Statistical Analysis Plan with Amendment 02

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

Study Number C38072-AS-30025

NCT02452190

Statistical Analysis Plan with Amendment 02 Approval Date: 01 May 2017

TEVA BRANDED PHARMACEUTICAL PRODUCTS R&D, INC.

STATISTICAL ANALYSIS PLAN

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

Study C38072-AS-30025 **Phase** 3

Date: 01-May-2017

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Prepared by: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACQ	Asthma Control Questionnaire
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Aminotransferase
AM	Morning
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AQLQ	Asthma Quality of Life Questionnaire
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
BMI	Body Mass Index
BP	Blood Pressure
CAE	Clinical Asthma Exacerbation
CBC	Complete Blood Count
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CPK	Creatine Phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
DoR	Day of Randomization
ECG	Electrocardiogram
EOT	End of Treatment
[redacted]	
ERS	European Respiratory Society
FDA	Food and Drug Administration
$FEF_{25\%-75\%}$	Forced Expiratory Flow at the 25% point to the 75% point of Forced Vital Capacity
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma

GLM	Generalized Linear Model
HLGT	High Level Group Term
HLT	High Level Term
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
IgE	Immunoglobulin E
IRT	Interactive Response Technology
ITT	Intent-to-Treat
iv	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LABA	Long-Acting Beta-Agonist
LAMA	Long-Acting Anti-Muscarinic Antagonist
LLT	Low Level Term
LS	Least Square
LTE	Long term extension
LTRA	Leukotriene Receptor Antagonist
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MNAR	Missing Not at Random
nAb	Neutralizing Antibody
NB	Negative Binomial
NHANES	National Health and Nutrition Examination Survey
OCS	Oral Corticosteroid
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
sc	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SGRQ	St. George's Respiratory Questionnaire
SMQ	Standardized MedDRA Query
[redacted]	
SOC	System Organ Class
ULN	Upper Limit of Normal
US	United States
VAS	Visual Analogue Scale
WHO	World Health Organization

PREFACE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for TEVA Branded Pharmaceuticals Products R&D, Inc. Study C38072-AS-30025 (A 52-Week Double-Blind, Placebo-Controlled, Parallel-Group Efficacy and Safety Study of Reslizumab 110 mg Fixed, Subcutaneous Dosing in Patients with Uncontrolled Asthma and Elevated Blood Eosinophils) and was written in accordance with SOP_GBP_RD_702 (Statistical Analysis Plan).

This phase 3 study is being completed to assess the safety and efficacy of reslizumab sc dosing.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): E9 Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association, and the Royal Statistical Society, for statistical practice.

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol C38072-AS-30025 Amendment 04, issued 24 October 2016
- Case Report Form (CRF) for Study C38072-AS-30025
- ICH E9 Guidance on Statistical Principles for Clinical Trials
- ICH E3 Structure and Content of Clinical Study Reports

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study. When differences exist in descriptions or explanations provided in the protocol and this SAP, the SAP prevails and the discrepancies will be explained in the CSR.

1. STUDY OBJECTIVES

1.1. Primary Objective

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

1.2. Secondary Objectives

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

1.3. Other Objectives

Other objectives of this study are to evaluate the safety, pharmacokinetics, pharmacodynamics, and immunogenicity of reslizumab.

2. STUDY DESIGN

2.1. General Design and Study Schema

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

Evidence of inadequate asthma control will include a history of at least 2 exacerbations requiring systemic corticosteroids (oral or injection) in the previous 12 months, a suboptimal screening ACQ-6 score (≥1.5), and persistent symptoms during run-in on the patient's usual asthma controller regimen. The study consists of up to 2 weeks to satisfy essential screening inclusion criteria (ie, confirmation of asthma with elevated blood eosinophils), a minimum 3-week run-in period on usual care to establish the patient's baseline level of control, and a 52-week double-blind treatment period.

Patients will begin screening up to approximately 5 weeks (±1 week) before DoR. During the screening period, a signed and dated informed consent form (and an assent form for children ages 12 through <18 years in accordance with local standards) will be obtained before a diagnosis of asthma is confirmed on the basis of patient history and by demonstration of airway reversibility. The patients will also be asked about their asthma medication compliance and to demonstrate their inhaler use technique. If the inhaler use technique is not optimal, patients will be taught the appropriate inhaler use technique during the screening period and should be reassessed before run-in. The patient will also have a complete blood count determined. If the patient's eosinophil count is 300 eosinophils/μL or greater, and if the patient's medication compliance and inhaler use technique are optimal, the patient will be eligible to continue in the study. Patient medical history, 12-lead ECG, physical examination, hematology and chemistry tests, urinalysis, vital signs measurements, beta-human chorionic gonadotropin serum pregnancy test (for all females of childbearing potential), and concomitant medication history will also be assessed at screening.

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

Patients who meet screening eligibility requirements will return to the research facility 3 weeks before baseline/DoR to confirm eligibility and begin the run-in period. At the start of run-in, patients will begin daily self-monitoring at home using an asthma control diary and PEF meter, while taking their usual asthma medications, in order to establish their baseline level of asthma control based on the frequency of symptoms, use of reliever SABA, nighttime awakenings due to asthma, and ambulatory lung function measurement. Improvement in asthma control during the treatment period will primarily be assessed by a reduction in the rate of clinically significant asthma exacerbations with reslizumab versus placebo over the 52-week treatment period.

Pulmonary function; AQLQ +12, ACQ, and SGRQ scores; asthma symptoms; use of reliever SABA; nighttime awakenings due to asthma; safety measures; PK; immunogenicity; and health care utilization events will be assessed periodically; final assessments will be made at the EOT visit (week 52) or at early withdrawal. Patients who withdraw from the study before completing the 52-week evaluation period will have visit 17 (week 52 or early withdrawal) procedures and assessments performed at their final visit. Patients will return 12 weeks after the EOT visit for follow-up hematology, PK, immunogenicity, and safety assessments.

The assessments and procedures performed during each study visit are detailed in Table 1. If a patient elects to withdraw (or is discontinued from treatment by the Investigator), every attempt will be made to continue the assessments subsequent to their withdrawal from the study (see Section 4.4 of the study protocol for additional information).

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

Table 1: Study Procedures and Assessments

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

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

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

[a] The screening visit (visit 1) will take place approximately 5 weeks (±1 week) before the baseline/DoR visit. It is understood that not all procedures can be completed on the same day. In particular, the patient may need to return to satisfy the medication hold for screening pre-bronchodilator FEV1 (see note "k" for timing).

[b] A minimum of 3 weeks run-in (extension allowed up to 4 weeks) on stable doses of the patient's usual asthma medication is required to establish a baseline level of control before randomization.
[c] Diary control inclusion must be met at baseline/DoR in order for the patient to be randomized. If the control criteria are not met, the patient should not be randomized and should be discontinued at that time; the run-in may only be extended up to 4 weeks.
[d] Beta-human chorionic gonadotropin serum pregnancy tests will be performed at screening (female patients who are not 2 years postmenopausal or surgically sterile only). Urine pregnancy tests will be performed at baseline/DoR, before study drug injection at each administration visit and at week 52, or early withdrawal, and at follow-up V18. Pregnancy tests are not required for female patients who are 2 years postmenopausal or surgically sterile.
[e] The blood eosinophil count must meet the ≥300/μL inclusion criterion during the screening period. Given the known variability in this measure, the eosinophil count may be repeated once during screening (total of 2 attempts), at the discretion of the Investigator, in order to fulfill this inclusion criterion.
[f] CPK is collected with serum chemistry tests at scheduled visits. If a potentially clinically significant CPK level (≥3.1 × ULN) is reported, initiate the CPK/myalgia CRF and clinical monitoring as outlined in Protocol Section 7.1.7.2.
[g] CPK measurement only. CPK will be collected with PK sample.
[h] Physical examination, vital signs, and ECG should be obtained before spirometry procedures and IP administration.
[i] Patients aged 21 years and over will have their height and weight assessed at screening only. Patients aged 12 to 21 years will have height and weight assessed at screening, week 24, and EOT.
[j] A failed reversibility test may be repeated once, within the 2-week (±3 days) screening period. Reversibility testing will be confirmed before entering the run-in period. Documented historical reversibility within 12 months of signing the Informed Assent Form/Informed Consent Form is acceptable as per inclusion criterion f.
[k] Pre-bronchodilator spirometry assessments should only be performed after withholding short-acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule. Spirometry should be performed prior to IP administration, if applicable.
[l] The ACQ will be completed by the patient at the clinic. ACQ should be completed through question 6. NOTE: The screening V1 ACQ-6 score must be ≥1.5 in order to continue in this study. A screening visit ACQ score <1.5 may not be repeated and the patient should be screen-failed at that time.
[m] If a patient experiences worsening of his or her asthma symptoms, the patient is to call the study center within 48 hours (if possible) to be evaluated for his or her asthma symptoms. A diary alert, based on a sustained fall in peak flow from baseline, will also help support the patient's subjective experience. Procedures and assessments to be performed if an unscheduled visit occurs are described in Protocol Section 3.16.5.
[n] Patients at sites in the United States will return for a PK assessment at approximately 1 week, which corresponds approximately to maximum plasma drug concentration (Cmax) for subcutaneous reslizumab.
Note: All blood sampling (including hematology and chemistry) will be drawn before administration of IP unless otherwise indicated.
[o] Blood for ADA assessment will be collected at baseline/DoR, and other scheduled time points, and upon observation of any severe hypersensitivity reaction (eg, anaphylaxis). Blood for ADA assessment will be collected before dosing, if both occur on the same day. An additional, late follow-up for immunogenicity testing will be performed 28 weeks (±2 weeks) after the last dose of study drug (~week 76).
[p] Adverse event inquiry will occur before and after study drug administration at V3 to V16. Follow-up any prior messages from the post-injection eDiary symptom inquiry, as necessary. For systemic or severe hypersensitivity reactions possibly related to the study drug, initiate the anaphylaxis CRF. When such reactions are observed after study drug administration in the clinic, vital signs must be monitored using the unscheduled vital signs CRF. At the time of myalgia/muscular adverse events, CPK should be collected (initiate myalgia CRF).

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

2.2. Primary and Secondary Measures and Endpoints

2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the frequency of clinical asthma exacerbations (CAEs) per patient during the 52-week treatment period. Refer to Section 6.2.1 for additional details regarding the definition of CAE.

