Statistical Analysis Plan Amendment 01

A Phase 3, 24-Week Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study of Reslizumab Subcutaneous Dosing (110 mg Every 4 Weeks) in Patients With Oral Corticosteroid Dependent Asthma and Elevated Blood Eosinophils

Study Number C38072-AS-30027

NCT02501629

Date: 08 March 2017

TEVA BRANDED PHARMACEUTICAL PRODUCTS R&D, INC.

STATISTICAL ANALYSIS PLAN

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Study C38072-AS-30027 **Phase** 3

Date: 08-March-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
[redacted]	
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
EQ-5D	European Quality of Life 5-Dimension
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
GLM	Generalized Linear Model
[redacted]	

HLGT	High Level Group Term
HLT	High Level Term
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
im	Intramuscular
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
OR	Odds Ratio
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

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for TEVA Branded Pharmaceuticals Products R&D, Inc. study C38072-AS-30027 (A Phase 3, 24-Week Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study of Reslizumab Subcutaneous Dosing (110 mg Every 4 Weeks) in Patients With Oral Corticosteroid Dependent 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-30027 Amendment 02, issued 18 July 2016
- Case report form (CRF) for Study C38072-AS-30027
- 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 the study is to determine the ability of reslizumab (110 mg) administered sc once every 4 weeks to produce a corticosteroid-sparing effect (as demonstrated by percent reduction in daily OCS use) in patients with OCS-dependent asthma and elevated blood eosinophils, without loss of asthma control.

1.2. Secondary Objective

The secondary objective of this study is to evaluate the clinical benefits of reslizumab in the context of OCS reduction.

1.3. Other Efficacy Objective

Another efficacy objective of this study is to evaluate the effect of reslizumab on standard asthma control measures during tapering of OCS in patients with OCS-dependent asthma.

1.4. Target Biomarker Objective

The target biomarker objective is to evaluate the effect of sc dosing of reslizumab on blood eosinophil counts.

1.5. Immunogenicity Objective

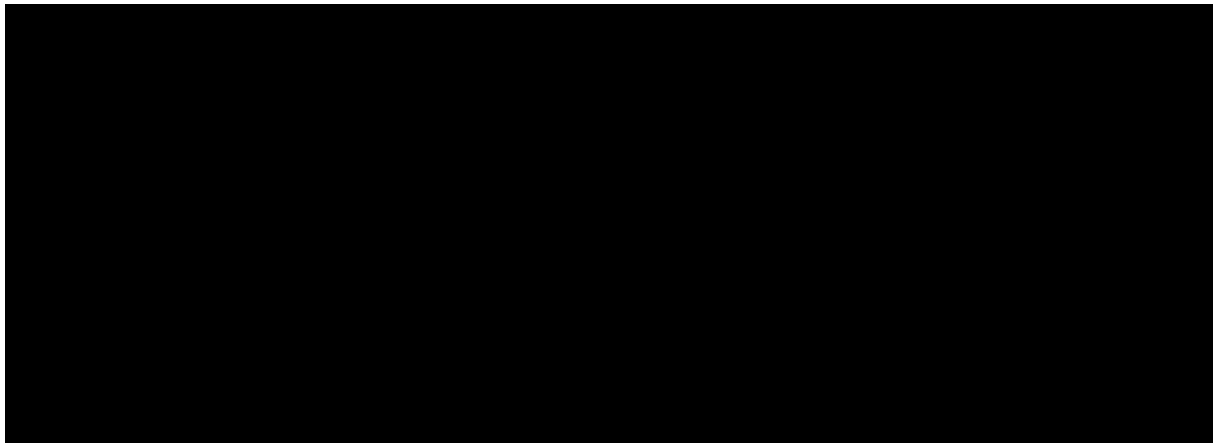
The immunogenicity objective is to evaluate the potential of sc dosing of reslizumab to raise ADAs.

1.6. Pharmacokinetic Objective

The PK objective is to characterize the PK of sc reslizumab in the study population.

