.2 µmol/L	Increase >0	≥34.2 µmol/L	Increase >0
Creatine phosphokinase		Grade 3: 3.1 to 10 x ULN Grade 4: >10 x ULN	Increase >0	Grade 3: 3.1 to 10 x ULN Grade 4: >10 x ULN	Increase >0
Hematology					
Hematocrit:	Men	<0.37 L/L	Decrease >0	<0.30 L/L	Decrease >0
	Women	<0.32 L/L	Decrease >0	<0.30 L/L	Decrease >0
Hemoglobin:	Men	≤115 g/L	Decrease >0	≤100 g/L	Decrease >0
	Women	≤95 g/L	Decrease >0	≤100 g/L	Decrease >0
White blood cell counts		≤3 x 10^9/L	Decrease >0	≤3 x 10^9/L	Decrease >0
		≥20 x 10^9/L	Increase >0	≥20 x 10^9/L	Increase >0
Eosinophils		≥1.5 x 10^9/L	Increase >0	≥1.5 x 10^9/L	Increase >0
Absolute neutrophil counts		≤1 x 10^9/L	Decrease >0	≤1 x 10^9/L	Decrease >0
Platelet counts		≤75 x 10^9/L	Decrease >0	≤75 x 10^9/L	Decrease >0
		≥700 x 10^9/L	Increase >0	≥700 x 10^9/L	Increase >0

ULN=upper limit of normal range.
If both the baseline and post-baseline values are beyond the same PCS limit, then the post-baseline value will be considered PCS only if it is more extreme (farther from the limit) than the baseline value. If the baseline value is beyond the low PCS limit and the post-baseline value is beyond the high PCS limit (or vice-versa), then the post-baseline value will be considered PCS

8.6. Physical Examinations

Physical examinations, including height and weight, will be performed at the time points detailed in Table 1 of the protocol.

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.

Shifts (normal and abnormal) from baseline to each visit will be summarized using patient counts and percentages for each category.

8.7. Vital Signs

Summary statistics for vital signs (blood pressure [BP] (systolic/diastolic), respiratory rate, body temperature, and pulse) will be measured at the time points detailed in Table 1 of the protocol. Actual values and changes from baseline to each visit will be summarized.

The incidence of potentially clinically significant vital signs will be summarized. Summaries of potentially clinically significant values will include all relevant post-baseline values (including scheduled, unscheduled, and early termination visits).

Table 6 specifies the criteria for identifying vital signs as potentially clinically significant for adults and adolescents. In order to be identified as potentially clinically significant vital sign, the result would need to meet both identified conditions (ie, satisfies the specified criteria and results in a change from baseline of at least the magnitude specified). A listing for potentially clinically significant vital signs will be presented.

Table 6: Criteria for Potentially Clinically Significant Vital Signs

	Adults (≥18 years)		Adolescents (12 to <18 Years)	
Vital Sign	**Criterion value**	**Change from baseline**	**Criterion value**	**Change from baseline**
Heart rate	>100 bpm	Increase of ≥30	>100 bpm	Increase of ≥30
	<50 bpm	Decrease of ≥30	<60 bpm	Decrease of ≥30
Systolic BP	>160 mmHg	Increase of ≥30	>130 mmHg	Increase of ≥30
	<90 mmHg	Decrease of ≥30	<90 mmHg	Decrease of ≥30
Diastolic BP	>100 mmHg	Increase of ≥12	>85 mmHg	Increase of ≥12
	<50 mmHg	Decrease of ≥12	<55 mmHg	Decrease of ≥12
Respiratory rate	>24 breaths/min	Increase of ≥10	>20 breaths/min	Increase of ≥10
	<6 breaths/min	Not applicable	<10 breaths/min	Not applicable
Temperature	>38.1°C	Increase of ≥1.1	>38.1°C	Increase of ≥1.1
	<35.8°C	Not applicable	<35.8°C	Not applicable

8.8. Electrocardiography

Summary statistics for ECG will be measured at the time points detailed in Table 1 of the protocol.

Shifts (normal and abnormal) from baseline to week 36 will be summarized using patient counts. Summary statistics for ECG variables will be presented at week 36. Actual values and changes from baseline to week 36 will be summarized.

The following categorical analyses represent the criteria for potentially clinically significant QTc results. Both QTc Bazett and Fridericia interval will be presented using descriptive statistics.