2.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- change in pre-bronchodilator FEV_1 from baseline/DoR at week 52
- change in Asthma Quality of Life Questionnaire for patients 12 years and older (AQLQ +12) score from baseline/DoR at week 52
- change in 6-item Asthma Control Questionnaire (ACQ-6) score from baseline/DoR at week 52
- change in total asthma symptom scores (day and night) from baseline at week 52
- percentage of asthma control days from baseline/DoR to week 52
- change in St. George's Respiratory Questionnaire (SGRQ) from baseline/DoR at week 32
- time to first clinical asthma exacerbation during the 52-week treatment period
- frequency of exacerbations requiring hospitalization or emergency department visits per patient during the 52-week treatment period
- frequency of moderate exacerbations defined as exacerbations requiring additional asthma controller medication that was not a systemic corticosteroid and that did not result in an asthma-specific hospitalization or emergency department visit during the 52-week treatment period

[redacted]

2.2.4. Target Biomarker Endpoints

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

2.2.5. Immunogenicity Endpoints

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

2.2.6. Pharmacokinetic Endpoints

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

[redacted]

2.2.8. Safety Endpoints

The safety endpoints for this study are as follows:

- adverse events throughout the study

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

2.3. Sample Size and Power Considerations

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

Power calculations were based on the below assumptions:

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

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

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

2.4. Randomization and Blinding

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

The randomization list and treatment will be assigned to the relevant treatment groups through a qualified contract research organization (CRO), eg, via Interactive Voice Response System (IVRS)/ Interactive Web Response System (IWRS). The generation of the medication list and

management of the IRT system will be done by a qualified CRO under the oversight of Teva's Clinical Supply Chain.

The sponsor's clinical personnel involved in the study will be blinded to the study drug identity after the run-in period until the database is locked for analysis and the treatment assignment is revealed, with the exception of the bioanalytical group who will not be blinded to facilitate PK and ADA sample analysis. Eosinophils and monocytes will be redacted from the post-baseline differential cell count reports to avoid the possibility of unblinding patients.

2.5. Sequence of Planned Analyses

2.5.1. Interim Analyses

No interim analysis is planned for this study.

2.5.2. Final Analyses and Reporting

All final, planned analyses identified in this SAP will be performed only after the last patient has completed the study. The randomization codes will not be unblinded until this SAP has been approved.

Any exploratory analyses completed to support study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR.

3. POPULATIONS/ANALYSIS SETS

Site [redacted] was terminated due to numerous unresolved Good Clinical Practice (GCP) issues, including an overall lack of adequate source documentation (letter to FDA dated 2 December 2016). The data from this site are deemed invalid and the 4 patients randomized at this site will be excluded from the efficacy analysis but will be included as part of the safety analysis. In addition, these patents will be summarized as randomized, but not analyzed, as part of the ITT analysis set in the disposition summary (Section 5.2).

3.1. Intent-to-Treat Analysis Set

The intent to treat (ITT) analysis set will include all randomized patients, with the exception of patients from Site [redacted] who will be excluded. In this population, treatment will be based on the treatment to which patients were randomized, regardless of which treatment they actually received.

Two analytic approaches are planned using the ITT analysis set.

- In the first approach, all data collected from patients will be included, regardless of continued adherence to their assigned study treatment.
- In the second approach, data collected from patients during the treatment period will be included, up to the point at which patients discontinue from their assigned study treatment (on-treatment). 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 52) 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.

The analytic approach including all data collected from patients will be utilized as the primary approach to analysis for the primary endpoint (frequency of CAE). The on-treatment approach will be conducted as a sensitivity analysis for the primary endpoint. For the analysis of all other efficacy endpoints, the on-treatment approach will be utilized as the main approach to analysis. The analytic approach including all data collected from patients will additionally be conducted as sensitivity analyses for selected secondary endpoints.

3.1.1. ITT Analysis Set (Patients 12-70 Years)

Since AQLQ +12 has only been validated for patients aged 12 to 70 years, the analysis of this variable will be restricted to the subset of the ITT analysis set (excluding patients from Site [redacted]) within the specified age range (12 to 70 years) at baseline.

3.2. Safety Analysis Set

The safety analysis set will include all patients who receive at least 1 dose of study drug (including patients from Site [redacted]). In this population, treatment will be based upon the treatment patients actually received, regardless of the treatment to which they were randomized. Patients dosed in error, but who otherwise received at least 1 dose of reslizumab, will be assigned to reslizumab for the analysis of safety.

In this analysis, data collected from patients during the treatment period will be included, up to the point at which patients discontinue from their assigned study treatment. 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 52) 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. This analysis will be used as the default approach for all safety endpoints.

3.3. Per-Protocol Analysis Set

The per-protocol (PP) analysis set is a subset of the ITT analysis set (excluding patients from Site [redacted]) including only patients without major protocol violations. The PP analysis set will only be presented for the primary endpoint. In this analysis, data collected from patients during the treatment period will be included, up to the point at which patients discontinue from their assigned study treatment.

3.3.1. Major Protocol Violations

Table 2 presents the planned list of major protocol violations prospectively identified as having the potential to influence and/or bias the primary efficacy results. A complete list of protocol violations resulting in exclusion of patients from the PP analysis will be determined at the end of the study based on team review of accumulated blinded study data. Updates to the following list will be documented in the minutes from the final Statistical Data Review meeting.

Table 2: Major Protocol Violations

Violation	Approach to identifying protocol violations
Patient does not have ≥2 asthma exacerbations within the past 12 months	Inclusion criteria (c); disposition CRF Asthma/allergy history CRF Protocol violation CRF
Patient does not have ACQ-6 score ≥1.5 at screening (Visit 1)	Inclusion criteria (d); disposition CRF Asthma control questionnaire CRF Protocol violation CRF
Patient does not have blood eosinophil ≥300/μL during the screening period (prior to Visit 2)	Inclusion criteria (e); disposition CRF Laboratory data Protocol violation CRF
Patient does not demonstrate FEV_1 reversibility (≥12%) after administration of inhaled SABA	Inclusion criteria (f); disposition CRF Spirometry data Protocol violation CRF Note: Historical reversibility is acceptable.
Patient was not on ICS at baseline (at least a medium total daily dose)	Inclusion criteria (g); disposition CRF Medication CRF Protocol violation CRF
Patient was not on an additional asthma controller medication (eg, LABA, LAMA, LTRA, or theophylline preparations)	Inclusion criteria (h); disposition CRF Medication CRF Protocol violation CRF

Violation	Approach to identifying protocol violations
Patients who were unblinded at any point during the study	Protocol violation CRF
Patients who received the incorrect study treatment at any point during the study	Protocol violation CRF

3.4. Subgroup Analysis Sets

3.4.1. Age Strata

Selected efficacy endpoints including CAEs (primary), pre-bronchodilator FEV_1, AQLQ+12, ACQ-6, and blood eosinophils will be analyzed separately for patients aged 12 to <18 years and ≥18 years. Age strata will be defined based on the age recorded in the clinical database.

3.4.2. Eosinophil Strata

Selected efficacy endpoints including CAEs (primary), pre-bronchodilator FEV_1, AQLQ+12, ACQ-6, and blood eosinophils will be analyzed separately for patients with baseline blood eosinophil levels 300/µL to <400/µL and ≥400/µL. Eosinophil strata will be defined based on the baseline blood eosinophil level recorded in the clinical database.

[redacted]

3.4.4. Asthma Background Medication

Patient classifications based on Global Initiative for Asthma (GINA) guidelines (GINA 2015) will be derived. Selected efficacy endpoints including CAEs and pre-bronchodilator FEV_1 will be examined for the following medication classes taken at baseline. Medications at baseline will be defined as those taken at the time of randomization.

- **GINA 4** – ICS/LABA+ (Yes, No)
  Note: "Yes" is defined as patients taking ICS (medium or high-dose); and LABA or leukotriene or xanthine as a second controller; and no OCS use
  - ICS/LABA (Yes, No)
    Note: "Yes" is defined as patients taking ICS (medium or high-dose); and LABA as a second controller; and no OCS use
  - High-dose ICS/LABA (Yes, No)
    Note: "Yes" is defined as patients taking ICS (high-dose); and LABA as a second controller; and no OCS use
  - Medium-dose ICS/LABA (Yes, No)
    Note: "Yes" is defined as patients taking ICS (medium-dose); and LABA as a second controller; and no OCS use

- **GINA 5** – OCS (Yes, No)
  Note: "Yes" is defined as patients taking OCS

3.4.5. Other Subgroups

Selected efficacy endpoints including CAEs (primary), pre-bronchodilator FEV_1, AQLQ+12, ACQ-6, and blood eosinophils will also be examined for the following demographic subgroups:

- Gender (Male, Female)
- Race (White, Black, Asian, Other; Black, non-Black)
- Region (North America, Eastern Europe, Western Europe, Latin America, Asia/Pacific, Middle East/Africa; US, non-US)
- Phadiatop result (Positive, Negative)
- Age of asthma onset (<40, ≥40 years)
- BMI (<30, ≥30 kg/m^2)
- ADA status (Positive, Negative) – for reslizumab-treated patients only

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) of the mean, median, minimum, and maximum. If inferential statistics are computed, the least square (LS) mean and standard error of the LS mean will be included. Descriptive statistics for categorical variables include patient counts and percentages.

4.2. Specification of Baseline Values

4.2.1. Diary

Baseline for diary variables (eg, PEF, total asthma symptom score, total reliever use) will be derived as the average of the run-in values over the 7 days preceding baseline/DoR (see Table 3 for the definition of analysis days for diary data). 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.

4.2.2. Lung Function

The baseline value for lung function variables (eg, pre-bronchodilator FEV_1, FVC, $FEF_{25\%-75\%}$) will be the last observed pre-bronchodilator value prior to the first dose of study drug. Baseline for post-bronchodilator FEV_1 will be the last observed post-bronchodilator value prior to the first dose of study drug.

4.2.3. Patient Reported Outcomes

The baseline value for patient reported variables (eg, ACQ-6, AQLQ +12, SGRQ, [redacted]) will be the last observed value prior to the first dose of study drug.

4.2.4. Biomarkers

The baseline value for blood eosinophil levels will be the maximum value of the observed assessments from the screening visit to baseline/DoR (inclusive).

4.2.5. Safety

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

4.3. Multiple Comparisons and Multiplicity

A fixed sequence multiple testing procedure will be implemented to test the primary and secondary variables while controlling the overall type I error rate at 0.05. If the resulting two-sided p-value from the primary comparison is ≤0.05, then the next comparison of interest (first secondary variable) will be interpreted inferentially at 0.05. This process continues through the secondary variables until either all comparisons of interest are interpreted inferentially, or until the point at which the resulting two-sided p-value for a comparison of interest is >0.05. At the

point where p>0.05, no further comparisons will be interpreted inferentially. The hierarchy of endpoints is as defined in Section 6.3.1.

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

4.4. Handling Withdrawals and Missing Data

The primary analysis will include multiple imputations for missing data as detailed in Section 6.2.2 and Appendix A. For all other variables, only the observed data from the patients will be used in the statistical analyses (ie, there is no plan to estimate missing data).

4.5. Study Days and Visit Windows

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, as recorded on the study drug diary. 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 analysis. This includes assessments at the scheduled and unscheduled visits.

'Endpoint' for safety analyses and 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 52) 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 efficacy-by-visit summaries, only the assessments at the scheduled visit will be summarized. The assessments at unscheduled visits will 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 medication intake.

Efficacy-by visit summaries will be presented on-treatment. In this context, 'endpoint' will be defined as the last observation obtained at a scheduled or qualified early termination visit 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 52) 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 selected variables, additional sensitivity analyses may be presented utilizing all data collected over the entire course of the study including data collected after withdrawal for patients who prematurely discontinue from treatment. In this context, 'endpoint' will be defined as the last observation obtained at any post-baseline scheduled or qualified early termination visit.