1.7. Exploratory Objective

The exploratory objectives are:



[redacted]

1.8. Safety Objective

The safety objective is to evaluate the safety of chronic sc dosing of reslizumab and tapering of OCS as assessed by the following:

- Occurrence of adverse events
- Clinical laboratory evaluations of serum chemistry and hematology
- Vital signs (pulse, respiratory rate, and blood pressure) measurements
- ECG findings
- Physical examination findings, including body weight measurements
- Signs and/or symptoms of adrenal insufficiency (OCS withdrawal effects)
- Concomitant medication usage

2. STUDY DESIGN

2.1. General Design and Study Schema

This is a Phase 3, 24-week, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of sc reslizumab treatment at a dosage of 110 mg every 4 weeks in patients 12 years of age and older with OCS-dependent asthma and elevated blood eosinophils. The study will consist of a screening period of up to 2 weeks, followed by an optimization period of up to 10 weeks, a run-in period of at least 2 weeks, a 24-week double-blind treatment period, an 8-week follow-up period, and an additional 16-week follow-up period to collect drug wash-out samples for immunogenicity assessments.

2.1.1. Screening Period

Patients will begin screening up to 14 weeks before day of randomization. During the screening period, a signed and dated informed consent form (ICF) (and an assent form for children 12 through <18 years of age 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 (CBC) determined. If the patient's eosinophil count is 300/μL or greater while on daily OCS and if the patient's medication compliance and inhaler use technique are optimal, the patient will be eligible to continue. A patient will meet inclusion criteria if an eosinophil count of 300/μL or greater becomes manifest during the OCS optimization period or at the week -2 visit (end of optimization period/beginning of run-in period). Patient medical history; pre-bronchodilator spirometry; 12-lead ECG; physical examination; urinalysis; vital signs measurements; beta human chorionic gonadotropin serum pregnancy test (for all females of childbearing potential); testing for human immunodeficiency virus, hepatitis B, and hepatitis C; and concomitant medication history will also be assessed at screening.

To be eligible to enroll in the study, a patient will have an airway FEV_1 reversibility of at least 12% to beta-agonist administration, a blood eosinophil count of at least 300/μL while on daily OCS or during the OCS optimization period or at the week -2 visit or a documented blood eosinophil level of at least 300/μL during the previous 12 months while on at least medium dose ICS, a current fluticasone propionate dosage of at least 880 μg daily or equivalent plus another controller, and will have met all the inclusion and none of the exclusion criteria.

2.1.2. Optimization Period

Patients who meet screening eligibility requirements will enter the optimization period for up to 10 weeks to determine the patient's minimal effective OCS requirement. The patient's previous OCS will be standardized to an equivalent dose and regimen of prednisone to facilitate optimization; the same formulation should be maintained through the end of treatment (EOT) visit. It is expected that the optimization period will be shorter than 10 weeks for those patients who are at or near their optimal corticosteroid dose at enrollment. The patient's previous non-

OCS background asthma controller medications will be continued unchanged throughout the pre-randomization period and the entire study. At the beginning of the optimization period, an asthma symptom diary and electronic peak flow meter will be distributed where the patient will record asthma symptoms, number of reliever bronchodilator inhalations, nighttime awakenings due to asthma requiring rescue inhaler, and AM and PM PEF.

For optimization, the prednisone dose should be reduced at 1-week intervals, according to the algorithm shown in Table 1, for up to 10 weeks, or until there is a worsening of asthma signs and symptoms. Worsening of asthma signs and symptoms should be based on the following:

- FEV_1 <80% of the screening value AND/OR
- The physician's global assessment of asthma worsening based on trends in daily diary measures for the past 7 days compared with the week prior, as well as any physical examination signs

When either a lung function or a symptomatic deterioration occurs, the patient will be returned to the previously effective OCS level, which will then constitute the minimally effective dose for the purpose of run-in. If this previously effective dose is no longer effective, the investigator can determine the clinically appropriate minimally effective dose for the purpose of run-in.