- Absolute value at week 36
  - QTc interval >450 msec
  - QTc interval >500 msec
- Change from baseline to week 36
  - QTc interval increase >30 msec
  - QTc interval increase >60 msec
- Combined absolute value and change from baseline to week 36
  - QTc interval >450 msec and QTc interval increase >30 msec
  - QTc interval >450 msec and QTc interval increase >60 msec
  - QTc interval >500 msec and QTc interval increase >30 msec
  - QTc interval >500 msec and QTc interval increase >60 msec

8.9. Concomitant Medications or Therapies

All concomitant medications will be coded using the WHO Drug dictionary; the final version number will be indicated in the summary tables. The incidence of concomitant medications will be summarized by therapeutic class and preferred term. Patients are only counted once in each therapeutic class and once in each preferred term.

Concomitant medications include all medications taken while the patient is treated with reslizumab in this study. Medications with a start date greater than the upper bound of the treatment period (Section 8.2) in this study will be considered post-treatment. Medications will be categorized in every period (prior, concomitant, post-treatment) in which it was taken. If the medication start/stop date is missing or partial, the medication will be considered concomitant unless there is evidence to the contrary (eg, month and year of stop date is present and is less than the month and year of the first dose of study drug).

9. TOLERABILITY VARIABLES AND ANALYSIS

Local tolerability at the injection site 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.

Proportion of patients in each domain/response (refer to Section 8.3.1.1 for details on analysis) will be summarized by each visit and previous double-blind treatment group.

10. PHARMACODYNAMIC ANALYSIS

10.1. Biomarkers Analysis

The target biomarker endpoint is the blood eosinophil counts at time points detailed in Table 1 of the protocol. Summary statistics of actual values, change from baseline, and percent change from baseline to each scheduled visit will be provided by previous double-blind treatment group and for all patients. A line graph presenting the mean change from baseline over time (at each visit) will be provided by previous double-blind treatment group.

All summaries and analyses of other biomarkers (if analyzed) will be explored outside the scope of this SAP and reported separately from the clinical study report.

11. 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

Two types of antibody assay will be performed, an immunogenicity status assay (ADA) and neutralizing antibody assay (NAb). For the ADA assay, a screening assessment will be performed which produces a positive or negative result. For samples with a positive result, a neutralizing antibody assay will be performed, which also produces a positive or negative result; a titer value will be obtained to quantify the degree of binding.

A patient will be classified as having a treatment-emergent ADA response if a sample tested positive at any of the post-baseline time points but not at the baseline time point, or if the post-baseline ADA titer increased ≥4-fold from a positive baseline ADA sample (Shankar et al 2014). In this open-label extension study, the baseline sample data for the purpose of analysis will be derived from the pre-dose samples obtained on thethe DOR in the previous study (30025 or 30027).

Anti-reslizumab antibody data, including neutralizing antibody and titer results for patients who have tested ADA positive, will be listed. The number of patients with positive/negative results will be summarized at each scheduled visit by previous double-blind treatment group and for all patients, if appropriate. ADA status will be correlated with variables of efficacy and safety via examination of eosinophils and adverse events, respectively, by ADA status (positive, negative).

12. PLANNED INTERIM ANALYSIS

There will be a planned data cut with statistical output produced before the sBLA submission and a planned data cut with statistical output produced before the Day 120 safety update report (see Section 2.5.1 for additional details).

13. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS® version 9.3 or later.

14. CHANGES TO ANALYSES SPECIFIED IN THE STUDY PROTOCOL

Table 7: Changes to the Protocol Specified Analyses

Protocol Section	Protocol Description	Change/Rationale
Section 9.11	There will be a planned data cut with statistical output produced before the supplemental Biologics License Application submission.	There will be a planned data cut with statistical output produced before the supplemental Biologics License Application submission and a planned data cut with statistical output produced before the Day 120 safety update report.

15. REFERENCES

SAS Institute Inc. 2012. SAS® 9.3 In-Database Products: User's Guide, 4th ed. Cary, NC: SAS Institute Inc.

Shankar G, Arkin S, Cocea L, Devanarayan V, Kirshner S, Kromminga A, Quarmby V, Richards S, Schneider CK, Subramanyam M, Swanson S, Verthelyi D, Yim S. Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and and Peptides-Harmonized Terminology and Tactical Recommendations. AAPS J. 2014;16:658-73.

16. APPENDIX

Not applicable.