For summaries of diary data (eg, rescue medication use, asthma symptom score), 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 3. Weekly average data will be generated using 7-day windows derived based on these analysis days.

Table 3: 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
	Day 3	3	PM
		4	AM
	…	..	PM
		..	AM
	Day 364	364	PM
		365	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 ITT analysis set will be used for all study population summaries, unless otherwise noted. Population summaries will be presented by treatment group and overall.

5.2. Patient Disposition

Data from patients screened, patients screened but not randomized, and the reason the patients were not randomized will be summarized overall (for all screened patients). Patients randomized (ITT analysis set), patients randomized but not treated, patients randomized but not analyzed (Section 3), patients in the safety analysis set, patients in the PP analysis set, patients who completed treatment (all 52 weeks while on study treatment), patients who completed the planned treatment phase (remained active in the study for the full 52 week duration, either on- or off-treatment), and patients who completed the study will be summarized. Patients will be categorized as completed the study if they either complete the study visits up to and including follow-up (Week 64, for patients not participating in the LTE study) or up to and including end of treatment (Week 52, for patients participating in the LTE study). Data from patients who withdrew early will be summarized by reason for withdrawal, and the number of patients who discontinued treatment but continued to attend study visits will be tabulated.

KM plots will be provided for time to discontinuation from treatment to identify if there is a differential dropout pattern between the treatment groups.

5.3. Demographics and Baseline Characteristics

Baseline demographics (eg, age, sex, race, ethnicity) and patient characteristics (eg, spirometry, airway reversibility) including smoking history, medical history, phadiatop test results, and prior medications will be summarized to assess the comparability of the treatment groups. Baseline stratification factors (age and blood eosinophil counts) and patients taking the various classes of background asthma medication (defined in Section 3.4.4) will also be summarized. Baseline demographics and patient characteristics will also be summarized separately for patients who discontinue from treatment and patients who complete treatment to investigate whether patients with and without missing values may have different characteristics at baseline.

Age will be calculated based on the date of birth relative to the screening visit (date of informed consent). 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 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.

Asthma- and allergy-specific history will also be collected and reported. In addition, descriptive statistics will be provided for time since asthma diagnosis, time since most recent exacerbation, number of exacerbations within the last 12 months, and number of days missed school/work due to asthma in the past year.

History of nasal polyp, whether sinus surgery was performed, time since sinus surgery, whether diagnosed by CT scan, time since CT scan, and anosmia will be summarized.

5.5. Prior Medications

All prior medications will be coded using the World Health Organization dictionary of medical codes (WHO Drug). The incidence of prior 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. Prior medications include all medications with a start date prior to the first day of study drug.

Prior medications for asthma will be summarized separately. In addition, total ICS dose taken at baseline will be summarized. The reported ICS doses will be converted to fluticasone equivalents using the following conversion factors. ICS dose at baseline will be defined as the dose taken at the time of randomization.

Table 4: Conversion of ICS to Fluticasone-Equivalent Doses

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

[a] Nebulized budesonide is typically recorded in mg and, if applicable, the reported dose (in mg) may need to first be converted to mcg (x1000) prior to applying the indicated conversion factor for budesonide.

5.6. Electrocardiography

Electrocardiogram findings (normal, abnormal) at baseline will be summarized.

5.7. Physical Examinations

Patients with at least 1 abnormal finding (overall) and abnormal findings for each category will be summarized at baseline.

5.8. Protocol Violations

Patients with at least 1 protocol violation for each category will be summarized.

5.9. Childbearing Potential

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.

6. EFFICACY ANALYSIS

6.1. General

The ITT analysis set will be used as the default patient population for all efficacy variables, unless otherwise noted. Summaries will be presented by treatment group as randomized.

6.2. Primary Efficacy Variable(s) and Analysis

Note: For consistency, all variables related to or derived from the primary efficacy variable (clinical asthma exacerbations) are discussed within this section. This includes the secondary efficacy variables of moderate exacerbations, the subset of exacerbations requiring hospitalization or emergency department visits, and the analysis of time to first exacerbation, all of which are otherwise listed in Section 6.3 (Secondary Efficacy Variable(s) and Analysis).

6.2.1. Variable Definition

The primary efficacy variable for this study is the frequency of CAEs per patient during the 52-week treatment period. CAE is defined as a clinically judged deterioration in asthma control as determined by the investigator and as evidenced by new or worsening asthma signs or symptoms based on the patient history, asthma control diary, physical examination, and/or ambulatory or clinic visit assessment of lung function AND that results in a medical intervention, including at least 1 of the following:

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

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

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

6.2.2. Primary Analysis

The primary analysis of frequency of CAEs will be analyzed using the general linear model (GLM) for data from the negative binomial distributions that is commonly referred to as the negative binomial (NB) regression model. The primary NB model will include the treatment group, randomization stratification factors (age and blood eosinophil categories, as defined in Section 2.4), and the number of exacerbations in the previous year as model factors and an offset variable. The offset variable will be calculated as the logarithm of follow-up duration minus the summed duration of exacerbations during the follow-up. Age and blood eosinophil categories will be based on data recorded in the clinical database.

The ratio of CAE rate between the treatment groups and its 95% confidence interval (CI) will be estimated from the NB model. Treatment effect will be evaluated using the likelihood based chi-square test. Clinical asthma exacerbations that occur between the first dose of study drug and 2 weeks after the end of treatment/early withdrawal visit will be counted towards the CAEs for analysis.

The primary analysis will incorporate data from all randomized patients. The analysis will include all exacerbations observed over 52 weeks, for patients who completed the 52 week treatment period and for patients who withdrew from treatment earlier than 52 weeks but from whom the sponsor was able to collect data post withdrawal. For early withdrawal patients that the sponsor will fail to retrieve data post withdrawal despite all attempts to contact the patient, a multiple imputation will be performed for the frequency of exacerbation post withdrawal. The multiple imputations will utilize the post withdrawal data observed for patients who withdrew early and for which the sponsor succeeded to retrieve the data. The methodology and algorithm used for imputations is described in Appendix A.

The following sample Statistical Analysis Software (SAS®) code pertains to the primary efficacy analysis of CAEs.

```
proc genmod data=<<>>;
    class treatment strata1 strata2;
    model cae=treatment strata1 strata2 nexac /dist=negbin link=log offset=log_futime;
    estimate "CAE rate ratio" treatment 1 -1;
    lsmeans treatment /diff exp cl;
    ods output lsmeans=<<>>;
    ods output lsmeandiffs=<<>>;
run;
```

A frequency distribution bar graph will be provided for the number of CAEs by treatment group.

6.2.3. Sensitivity Analyses for the Primary Variable

The following list of sensitivity analyses are pre-specified for this study, with an aim toward assessing the robustness of the primary efficacy results:

- The primary analysis with offset variable calculated as the logarithm of follow-up duration (ie, not excluding the summed duration of exacerbations).
- The primary analysis with control variables for age and blood eosinophil categories based on data recorded in the IRT (as randomized). This analysis will only be

performed if the number of discrepancies between data recorded in the IRT and the clinical database are sufficiently large (eg, 5% of total population).

- On-treatment: analysis of the primary endpoint including exacerbations during the treatment period (ie, observed until treatment completion or until withdrawal from treatment, excluding any exacerbations observed after withdrawing from treatment).
  - For patients who complete treatment, the treatment period will be defined from the first dose of study drug to the end of treatment (week 52) 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.
- Per-protocol: on-treatment analysis of the primary endpoint including exacerbations during the treatment period (ie, observed until treatment completion or until withdrawal from treatment, excluding any exacerbations observed after withdrawing from treatment), based on the PP analysis set.
- "Tipping point" multiple imputation: analysis of the primary endpoint to assess deviations from missing at random (MAR). The details regarding this analysis are provided in Appendix B.

6.2.4. Component Analysis for the Primary Variable

The frequency of the following individual components of the composite CAE definition will be examined separately.

- asthma exacerbations requiring 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 exacerbations requiring either hospitalization or emergency department visit

The following individual components will also be examined, however due to the low event rates expected, these events will only be presented descriptively.

- asthma exacerbations requiring hospital admission
- asthma exacerbations requiring an emergency department visit

These analyses will be restricted to on-treatment events.

6.2.5. Subgroup Analysis for the Primary Variable

The primary efficacy variable will additionally be examined for the subgroups defined in Section 3.4. The analysis will be similar to the on-treatment analysis described for the primary endpoint (Section 6.2.3). An interaction p-value will be derived from a separate NB model including additional terms for subgroup and treatment by subgroup interaction. Subgroup analyses for the primary efficacy variable will be presented graphically using forest plots.

6.2.6. Time to First Clinical Asthma Exacerbation

The Kaplan-Meier (KM) method will be used to estimate and compare the distributions of time to first CAE between treatment groups. Time to first event will be analysed for on-treatment events.

The time period for the on-treatment analysis will extend from the date of first dose of study drug to the cessation of study treatment, defined as the date of the end of treatment (week 52) visit for patients who completed treatment and the date of last dose (+4 weeks) for patients who discontinued treatment early. Patients without an event during the treatment period will be censored at either the date of the end of treatment (week 52) visit for patients who completed treatment or at the date of last dose (+4 weeks) for patients who discontinued early.

The hazard ratio (95% CI) and p-value will be estimated using a Cox proportional hazards regression model adjusting for the stratification factors.

The following sample SAS® code pertains to the analysis of time to first CAE.

```
proc lifetest data=<<>> outsurv=<<>>;
    time ttcae*censor(0);
    strata treatment;
    ods output quartiles=<<>>;
run;

proc phreg data=<<>>;
    class treatment (ref='PBO');
    model ttcae*censor(0) = treatment / rl ties=discrete;
    strata strata1 strata 2;
    ods output parameterestimates=<<>>;
    ods output globaltests=<<>>;
run;
```

A KM plot will be provided for the time to first CAE by treatment group.

6.2.7. Moderate Exacerbations

A moderate exacerbation is defined as a clinically judged deterioration in asthma control as determined by the investigator and as evidenced by new or worsening asthma signs or symptoms based on the patient history, asthma control diary, physical examination, and/or ambulatory or clinic visit assessment of lung function AND that results in a medical intervention requiring additional asthma controller medication that was not a systemic corticosteroid and did not result in an asthma-specific hospitalization or emergency department visit (ie, medical intervention that did not otherwise meet the criteria for the primary endpoint).

Additional medication that would satisfy the moderate exacerbation definition occurring within 7 days of the last day of a prior event will be considered as part of the same event for analysis purposes. Similarly, additional medication that would satisfy the moderate exacerbation definition occurring within 7 days prior to the start date of another event satisfying the definition of a CAE (or occurring concurrently with a CAE) will be considered part of the CAE event and will not be counted towards the analysis of moderate exacerbations.

The analysis for moderate exacerbations will be similar to the on-treatment analysis described for the primary endpoint (Section 6.2.3). In addition, the analysis of moderate exacerbations will not exclude exacerbation duration from the offset.