Regarding the amount and rate of OCS reduction during dose optimization, in order to provoke a worsening of asthma signs and symptoms within the 10-week monitored optimization period, OCS reduction should be attempted approximately every 1 week after evaluation in the clinic. The magnitude of OCS reduction will be based on the following Optimization Phase OCS Dose Reduction Algorithm (Table 1).

Table 1: Optimization Phase Prednisone Dose Reduction Algorithm

Time Course	Oral OCS Dose (mg/day)								
Visit 2 starting dose[a]	40+[b]	35	30	25	20	15	10	7.5	5
1st reduction at Visit 2	35	30	25	20	15	10	7.5	5	2.5[c]
+ 1 week	30	25	20	15	10	7.5	5	2.5[c]	
+ 1 week	25	20	15	10	7.5	5	2.5[c]		
+ 1 week	20	15	10	7.5	5	2.5[c]			
+ 1 week	15	10	7.5	5	2.5[c]				
+ 1 week	10	7.5	5	2.5[c]					
+ 1 week	7.5	5	2.5[c]						
+ 1 week	5	2.5[c]							
+ 1 week	2.5[c]								
+ 1 week									

[a] Starting doses that fall between values shown in this table should utilize the algorithm for the higher of the 2 doses.

[b] Patients who the investigator believes may be able to decrease OCS dose to 40 mg during the optimization period may be enrolled. OCS dose reduction during optimization for patients on >40 mg daily at that start of optimization should follow weekly reductions with magnitudes similar to those in the table (this may be discussed with medical monitor). Patients who require >40 mg OCS to maintain asthma control at the end of optimization will not be randomized.

[c] Patients must be using an average daily dose of ≥5 mg OCS after optimization. Patients who require <5 mg OCS to maintain asthma control will not be randomized.

OCS=oral corticosteroid

Regarding eosinophil counts during the optimization period, blood eosinophils ≥300/μL that become manifest during OCS reductions during optimization, will count toward the eosinophil inclusion criterion for this study.

2.1.3. Run-In Period

Patients whose minimal effective OCS dose remains between ≥5 mg and ≤40 mg of prednisone daily at the end of optimization may advance to run-in (for at least 2 weeks). During run-in, patients will continue to keep their daily asthma control diary and a PEF meter to perform daily self-monitoring of asthma symptoms while maintaining their minimally effective OCS dose and previous background asthma medications unchanged. The frequency of symptoms, use of inhaled reliever bronchodilator, nighttime awakenings due to asthma requiring rescue inhaler, and ambulatory lung function during the last 7 days of run-in will constitute the baseline level of control for analysis and the basis for OCS reduction algorithm to be used during the treatment period.

2.1.4. Treatment Period

Patients continuing to meet eligibility criteria on the day of randomization (day 1, week 0) will be randomly assigned in a 1:1 ratio to receive placebo or reslizumab 110 mg once every 4 weeks

through week 20, followed by an EOT visit at week 24. Patients will begin treatment on day 1 after completing baseline assessments, and they will return to the research facility for outpatient visits every 4 weeks through week 24 (EOT visit) for safety, PK, PD, immunogenicity, and efficacy assessments as applicable.

During the treatment period, the patient will continue his/her usual non-OCS background asthma medication without change; the OCS dose will be tapered per protocol. The treatment period consists of the following:

- **Induction**: The minimally effective dose of OCS will be maintained, unchanged, during the first 4 weeks of the treatment period to allow sufficient time for any potential treatment effect to become established.
- **OCS reduction**: The minimally effective OCS dose will be reduced per protocol at scheduled clinic visits from the beginning of week 5 (ie, end of the induction period) through week 20, as long as all 5 criteria in Table 2 are met and there are no clinical manifestations of adrenal insufficiency. These 5 eligibility criteria assure that the patient's asthma control is not significantly worsened compared to baseline. The last possible dose reduction can occur at week 20. The algorithm for OCS reductions during the treatment period is given in Table 3. If the OCS dose could not be decreased, it should be held constant or may be increased to a previous level, at the investigator's discretion, until dose reduction criteria are met.
- **Maintenance:** OCS dose will be held stable from week 20 through EOT at week 24.