6.3. Secondary Efficacy Variable(s) and Analysis

As described previously in Section 4.5, an on-treatment approach will be adopted as the primary analysis for the efficacy variables assessed by-visit. In this analysis, the treatment period will be defined from the first dose of study drug to the end of treatment (week 52) visit for patients who completed treatment and from the first dose of study drug to the last dose of study drug (+4 weeks) for patients who discontinued treatment early. Measurements collected outside of these defined timeframes will be excluded from the analyses and endpoint will be defined within these timeframes. All results will be included in the patient listings. For selected key variables, additional sensitivity analyses may also be performed in which all post-baseline measurements collected during the study will be included and endpoint will be defined within this extended timeframe.

6.3.1. Secondary Variables

The secondary efficacy endpoints are as follows:

- change in pre-bronchodilator FEV_1 from baseline/DoR at week 52
- change in Asthma Quality of Life Questionnaire for patients 12 years and older (AQLQ +12) score from baseline/DoR at week 52
- change in 6-item Asthma Control Questionnaire (ACQ-6) score from baseline/DoR at week 52
- change in total asthma symptom scores (day and night) from baseline at week 52
- percentage of asthma control days from baseline/DoR to week 52
- change in St. George's Respiratory Questionnaire (SGRQ) from baseline/DoR at week 32
- time to first clinical asthma exacerbation during the 52-week treatment period
- frequency of exacerbations requiring hospitalization or emergency department visits per patient during the 52-week treatment period
- frequency of moderate exacerbations defined as exacerbations requiring additional asthma controller medication that was not a systemic corticosteroid and that did not result in an asthma-specific hospitalization or emergency department visit during the 52-week treatment period

Testing of the secondary variables will be performed using the sequential testing procedure in the order as specified above, as described in Section 4.3.

[redacted]

6.3.3. Pulmonary Function Tests

6.3.3.1. Variable Definition

Pulmonary function tests will be measured using spirometry, according to ATS/ERS 2005 procedural guidelines. Pre-bronchodilator assessments (FVC, FEV_1, $FEF_{25\%-75\%}$) are measured at weeks 2, 4, 8, 12, 16, 32, and 52 and post-bronchodilator assessments (FEV_1) are measured at weeks 16, 32, and 52.

The FVC is the volume of air, in liters (L), that can be forcibly blown out after full inspiration. The FEV_1 is the volume of air (L) that can be forcibly exhaled from the lungs in the first second. The $FEF_{25\%-75\%}$ is the forced expiratory flow (L/second) at 25% to 75% forced vital capacity. The percent (%) predicted FEV_1 is derived as the actual FEV_1 divided by the standard predicted FEV_1 (multiplied by 100). The National Health and Nutrition Examination Survey (NHANES) III reference equations will be used. An additional correction factor will be applied for Asian patients (Hankinson et al 2010).

6.3.3.2. Analysis

Summary statistics of actual values and change from baseline to each scheduled visit will be provided by treatment group.

Analysis of the change from baseline to each scheduled visit will be performed using a mixed effect model for repeated measures (MMRM) including fixed effects for treatment, visit, treatment by visit interaction, age group (12 to <18 years and ≥18 years), blood eosinophil counts at enrollment (300 to <400/µL and ≥400/µL), and sex, height and baseline value as covariates, and patient as a random effect. Age and blood eosinophil categories will be based on data recorded in the clinical database. An unstructured covariance matrix will be used for the within patient correlation modeling. If the fit of the unstructured (UN) covariance matrix fails to converge, the following covariance structures will be tried in order until convergence is reached: first order autoregressive (AR[1]) and compound symmetry (CS). Based on the MMRM model, the treatment effect, the difference from placebo, and the associated 95% CI will be presented together with the corresponding p-value.

The following sample SAS® code pertains to the MMRM analysis.

```
proc mixed data=<<>>;
    class patient visit treatment strata1 strata2 sex;
    model change=treatment strata1 strata2 sex height baseline visit treatment*visit
                /ddfm=kr alpha=0.05;
    repeated visit /type=un subject=patient r;
    lsmeans treatment*visit / diff cl;
    ods output lsmeans=<<>>;
    ods output diffs=<<>>;
run;
```

Model results will only be reported if there are at least 15 patients contributing to the analysis in each treatment group; otherwise only the descriptive statistics will be displayed. A line graph presenting the LS mean change from baseline over time (at each visit) will be provided for pre-bronchodilator FEV_1, [redacted] by treatment group.

Pre-bronchodilator FEV_1 at Week 52 will additionally be examined for the selected subgroups defined in Section 3.4. The analysis of subgroups will use a MMRM model similar to the one described above. Subgroups will be presented graphically using forest plots.

The proportion of patients achieving an increase of ≥100 mL in FEV_1 from baseline to each scheduled visit will be summarized. A stratified (based on randomization strata) Cochran-Mantel-Haenszel (CMH) test will be used to analyze the proportion of patients achieving an increase of ≥100 mL in FEV_1 from baseline to Week 52.

6.3.4. AQLQ +12

6.3.4.1. Variable Definition

The AQLQ +12 is a modified version of the standardized AQLQ which measures functional impairments experienced by adults ≥17 years of age. The AQLQ +12 is valid for patients aged 12-70 years.

The AQLQ +12 is a 32-item instrument administered as a self assessment at weeks 4, 8, 12, 16, 32, and 52. Patients are asked to recall their experiences during the previous 2 weeks and to score each question on a 7-point scale (7 = no impairment, 1 = severe impairment).

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

6.3.4.1.1. 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.

6.3.4.2. Analysis

Summary statistics of actual values and change from baseline to each scheduled visit will be provided by treatment group.

Analysis of the change from baseline to each scheduled visit will use the same MMRM model described in Section 6.3.3.2 with the exception of inclusion of sex and height in the model. A line graph will be provided for the LS mean change from baseline over time (at each visit).

AQLQ +12 at Week 52 will additionally be examined for the selected subgroups defined in Section 3.4. The analysis of subgroups will use a MMRM model similar to the one described above. Subgroups will be presented graphically using forest plots.

The proportion of patients achieving an increase of ≥0.5 in the AQLQ +12 score from baseline to each scheduled visit will be summarized. A stratified (based on randomization strata) Cochran-Mantel-Haenszel (CMH) test will be used to analyze the proportion of patients achieving an increase of ≥0.5 in the AQLQ +12 score from baseline to Week 52.

6.3.5. ACQ-6

6.3.5.1. Variable Definition

The ACQ-6 was developed to measure asthma control. The ACQ-6 is a 6-item instrument; each item is scored on a scale of 0 to 6 (higher scores are an indication of poorer asthma control). At weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, 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 change from baseline to each scheduled visit will be provided by treatment group.

Analysis of the change from baseline to each scheduled visit will use the same MMRM model described in Section 6.3.3.2 with the exception of inclusion of sex and height in the model. A line graph will be provided for the LS mean change from baseline over time (at each visit).

ACQ-6 at Week 52 will additionally be examined for the selected subgroups defined in Section 3.4. The analysis of subgroups will use a MMRM model similar to the one described above. Subgroups will be presented graphically using forest plots.

The proportion of patients achieving a reduction of ≥0.5 in the ACQ-6 score from baseline to each scheduled visit will be summarized. A stratified (based on randomization strata) CMH test will be used to analyze the proportion of patients achieving a reduction of ≥0.5 in the ACQ-6 score from baseline to Week 52.

6.3.6. SGRQ

6.3.6.1. Variable Definition

St. George's Respiratory Questionnaire (SGRQ) is a health status survey specific for chronic obstructive pulmonary disease and other respiratory diseases. The SGRQ consists of 2 parts: Part 1 produces a symptom score and Part 2 produces an activity and impacts score. A total score is also calculated. The SGRQ is administered as a self assessment at weeks 32 and 52.

The questions in the SGRQ are divided into 3 domains:

- Symptoms: Questions 1-8
- Activity: Questions 11, 15

- Impacts: Questions 9-10, 12-14, 16-17

The SGRQ requests a single response to each of Questions 1-10 and 17; whereas Questions 11-16 each request multiple responses, resulting in a total of 50 responses across the questionnaire.

6.3.6.1.1. Missing data handling and total score calculation

Each questionnaire response has a unique empirically derived 'weight' (the lowest possible weight is 0 and the highest is 100). The weights associated with each response is provided in Appendix C. Derivation of each domain and total score is as follows:

1. The weights for all items with a positive response are summed.
2. The weights for missing items are deducted from the maximum possible weight for each domain (or total) score. The maximum possible weights for each domain and total score are 662.5 (symptoms), 1209.1 (activity), 2117.8 (impacts), and 3989.4 (total).
3. The score is calculated by dividing the summed weights (from Step 1) by the adjusted maximum possible weight for the domain or total score (from Step 2) and expressing the result as a percentage:

   Score = 100 x (Sum of weights from positive items in the domain (or total) / Sum of weights for all items in the domain (or total))

Thus, scores are expressed as a percentage of overall impairment, where 100 represents the worst possible health status and 0 represents the best possible health status. The questionnaire requests a single response to each of Questions 1-10 and 17. If multiple responses are given to any one of these questions, then the weights for the positive responses for that question will be averaged.

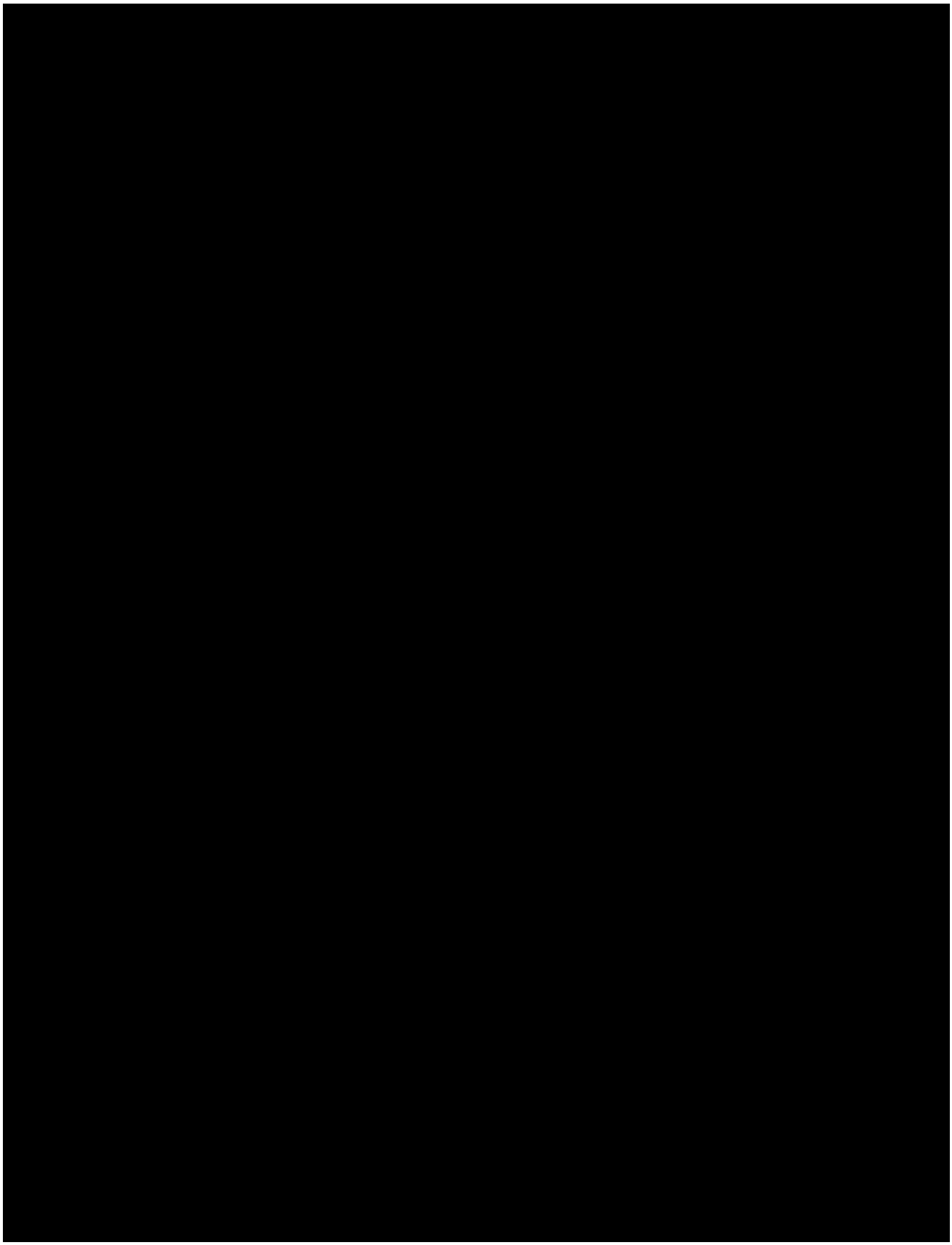
A score will only be calculated if at least 75% of the responses for the total and/or domain score are non-missing for a given visit. If more than 25% of the questions are missing, then the total and/or domain score will be considered missing for that visit. For the symptoms domain (8 total responses), this threshold translates to a maximum of 2 missed responses that can be tolerated. For the activity domain (16 total responses), a maximum of 4 missed responses can be tolerated. For the impacts domain (26 total responses), a maximum of 6 missed responses can be tolerated. For the total score (50 total responses), a maximum of 12 missed responses can be tolerated.

6.3.6.2. Analysis

Summary statistics of actual values and change from baseline to each scheduled visit will be provided by treatment group.

Analysis of the change from baseline to each scheduled visit will use the same MMRM model described in Section 6.3.3.2 with the exception of inclusion of sex and height in the model.

The proportion of patients achieving a reduction of ≥4 in the SGRQ score from baseline to each scheduled visit will be summarized. A stratified (based on randomization strata) CMH test will be used to analyze the proportion of patients achieving a reduction of ≥4 in the SGRQ score from baseline to Week 32.



[redacted]

6.3.9. Asthma Control Diary

6.3.9.1. Variable Definition

6.3.9.1.1. Asthma symptom scores

The asthma symptom score will be determined every morning and evening by the patient and recorded in the daily asthma control diary. The asthma symptom score is used to measure how much patients are bothered by their asthma symptoms. Asthma symptom score will be rated on a scale, with higher scores indicating more severe symptoms. The daytime asthma symptom score (range: 0-5) will be assessed in the evening and indicate how the patient felt earlier that same day. The nighttime asthma symptom score (range: 0-4) will be assessed in the morning and indicate how the patient felt during the previous night. Total asthma symptom score (range: 0-9) will be derived as the sum of the daytime and nighttime symptom scores.

6.3.9.1.2. Total reliever use

The number of times SABA reliever therapy is used will be recorded by the patient, once in the morning and once in the evening. Total reliever use will be derived as the sum of the morning and evening counts.

6.3.9.1.3. Nighttime awakenings

Nighttime awakenings will be recorded daily in the morning to indicate whether the patient was awakened during the previous night due to asthma. An awakening-free night (y/n) is defined as a night during which the patient did not experience a nighttime awakening.

6.3.9.1.4. Peak expiratory flow

Peak expiratory flow (PEF) is the maximum speed of exhalation, measured by a PEF meter. Morning (AM) and evening (PM) ambulatory PEF will be measured daily by the patient and the maximum of 3 separate readings will be recorded in the asthma control diary.

6.3.9.1.5. Asthma control days

An asthma control day (y/n) is defined as a day on which the patient used ≤2 puffs of inhaled SABA therapy, had no nighttime awakenings, and experienced no CAEs or moderate exacerbations.

6.3.9.2. Analysis

Compliance with the daily diary assessments will be derived for each patient as an additional measure of protocol adherence. A diary compliant day will be defined as a day with non-missing values for all diary assessments, including AM/PM asthma symptom score, [redacted],

[redacted]. Diary compliance will be derived as a percentage over the treatment period:

- Diary compliance (%) = 100 x (total number of diary compliant days / total number of days during the treatment period)

The treatment period for diary compliance extends from the first day of study drug to the last day of study drug. Note that, in this analysis, missing data will be treated as non-compliant (eg, if compliance cannot be assessed for a given day due to missing data, then the day will not be counted as a diary compliant day).

[redacted]

A weekly average of the daily diary measures ([redacted], total asthma symptom score, and [redacted]) will be derived (see Table 3 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.

[redacted] and asthma control days will be derived and analyzed as percentages over the relevant analysis period, derived as:

- Asthma control days (%) = 100 x (total number of asthma control days / total number of days during the analysis period)
- [redacted]

The analysis periods are as defined in Section 6.3. Note that, in this analysis, missing data will be treated as non-responders (eg, if asthma control cannot be assessed for a given day due to missing data, then the day will not be counted as an asthma control day).

Summary statistics of actual values and change from baseline to each week will be provided by treatment group.

Analysis of the change from baseline to each week will use a similar MMRM model as described in Section 6.3.3.2 with the exception of inclusion of sex and height in the model.

Analysis of the percentage of [redacted] and percentage of asthma control days will be performed using an analysis of variance (ANOVA) model with fixed effects for treatment, age group, and blood eosinophil counts at enrollment.

A line graph presenting the LS mean change from baseline over time (at each week) will be provided for [redacted] total asthma symptom score, and [redacted] by treatment group.

7. SAFETY ANALYSIS

7.1. General

The safety analysis set will be used for all safety analyses, unless otherwise noted. Summaries will be presented by treatment group actually received.

In this study, patients are encouraged to remain in the study and complete the remaining study assessments even after withdrawing from treatment. The assessment of safety in this context will be based on measurements and events recorded during the treatment period (on-treatment). On-treatment assessments will be defined as events and measurements occurring between the first dose of study drug and the end of treatment (week 52) visit for patients who complete treatment and between the first dose of study drug and the last dose of study drug + 4 weeks for patients who discontinued treatment early.

7.2. 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 treatment group and overall, and by baseline stratification factors.

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

- Completed: End of treatment (week 52) visit date – first dose date + 1
- Discontinued: Last dose date – first dose date + 29

7.3. 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 advese event summaries will be presented by treatment group and overall, 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 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.

Summaries for the most common adverse events (incidence ≥2% in reslizumab-treated patients) and adverse events occurring with greater frequency for reslizumab-treated patients compared to placebo will also be presented.

All adverse events, including pre-treatment events, will be included in the patient listings. The mapping of MedDRA dictionary terms for adverse event descriptions will also be provided.

7.3.1. Adverse Events of Special Interest

7.3.1.1. Administration Site Reactions

Administration site reactions will be defined based on:

- MedDRA HLGT: Administration Site Reactions

Summaries will be presented by high level term (HLT), preferred term, and 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.

7.3.1.2. 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 treatment group.

Adverse events suspected by the investigator to be anaphylaxis events will be summarized by preferred term and 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.

7.3.1.3. Malignancies

Malignancies will be defined based on:

- MedDRA SMQ: Malignant Tumors

Summaries will be presented by preferred term and treatment group.

7.3.1.4. Helminth infections

Helminth infections will be defined based on:

- MedDRA HLGT: Ectoparasitic Disorders
- MedDRA HLT: Parasite Identification and Serology

- MedDRA HLT: Parasitic Lower Respiratory Tract Infections
- MedDRA HLT: Skin and Subcutaneous Arthropod and Parasitic Infestations

Summaries will be presented by high level term (HLT), preferred term, and treatment group.

7.3.1.5. Muscle Disorders

Muscle disorders will be defined based on:

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

Summaries will be presented by high level term (HLT), preferred term and treatment group.

7.3.1.6. 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 5. The FDA terms provided are from the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents.

Summaries will be presented by preferred term and treatment group.

Table 5: List of Terms for Opportunistic Infections

Term	Code	Level	FDA term (if applicable)	If LLT- under which PT
Acinetobacter infection	10051894	PT	Acinetobacter infection	
Aspergillus infection	10074171	PT	Aspergillosis	
Blastomycosis	10005098	PT	Blastomycosis, extrapulmonary	
Burkitt's lymphoma	10006595	PT	Burkitt's lymphoma	
Oesophageal candidiasis	10030154	PT	Candidiasis of esophagus	
Cerebral toxoplasmosis	10057854	PT	Toxoplasmosis of brain	
Cervix carcinoma	10008342	PT	Cervical cancer invasive	
Coccidioidomycosis	10009825	PT	Coccidioidomycosis, dissemintaed or extrapulmonary	
Cryptococcosis	10011490	PT	Cryptococcosis, extrapulmonary	
Cryptosporidiosis infection	10011502	PT	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)	

Table 5: List of Terms for Opportunistic Infections (Continued)

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 infection	10011831	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus mononucleosis	10011834	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
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 syndrome	10056262	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus urinary tract infection	10051350	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Cytomegalovirus viraemia	10058854	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	
Disseminated cytomegaloviral infection	10049075	PT	Cytomegalovirus disease (other than liver, spleen, or nodes)	

Table 5: List of Terms for Opportunistic Infections (Continued)

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	
Hepatitis C	10019744	PT	Hepatitis C	
Herpes simplex skin chronic ulcers	10058426	LLT	Herpes simplex ulcers chronic (>1mo)	Under "Herpes dermatitis" PT
Herpes simplex	10019948	PT	Herpes simplex bronchitis	
Herpes simplex pneumonia	10065046	PT	Herpes simplex pneumonitis	
Herpes simplex oesophagitis	10074242	PT	Herpes simplex oesophagitis	
Shingles	10040555	LLT	Shingles when 2 distinct episodes or more than 1 dermatome	Under "Herpes zoster" PT
Histoplasmosis	10020141	PT	Histoplasmosis extrapulmonary	
Histoplasmosis disseminated	10020144	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 sarcoma	10023284	PT	Kapposi’s sarcoma	
Lymphoid interstitial pneumonia	10062997	LLT	Lymphoid interstitial pneunmonia	Under "Interstitial lung disease" PT
Listeriosis	10024641	PT	Listeriosis	
Mycobacterial infection	10062207	PT	Mycobacterium infections, other species or unidentified species, disseminated or extrapulmonary (eg, M. haemophilium, M. fortuitum, or M. marinum)	
Mycobacterium avium complex infection	10058806	PT	Mycobacterium avium complex disseminated or extrapulmonary	
Mycobacterium kansasii infection	10028447	PT	M. Kansasii, disseminated or extrapulmonary	
Nocardiosis	10029444	PT	Nocardiosis	

Table 5: List of Terms for Opportunistic Infections (Continued)

Pneumocystis jirovecii infection	10073756	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)	
Primary central nervous system lymphoma	10036685	LLT	Lymphoma primary of brain	
Candidiasis of bronchi	10064443	LLT	Candidiasis of bronchi	Under "Respiratory moniliasis" PT
Candidiasis of trachea	10064459	LLT	Candidiasis of trachea	Under "Respiratory moniliasis" PT
Candidiasis of lung	10007155	LLT	Candidiasis of lungs	Under "Respiratory moniliasis" PT
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
Active tuberculosis	10071157	LLT	Any active TB	Under "Tuberculosis" PT
Mycobacterium tuberculosis NOS	10028461	LLT	Mycobacterium tuberculosis, any site, latent or active	Under "Tuberculosis" PT

7.3.2. Adverse Events by Subgroup

Overall adverse event categories will be presented for selected subgroups defined in Section 3.4. The categories of adverse events will include:

- Patients with at least one AE
- Patients with at least one treatment-related AE
- Patients with at least one SAE
- Patients with at least one SAE resulting in death
- Patients with at least one AE leading to discontinuation

Selected summaries will also be presented for adverse events by system organ class (SOC), preferred term and subgroup.