Table 2: Eligibility Criteria for Scheduled Oral Corticosteroid Reductions During the Treatment Period (Must Meet All)

1.	Forced expiratory volume in 1 second (FEV_1) ≥80% of baseline[a]
2.	AM PEF ≥80% of baseline mean AM PEF on at least 5 of the 7 days preceding the visit
3.	Mean nighttime awakenings due to asthma requiring rescue inhaler over the preceding 7 days ≤150% increase over the baseline period
4.	Reliever bronchodilator inhaler use does not exceed 150% of the baseline inhaler use per 24 hours on more than 2 of the preceding 7 days
5.	No increase in OCS dose since the previous visit[b]

[a] Baseline for clinic visit measures (FEV_1) is the DoR value. Baseline for diary measures is the average over the 7 days prior to DoR.

[b] If a dose increase results in a return to the previous dose, then it is acceptable to attempt dose decrease again at the investigator's discretion.

AM=morning; DoR=date of randomization; FEV_1=forced expiratory volume in 1 second; PEF=peak expiratory flow; OCS=oral corticosteroid.

Table 3: Oral Corticosteroid Decrements During the Treatment Period

Time Course	Oral OCS Dose (mg/day)								
Optimized OCS dose	40	35	30	25	20	15	10	7.5	5
1st reduction	30	25	20	15	10	10	7.5	5	2.5
+ 4 weeks	20	15	10	10	7.5	7.5	5	2.5	0
+ 4 weeks	10	10	5	5	5	5	2.5	0	
+ 4 weeks	5	5	2.5	2.5	2.5	2.5	0		
+ 4 weeks	2.5	2.5	0	0	0	0			

2.1.4.1. Handling of Asthma Exacerbations During the Treatment Period

Patients should be treated with an OCS burst: 40 to 60 mg (or at least double the current dose) of OCS tapered over a 7- to 10-day period to a new maintenance dose of 2.5 mg above the pre-burst dose. It is understood that im or iv corticosteroid may also be administered as part of the treatment of the asthma exacerbation. If a second OCS burst (doubling of current dose) is required, the patient should be maintained on a fixed OCS dose without any tapering attempts for the remainder of the double-blind treatment phase and the follow-up period.

Patients who complete all scheduled visits will have final procedures and assessments performed at the EOT visit (visit 19). Patients who withdraw from the study before completing the 24-week treatment period will have visit 19 (week 24 ± 7 days or early termination) procedures and assessments performed at their final visit. Patients will return for a follow-up evaluation 8 weeks (±7 days) after the EOT visit in this study for assessment of pre-bronchodilator spirometry, ACQ-6 score, PK samples, adverse events, blood eosinophils, CAEs and related health care utilizations, and blood for ADA.

The assessments and procedures performed during each study visit are detailed in Table 4. If a patient elects to withdraw (or is discontinued from treatment by the investigator), every attempt will be made to continue the assessments subsequent to his/her withdrawal from the study.

Table 4: Study Procedures and Assessments

Procedures and assessments	Pretreatment			Double-blind treatment period (visit/week)							Follow-up	Late follow-up
	V1	V2-V11	V12	V13[a]	V14[a]	V15[a]	V16[a]	V17[a]	V18[a]	V19[a]	V20	V21
	Start of screening period	Standardize and optimize maintenance OCS[abc]	Start run-in									
	Week −14[d]	Between weeks −12 and −3	W −2	DoR	W4±7d	W8±7d	W12±7d	W16±7d	W20±7d	W24±7d/ EOT/ early termination	W32/EOT + 8w ±7d	W48/EOT + 24w ±14d
Informed assent/consent	X											
Medical history	X											
Medication history	X											
Inclusion and/or exclusion criteria	X	X[e]	X	X								
Randomization criteria				X								
Reversibility testing[f]	X											
Pregnancy testing[g]	X			X	X	X	X	X	X	X	X	
Blood for HIV, hepatitis B, and hepatitis C	X											
CBC with differential[h]	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry tests[i]	X			X	X[j]	X[j]	X	X[j]	X[j]	X		
Urinalysis	X											
Full physical examination[k]	X											
Brief physical examination[k]		X	X	X	X	X	X	X	X	X		
Vital signs measurement[k]	X	X	X	X	X	X	X	X	X	X		
Height[l] and weight	X			X						X		