7.4. Deaths

If any patient dies during the study all relevant information will be discussed in the patient's narratives included in CSR. A patient listing of deaths will be provided.

7.5. Clinical Laboratory Tests

Analysis of laboratory tests will be based on on-treatment results, as described in Section 7.1. Measurements collected outside of the defined treatment periods will be excluded. All results will be included in the patient listings.

Summary statistics for laboratory tests will be presented at baseline and at each scheduled visit. Actual values and changes from baseline to each visit will be summarized. 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 be prompted to collect additional information 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 laboratory values will be summarized using the criteria specified in Table 6; 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 on treatment value for CPK.

Table 6: 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

Table 6: Criteria for Potentially Clinically Significant Laboratory Values (Continued)

		Adults (≥18 years)		Adolescents (12 to <18 Years)	
Test		**Criterion value**	**Change from baseline**	**Criterion value**	**Change from baseline**
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
Urinalysis					
Blood (HGB)		≥2 unit increase from baseline		≥2 unit increase from baseline	
Glucose		≥2 unit increase from baseline		≥2 unit increase from baseline	
Ketones		≥2 unit increase from baseline		≥2 unit increase from baseline	
Total protein		≥2 unit increase from baseline		≥2 unit increase from baseline	

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.

7.6. Vital Signs

Analysis of vital signs will be based on on-treatment results, as described in Section 7.1. Measurements collected outside of the defined treatment periods will be excluded. All results will be included in the patient listings.

Summary statistics for vital signs will be presented at baseline and at each visit. 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). A scatter plot will be provided for the baseline and the maximum on treatment value for weight.

Table 7 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 7: 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	>100.5°F	Increase of ≥2	>100.5°F	Increase of ≥2
	<96.5°F	Not applicable	<96.5°F	Not applicable

7.7. Electrocardiography

Analysis of ECG findings will be based on on-treatment results, as described in Section 7.1. Measurements collected outside of the defined treatment periods will be excluded. All results will be included in the patient listings.

Shifts (normal and abnormal) from baseline to week 52 and to overall will be summarized using patient counts. For overall, the worst post-baseline finding (eg, the abnormal finding if there are both normal and abnormal findings) for the patient will be summarized. Summary statistics for ECG variables will be presented at week 52. Actual values and changes from baseline to each

visit will be summarized. ECG results at weeks 24 and 36 will be presented in the patient listings.

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 52
  - QTc interval >450 msec
  - QTc interval >500 msec
- Change from baseline to week 52
  - QTc interval increase >30 msec
  - QTc interval increase >60 msec
- Combined absolute value and change from baseline to week 52
  - 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

7.8. Physical Examinations

Analysis of physical exam findings will be based on on-treatment results, as described in Section 7.1. Measurements collected outside of the defined treatment periods will be excluded. All results will be included in the patient listings.

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

7.9. Other Safety Measures and Variables

7.9.1. Concomitant Therapy or Medication

All concomitant medications will be coded using the WHO Drug. 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 during the treatment period. Medications with a start date greater than the upper bound of the treatment period 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).

8. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

The safety analysis set will be used for the following analyses, unless otherwise noted.

8.1. Pharmacokinetic Analysis

The PK endpoints are the serum reslizumab concentrations at baseline/DoR; weeks 1 (patients in US study centers only), 2, and prior to study drug administration at weeks 4, 8, 12, 16, 20, 32, 48, 52 or early withdrawal; and the follow up visit (approximately week 64). An additional PK sample will be collected 28 weeks (±2 weeks) after the last dose of study drug (approximately week 76) for validation of the ADA assessment.

Reslizumab concentration data will be summarized descriptively for reslizumab-treated patients by time point. Reslizumab concentration data will additionally be summarized by ADA status. Samples from placebo-treated patients will not be analyzed. Listings for reslizumab concentration data will be presented.

The data will be pooled with data from other studies and analyzed using population PK and PK/PD analysis and reported in a separate report.

8.2. Pharmacodynamic Analysis

8.2.1. Target Biomarker (Blood Eosinophil Counts)

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

Summary statistics of actual values, change from baseline, and percent change from baseline to each scheduled visit will be provided by treatment group, using the ITT analysis set. A line graph will be provided summarizing the mean blood eosinophil counts at each visit.

Blood eosinophils will additionally be examined for selected subgroups defined in Section 3.4. As described above, the analysis of eosinophils by subgroups will be summarized descriptively.

8.3. Immunogenicity

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

Two types of antibody assay will be performed, an immunogenicity status assay (ADA) and neutralizing 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 assay will be performed, which also produces a positive or negative result; a titre 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).

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. Samples from placebo-treated patients will not be analyzed.

9. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS®.

10. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

There are no changes to the analyses specified in the CSP, Amendment 04 to report.

- Table 8 summarizes the key changes that have been implemented since the original approved SAP.
- Table 9 summarizes the key changes that have been implemented since the approved SAP, Amendment 01.

Only substantive changes have been included; editorial and/or administrative changes are generally not listed.

Table 8: Key Changes to the Statistical Analysis Plan, Amendment 01

SAP Section	SAP Description	Change	Rationale
3.2	<<null>>	Patients dosed in error, but who otherwise received at least 1 dose of reslizumab, will be assigned to reslizumab for the analysis of safety data.	Clarified how safety analyses would be handled if a patient receives a combination of both treatments.
3.3.1 (Table 2)	<<null>>	• Patient was not on an ICS at baseline (at least a medium total daily dose) • Patients who received the incorrect study treatment at any point during the study	Two additional protocol violations.
3.4.1	The primary efficacy endpoint will be analyzed separately for patients aged 12 to <18 years and ≥18 years.	Selected efficacy endpoints including CAEs (primary), pre-bronchodilator FEV_1, and blood eosinophils will be analyzed separately for patients aged 12 to <18 years and ≥18 years.	Subgroup analyses planned for FEV_1 and eosinophils, in addition to CAE. Note: The same changes are applied to other subsequent subgroup sections (ie, 3.4.2, 3.4.5)
3.4.3	[redacted]		
3.4.4	<<null>>	Asthma Background Medication	Created new section for subgroups based on the identified classes of background asthma medication.
3.4.5	• Age group (<65, ≥65 years) • Race (White, Black, Asian, Other) • Region (US, non-US) • <<null>>	• <<deleted>> • Race (White, Black, Asian, Other; Black, non-Black) • Region (North America, Europe, Latin America, Asia/Pacific; US, non-US) • ADA status (Positive, Negative) – for reslizumab-treated patients only	Modifications to the race and region subgroups; removed additional subgroup category for age; included subgroup for ADA status.
4.2.4	The baseline value for blood eosinophil levels will be screening value (for	The baseline value for blood eosinophil levels will be the maximum value of the observed	Modified definition of baseline to potentially account for patients who fulfilled the eosinophil

SAP Section	SAP Description	Change	Rationale
	consistency with study entry criteria).	assessments from the screening visit to baseline/DoR (inclusive).	threshold prior to randomization, but not at the screening visit.
5.3	The baseline stratification factors (age and baseline blood eosinophil counts) will also be summarized. <<null>>	The baseline stratification factors (age and baseline blood eosinophil counts) and patients taking the various classes of background medication at baseline (defined in Section 3.4.4) will also be summarized. Age will be calculated based on the date of birth relative to the screening visit (date of informed consent). 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.	Additional summaries based on the asthma medication classes. Clarification, since derivation of age may not always be possible due to partial birth dates.
5.5	<<null>>	In addition, the total daily ICS dose taken at baseline will be summarized descriptively. The reported ICS doses will first be converted to fluticasone equivalents using the following conversion factors.	Additional summary based on ICS dose at baseline; included Table 4 for ICS conversion factors.
6.2.2	Any clinical asthma exacerbations that occur between the completion of the first dose of study drug and 2 weeks after the end of treatment/early withdrawal visit will be counted towards the CAEs for analysis.	Any clinical asthma exacerbations that occur between the day of randomization and 2 weeks after the end of treatment/early withdrawal visit will be counted towards the CAEs for analysis.	Clarified that the lower bound of treatment period will be the day of randomization (rather than first dose date), in the case that the day of randomization and first dose date do not coincide. Note: The same changes are applied to other sections (ie, 4.5, 6.2.3, 6.2.6, 6.3)
6.2.3	The primary analysis based on the per protocol analysis set.	Per protocol analysis: on-treatment analysis of the primary endpoint based on the per protocol analysis set.	Clarified that the per protocol analysis is based on on-treatment events.
6.2.6	Time-to-first event will be analysed separately for all exacerbation events and on-treatment events.	Time-to-first event will be analysed for on-treatment events.	Time-to-first event only planned to be summarized for on-treatment events.

SAP Section	SAP Description	Change	Rationale
	The time period for the primary time-to-event analysis will extend from the first dose of study drug to the end of treatment/early withdrawal visit (+2 weeks). Patients without an event during this time frame will be censored at the date of the end of treatment/early withdrawal visit (+2 weeks). For the on-treatment analysis, only events occurring during the treatment period will be counted. Patients without an event during this time frame will be censored at either the date of the end of treatment (week 52) visit for patients who completed treatment and at the date of last dose (+4 weeks) for patients who discontinued early.	<<deleted>> The time period for the on-treatment analysis will extend from the day of randomization to the cessation of study treatment, defined as the date of the end of treatment (week 52) visit for patients who completed treatment and the date of last dose (+4 weeks) for patients who discontinued treatment early. Patients without an event during the treatment period will be censored at either the date of the end of treatment (week 52) visit for patients who completed treatment or at the date of last dose (+4 weeks) for patients who discontinued early.	
6.3.3.2	Summary statistics of actual values and change from baseline to each scheduled visit ~~and to endpoint~~ will be provided by treatment group. Analysis of the ~~overall~~ change from baseline ~~over 52 weeks, and~~ to each scheduled visit will be performed using a mixed effect model for repeated measures (MMRM) including fixed effects for treatment, visit, treatment by visit interaction, age group (12 to <18 years and ≥18 years), blood eosinophil counts at enrollment (300 to <400/µL and ≥400/µL), baseline value as a covariate, and patient as a random effect.	Summary statistics of actual values and change from baseline to each scheduled visit will be provided by treatment group. Analysis of the change from baseline to each scheduled visit will be performed using a mixed effect model for repeated measures (MMRM) including fixed effects for treatment, visit, treatment by visit interaction, age group (12 to <18 years and ≥18 years), blood eosinophil counts at enrollment (300 to <400/µL and ≥400/µL), and sex, height and baseline value as	Summaries at endpoint have been removed. Sex and height have been included as additional factors in the model for pulmonary function tests. Analysis of the overall change over 52 weeks has been removed.

SAP Section	SAP Description	Change	Rationale
	Analysis of change from baseline to endpoint will be performed using an analysis of covariance (ANCOVA) model … Based on the ANCOVA model … with the corresponding p-value. <<null>>	covariates, and patient as a random effect. <<deleted>> Model results will only be reported if there are at least 15 patients contributing to the analysis in each treatment group; otherwise only descriptive statistics will be displayed.	ANCOVA analysis at endpoint has been removed. Pre-specified the approach to analysis in the case of small sample sizes (eg, in subgroups). Analyses based on less than 15 patients may result in convergence issues or general issues with interpretability. Note: The same changes are applied to other subsequent efficacy sections (ie, 6.3.4.2, 6.3.5.2, 6.3.6.2, 6.3.7.2, 6.3.8.2, 6.3.9.2).
6.3.4.2	A stratified (based on randomization strata) Cochran-Mantel-Haenszel (CMH) test will be used to analyze the proportion of patients achieving an increase of ≥0.5 in the AQLQ +12 score from baseline to each scheduled visit and endpoint.	The proportion of patients achieving an increase of ≥0.5 in the AQLQ +12 score from baseline to each scheduled visit will be summarized. A stratified (based on randomization strata) Cochran-Mantel-Haenszel (CMH) test will be used to analyze the proportion of patients achieving an increase of ≥0.5 in the AQLQ +12 score from baseline to Week 52.	Clarified that the planned analysis (CMH) will be done at Week 52; the rest of the visits will be summarized descriptively. Note: The same changes are applied to other subsequent efficacy sections (ie, 6.3.5.2, 6.3.6.2, 6.3.8.2).
6.3.8.1	[redacted]		
6.3.8.2			

Table 8: Key Changes to the Statistical Analysis Plan, Amendment 01 (Continued)

SAP Section	SAP Description	Change	Rationale
7.3	<<null>>	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. Summaries for the most common adverse events (incidence ≥2% in reslizumab-treated patients) and adverse events occurring with greater frequency for reslizumab-treated patients compared to placebo will also be presented.	Additional AE tables.
7.3.1	<<null>>	Adverse events of special interest updated to include: • Administration Site Reactions • Anaphylaxis and Hypersensitivity • Malignancies • Helminth Infections • Muscle Disorders/CPK	Categories of adverse events have been added, along with the derivations of each.
7.3.2	<<null>>	Adverse events by subgroup	Created separate section for subgroup analysis and clarified the analyses.
7.5	Summary statistics for laboratory tests will be presented at baseline, at each scheduled visit ~~and endpoint~~. Actual values and changes from baseline to each visit ~~and endpoint~~ will be summarized.	Summary statistics for laboratory tests will be presented at baseline and at each scheduled visit. Actual values and changes from baseline to each visit will be summarized. Shifts (below, within, and above the normal range) from baseline to	Summaries at endpoint have been removed. Note: The same changes are applied to other subsequent safety sections (ie, 7.6, 7.7, 7.8).

SAP Section	SAP Description	Change	Rationale
	Shifts (below, within, and above the normal range) from baseline to each visit ~~and~~ ~~endpoint~~ will be summarized using patient counts and percentages. ~~Shift tables of abnormal values (change from baseline: high/normal to low, low/normal to high, and other) will be provided for creatine phosphokinase (CPK) at each visit and endpoint~~. Shifts from baseline (Grades 0 to 4) to each visit ~~and endpoint~~ will also be summarized for CPK.	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.	Additional shift table has been removed.
7.5	<<null>>	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.	Modified the definition of potentially clinically significant values to account for presence of abnormal results at baseline.
	Scatter plots of the maximum on treatment values for total bilirubin vs. alanine aminotransferase and for total bilirubin vs. aspartate aminotransferase (each presented as multiples of the ULN) will be provided.	<<deleted>>	Formal plots are not planned.
	Table 4 and Table 5	Combined into one table (Table 4).	Combined for ease of review.
	Grade 0: ≤1 x ULN Grade 1: >1 x ULN to ≤2.5 x ULN Grade 2: >2.5 x ULN to ≤5 x ULN Grade 3: >5 x ULN to ≤10 x ULN Grade 4: >10 x ULN	Grade 0: <1.25 x ULN Grade 1: 1.25 x ULN to 1.5 x ULN Grade 2: 1.6 x ULN to 3 x ULN Grade 3: 3.1 x ULN to 10 x ULN Grade 4: >10 x ULN	Updated the CPK toxicity grade classifications.
	≥1.0 x 10^9/L	≥1.5 x 10^9/L	Updated the PCS value for eosinophils.

Table 8: Key Changes to the Statistical Analysis Plan, Amendment 01 (Continued)

SAP Section	SAP Description	Change	Rationale
7.6	<<null>> Table 6 and Table 7	Summaries of potentially clinically significant values will include all post-baseline values (including scheduled, unscheduled, and early termination visits). Combined into one table (Table 5).	Clarification Combined for ease of review.
8.2.1	Summary statistics of actual values and change from baseline to each scheduled visit ~~and to endpoint~~ will be provided by treatment group. Analysis of the overall change from baseline over 52 weeks and the change from baseline to each scheduled visit will use the MMRM model described in Section 6.3.3.2 with the exception of inclusion of sex and height in the model. Analysis of the change from baseline to endpoint will be performed using the ANCOVA model described in Section 6.3.3.2 with the exception of inclusion of sex and height in the model.	Summary statistics of actual values, change from baseline, and percent change from baseline to each scheduled visit will be provided by treatment group, using the ITT analysis set. <<deleted>>	Clarified that analysis of eosinophils will be based on the ITT analysis set. Included summary of percent change from baseline and removed summaries at endpoint. Eosinophils will be summarized descriptively.
8.2.3	The number of patients with positive or negative phadiatop results will be summarized at baseline and week 52.	<<deleted>>	Phadiatop allergy test is considered a baseline patient characteristic and will be summarized only at baseline.
8.3	<<null>>	Two types of antibody assay will be performed, an immunogenicity status assay (ADA) and neutralizing assay (NAb). For the ADA assay, a screening assessment will	Clarified the process for ADA samples.

SAP Section	SAP Description	Change	Rationale
		be performed which produces a positive or negative result. For samples with a positive result, a neutralizing assay will be performed, which also produces a positive or negative result and a titre 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).	

Table 9: Key Changes to the Statistical Analysis Plan, Amendment 02

SAP Section	SAP Description	Change	Rationale
2.1	A total of 400 patients are planned to be randomized in a 1:1 ratio (approximately 200 patients within each treatment group) to receive reslizumab 110 mg or matching placebo every 4 weeks for 52 weeks.	A total of 450 patients are planned to be randomized in a 1:1 ratio (approximately 225 patients within each treatment group) to receive reslizumab 110 mg or matching placebo every 4 weeks for 52 weeks.	Sample size aligned with amended protocol
2.3	Based on the assumptions above, 200 patients per group (400 total) will provide more than 90% power (99.6%) to detect significant treatment effect of reslizumab over placebo in the reduction of exacerbation rate. The sample size was increased beyond the sample size required to provide 90% power in order to allow sufficient number of patients to assess safety and immunogenicity. The current sample size also provides higher power for other efficacy endpoints.	Based on the assumptions above, 225 patients per group (450 total) will provide >90 % power to detect significant treatment effect of reslizumab over placebo in the reduction of exacerbation rate. The sample size was increased beyond the sample size required to provide 90% power in order to allow sufficient number of patients to assess safety and immunogenicity and to ensure adequate enrollment in the adolescent subset. The current sample size also provides higher power for other efficacy endpoints.	Sample size aligned with amended protocol
2.4	Patients who meet all inclusion criteria and none of the exclusion criteria will be randomly assigned to receive reslizumab 110 mg sc or matching placebo (approximately 200 patients per treatment group) in a 1:1 ratio.	Patients who meet all inclusion criteria and none of the exclusion criteria will be randomly assigned to receive reslizumab 110 mg sc or matching placebo (approximately 225 patients per treatment group) in a 1:1 ratio.	Sample size aligned with amended protocol
3	<<null>>	Site [redacted] was terminated due to numerous unresolved Good Clinical Practice (GCP) issues including an overall lack of adequate source documentation (letter to FDA dated 2 December 2016). The data from this site are deemed invalid and patients from this site will be excluded from the efficacy analysis but will be included as part of the safety analysis. In addition, these patents will be summarized as randomized, but not analyzed, as part of the	Termination of Site [redacted]

SAP Section	SAP Description	Change	Rationale
		ITT analysis set in the disposition summary (Section 5.2).	
3.1	<<null>>	Two analytic approaches are planned using the ITT analysis set. • In the first approach, all data collected from patients will be included, regardless of continued adherence to their assigned study treatment. • In the second approach, data collected from patients during the treatment period will be included, up to the point at which patients discontinue from their assigned study treatment (on-treatment). 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 52) 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. The analytic approach including all data collected from patients will be utilized as the primary approach to analysis for the primary endpoint (frequency of CAE). The on-treatment approach will be conducted as a sensitivity analysis for the primary endpoint. For the analysis of all other efficacy endpoints, the on-treatment approach will be utilized as the main approach to analysis. The analytic approach including all data collected from	Clarification

SAP Section	SAP Description	Change	Rationale
		patients will additionally be conducted as sensitivity analyses for selected secondary endpoints.	
3.2	<<null>>	In this analysis, data collected from patients during the treatment period will be included, up to the point at which patients discontinue from their assigned study treatment. 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 52) 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. This analysis will be used as the default approach for all safety endpoints.	Clarification
3.3	<<null>>	The PP analysis set will only be presented for the primary endpoint. In this analysis, data collected from patients during the treatment period will be included, up to the point at which patients discontinue from their assigned study treatment.	Clarification
3.4.1	Selected efficacy endpoints including CAEs (primary), pre-bronchodilator FEV_1, and blood eosinophils will be analyzed separately for patients aged 12 to <18 years and ≥18 years.	Selected efficacy endpoints including CAEs (primary), pre-bronchodilator FEV_1, AQLQ+12, ACQ-6, and blood eosinophils will be analyzed separately for patients aged 12 to <18 years and ≥18 years. Age strata will be defined based on the age recorded in the clinical database.	Inclusion of 2 additional efficacy endpoints and clarification regarding definition of age strata
3.4.2	Selected efficacy endpoints including CAEs (primary), pre-bronchodilator FEV_1, and blood eosinophils will be analyzed separately for patients with baseline blood eosinophil levels 300/µL to <400/µL and ≥400/µL.	Selected efficacy endpoints including CAEs (primary), pre-bronchodilator FEV_1, AQLQ+12, ACQ-6, and blood eosinophils will be analyzed separately for patients with baseline blood eosinophil levels 300/µL to <400/µL and ≥400/µL. Eosinophil strata will	Inclusion of 2 additional efficacy endpoints and clarification regarding definition of eosinophil strata

SAP Section	SAP Description	Change	Rationale
		be defined based on the baseline blood eosinophil level recorded in the clinical database.	
3.4.5	Selected efficacy endpoints including CAEs (primary), pre-bronchodilator FEV1, and blood eosinophils will also be examined for the following demographic subgroups:	Selected efficacy endpoints including CAEs (primary), pre-bronchodilator FEV1, AQLQ+12, ACQ-6, and blood eosinophils will also be examined for the following demographic subgroups:	Inclusion of 2 additional efficacy endpoints. In addition, Europe region split into Eastern and Western Europe and region for Middle East/Africa added.
4.5, 6.2.2, 6.2.3, 6.2.6, 6.3, 6.3.9.2	For patients who completed treatment in this study, the treatment period will be defined from the day of randomization to the end of treatment (week 52) visit. For patients who prematurely discontinue treatment, the treatment period will be defined from the day of randomization to the last dose of study drug + 4 weeks.	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 52) 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.	Reference start date changed from day of randomization to day of first dose of study drug administration
5.2	<<null>> <<null>>	Patients will be categorized as completed the study if they either complete the study visits up to and including follow-up (Week 64, for patients not participating in the LTE study) or up to and including end of treatment (Week 52, for patients participating in the LTE study). KM plots will be provided for time to discontinuation from treatment to identify if there is a differential dropout pattern between the treatment groups.	Clarification, based on inclusion of the long term extension study New analysis added
5.3	<<null>>	Baseline demographics and patient characteristics will also be summarized separately for patients who discontinue from treatment and patients who complete treatment to investigate whether patients with and without missing values may have different characteristics at baseline.	New analysis added

SAP Section	SAP Description	Change	Rationale
6.2.2, 6.3.3.2	<<null>>	Age and blood eosinophil categories will be based on data recorded in the clinical database.	Clarification
6.2.3	<<null>>	The primary analysis with control variables for age and blood eosinophil categories based on data recorded in the IRT (as randomized). This analysis will only be performed if the number of discrepancies between data recorded in the IRT and the clinical database are sufficiently large (eg, 5% of total population).	New analysis added
6.2.3	On-treatment analysis: analysis of the primary endpoint including all exacerbations observed until treatment completion or until withdrawal from treatment, excluding any exacerbations observed after withdrawing from treatment. Per-protocol analysis: on-treatment analysis of the primary endpoint based on the per-protocol analysis set.	On-treatment: analysis of the primary endpoint including exacerbations during the treatment period (ie, observed until treatment completion or until withdrawal from treatment, excluding any exacerbations observed after withdrawing from treatment). Per-protocol: on-treatment analysis of the primary endpoint including exacerbations during the treatment period (ie, observed until treatment completion or until withdrawal from treatment, excluding any exacerbations observed after withdrawing from treatment), based on the PP analysis set.	Clarification
6.2.5	An interaction p-value will be derived from a separate NB model including terms for treatment, subgroup, and treatment by subgroup interaction.	An interaction p-value will be derived from a separate NB model including additional terms for subgroup and treatment by subgroup interaction.	Clarification
6.3.3.2	<<null>>	The proportion of patients achieving an increase of ≥100 mL in FEV_1 from baseline to each scheduled visit will be summarized. A	New analysis added

SAP Section	SAP Description	Change	Rationale
		stratified (based on randomization strata) Cochran-Mantel-Haenszel (CMH) test will be used to analyze the proportion of patients achieving an increase of ≥100 mL in FEV_1 from baseline to Week 52.	
6.3.4.2	<<null>>	AQLQ +12 at Week 52 will additionally be examined for the selected subgroups defined in Section 3.4. The analysis of subgroups will use a MMRM model similar to the one described above. Subgroups will be presented graphically using forest plots.	New analysis added
6.3.5.2	<<null>>	ACQ-6 at Week 52 will additionally be examined for the selected subgroups defined in Section 3.4. The analysis of subgroups will use a MMRM model similar to the one described above. Subgroups will be presented graphically using forest plots.	New analysis added
6.3.6.2	A stratified (based on randomization strata) CMH test will be used to analyze the proportion of patients achieving a reduction of ≥4 in the SGRQ score from baseline to Week 52.	A stratified (based on randomization strata) CMH test will be used to analyze the proportion of patients achieving a reduction of ≥4 in the SGRQ score from baseline to Week 32.	Updated the timepoint for SGRQ responder analysis to be aligned with protocol.
7.3.1.6	<<null>>	Opportunistic Infections	New section added
7.5	Table 6	Table 6	PCS (potentially clinically significant) criteria for CPK changed to Grades 3-4
8.2.2	[redacted]		Clarification

SAP Section	SAP Description	Change	Rationale
		[redacted]	

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APPENDIX A. IMPUTATION AND ANALYSIS STEPS FOR ANALYSIS OF THE FREQUENCY OF ASTHMA EXACERBATION

The following represents an outline of the planned methodology for the multiple imputation procedure for the primary analysis of the CAE variable. Minor deviations from this outline can be addressed in the discussion of the results in the CSR. In the situation that more significant updates are warranted, changes will be addressed in a SAP amendment to be finalized prior to database lock.

Step 1: Seed generation.

The seed generation utilized the code below, resulting in a seed (40880) that will be used in the analysis after unblinding.

```
data derived.seed;
  seed = int(time());
  put seed=;
  call symput('seed', left(seed));
run;
```

Step 2: Classify patients with missing data.

Patients in this study will be partitioned into the following 3 categories:

1. ET0; patients who completed all 52 weeks of treatment
2. ET1; patients who withdrew early from treatment but remained in the study contributing post-treatment follow-up data through Week 52
3. ET2; patients who withdrew early from treatment but elected not to remain in the study through Week 52

Step 3: Imputation of missing data.

Using the dataset of ET1 patients for each treatment group, fit a negative binomial regression model to the period of time after treatment withdrawal and estimate the mean number of exacerbations and dispersion parameter k. Let λ denote the estimated rate parameter for one month of duration. For each patient with missing data, derive the duration of missing exposure (T_M) for that patient calculated in months.

Let λ_M denote the unknown rate of exacerbations during the missing exposure period. The exacerbation rate λ_M will be simulated using a Gamma distribution with parameters $\alpha=1/k$ and $\beta=\lambda*k$. Then, the number of events during the missing exposure period will be imputed using a negative binomial distribution with mean λ_M*T_M and dispersion k. For each patient in ET2, sum the observed number of exacerbations during the treatment period with the simulated number during the missing exposure period to obtain the imputed number of exacerbations. This process will be repeated 10 times.

After each iteration, the output dataset of imputed values for ET2 from Step 3 will be appended to the existing data from ET0 and ET1 (from Step 2) to generate 10 complete datasets.

Step 4: Re-run the primary analysis model.

The negative binomial model will be fitted to the complete set of data for each of the 10 datasets using the same covariates that were used for the primary analysis. The model will include

log(follow-up time) as an offset variable, either excluding/including the summed duration of exacerbations, depending on the analysis. For patients with imputed number of exacerbations, complete follow up of 1 year is assumed. The summed duration of exacerbations will be calculated as summed duration of any exacerbations observed prior to treatment withdrawal + 8 days for each additional (imputed) exacerbation. The assumption of 8 days for the duration of exacerbations is consistent with the minimal duration of exacerbation as derived previously in the BREATH IV program.

Step 5: Multiple imputation and associated combining rules applied to propagate imputation uncertainty (Little and Rubin 2002).

The output datasets from Step 4 will contain inferential statistics for each imputation iteration. The SAS® procedure PROC MIANALYZE will be used to generate an overall p-value and 95% CI for the treatment difference; results will be exponentiated back to their original scale.

APPENDIX B. TIPPING POINT ANALYSIS

The tipping point analysis evaluates several combinations of imputed missing data values until the analysis reaches a “tipping point” or point at which a particular combination of imputed missing data changes the study conclusions, as summarized by its p-value. This is a sensitivity analysis utilizing multiple imputations under the missing not at random (MNAR) assumption, and will only be conducted if a significant result ($p \leq 0.05$) is observed as part of the primary analysis. If the sensitivity analysis reveals that the tipping point consists of unreasonable values, then the robustness of the study results is supported. This is in accordance with the recommendation discussed in the "Prevention and Treatment of Missing Data in Clinical Trials Report" (National Research Council 2010).

The following represents an outline of the planned methodology for the “tipping point” multiple imputation sensitivity analysis of the CAE variable. Minor deviations from this outline can be addressed in the discussion of the results in the CSR. In the situation that more significant updates are warranted, changes will be addressed in a SAP amendment to be finalized prior to database lock.

Exacerbations will be imputed for patients who discontinued treatment prior to the endpoint of the study. Multiple imputation and associated combining rules will be applied to propagate imputation uncertainty (see Appendix A for additional details). In the following analysis, the number of exacerbations in the control group will be imputed assuming that missing data are MAR. For the treatment group, the number of exacerbations will be multiplied by a constant scale factor (>1) to allow for MNAR. In the treatment group, this scale will be progressively increased and the process repeated until the treatment effect is no longer significant at the 5% level. The value of the scale parameter at which the treatment effect is no longer significant is called the “tipping point”.

The tipping point analysis will be performed according to the following steps.

1. Values will be imputed assuming MAR in both treatment groups using the multiple impution procedures described in Appendix A (Steps 1-3). This process will be repeated 10 times.
2. To allow for MNAR in the reslizumab treatment group, a scale parameter will be used to adjust imputed values for the number of CAEs, by multiplying the imputed values by the scale parameter. The following pseudo-code can be used to demonstrate this concept, where OUTMI is the output dataset(s) from the Step 1, COMPLETER identifies the patients who discontinued treatment early with incomplete follow-up, NUMCAE is the number of exacerbations, and λ is the scale parameter.

   ```
   data outmi;
      set outmi;
      if armcd='RESLIZUMAB' and COMPLETER='N' then numcae=numcae*λ;
   run;
   ```

   After this step, 10 datasets with complete data have been created.
3. The negative binomial model will be fitted to the complete set of data for each of the 10 datasets using the same covariates that were used for the primary analysis, following the same outline described in Appendix A (Step 4).

4. Apply combining rules to the results from the 10 datasets using PROC MIANALYZE, as described in Appendix A (Step 5).
5. Repeat Steps 1-4 (above) using escalating values for the scale parameter (eg, 1, 2, 3, 4, etc.) resulting in estimates of the CAE rate ratio and p-values for each scale parameter.

The rate ratio of CAEs and associated p-value will be summarized corresponding to each selected scale value (eg, 1, 2, 3, 4, etc.) until the tipping point is achieved.

APPENDIX C. SGRQ – ITEM WEIGHTS FOR PROGRAMMING