Procedures and assessments	**Pretreatment**		**V12 Start run-in**	**Double-blind treatment period (visit/week)**							**Follow-up**	**Late follow-up**
	V1	**V2-V11**		**V13**[a]	**V14**[a]	**V15**[a]	**V16**[a]	**V17**[a]	**V18**[a]	**V19**[a]	**V20**	**V21**
	Start of screening period	**Standardize and optimize maintenance OCS**[abc]										
	Week −14[d]	**Between weeks −12 and −3**	**W −2**	**DoR**	**W4±7d**	**W8±7d**	**W12±7d**	**W16±7d**	**W20±7d**	**W24±7d/ EOT/ early termination**	**W32/EOT + 8w ±7d**	**W48/EOT + 24w ±14d**
ECG[k]	X									X		
Provide and collect PEF meter		X								X		
Provide/collect electronic asthma control diary; reinforce diary and PEF compliance		X	X	X	X	X	X	X	X	X		
OCS reduction attempts		X			X	X	X	X	X			
Pre-bronchodilator spirometry[m]	X	X[n]		X	X	X	X	X	X	X	X	
Post-bronchodilator spirometry[o]				X	X		X		X	X	X	
PK samples[p]				X	X	X	X	X	X	X	X	X
Blood for ADA[q]				X	X	X	X			X	X	X
[redacted]												
IP administration				X	X	X	X	X	X			
Injection site evaluation				X	X	X	X	X	X			
AQLQ+12				X	X	X	X	X	X	X		

Procedures and assessments	Pretreatment		V12 Start run-in	Double-blind treatment period (visit/week)							Follow-up	Late follow-up
	V1	V2-V11		V13[a]	V14[a]	V15[a]	V16[a]	V17[a]	V18[a]	V19[a]	V20	V21
	Start of screening period	Standardize and optimize maintenance OCS[abc]										
	Week −14[d]	Between weeks −12 and −3	W −2	DoR	W4±7d	W8±7d	W12±7d	W16±7d	W20±7d	W24±7d/ EOT/ early termination	W32/EOT + 8w ±7d	W48/EOT + 24w ±14d
ACQ-6				X	X	X	X	X	X	X	X	
EQ-5D				X						X		
St. George's Respiratory questionnaire				X			X			X		
Assess CAEs and related HCU[r]				X	X	X	X	X	X	X		
Phadiatop allergy test				X								
OCS withdrawal effects inquiry[s]			X	X	X	X	X	X	X	X		
Adverse event inquiry[t]		X	X	X	X	X	X	X	X	X	X	
Concomitant medication inquiry	X	X	X	X	X	X	X	X	X	X	X	

[a] The site will contact IWRS at every optimization and treatment visit.
[b] The patient's previous OCS should be switched to an equivalent, standardized prednisone formulation. Optimization may occur once OCS standardization is complete.
[c] Attempts at OCS reduction should be made at 1-week intervals, for up to 10 weeks or until there is a worsening of asthma signs and symptoms, to help determine the patient's lowest effective OCS dose. This period may be shortened if the lowest effective dose is achieved sooner. Eosinophil counts during the optimization period or at the week -2 visit may be considered in order to meet the eosinophil inclusion criteria for this study. Patients requiring an average daily dose of between ≥5 mg and ≤40 mg may proceed to run-in and maintained without change during run-in.
[d] The screening period (between V1 and V2) can be less than 2 weeks if all of the screening inclusion criteria are met sooner. 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 and reversibility testing.
[e] Verify that essential screening inclusion criteria for asthma are met before entering optimization.
[f] Reversibility testing is most conveniently performed at the same visit as the screening, pre-bronchodilator spirometry. All patients must undergo reversibility testing, even if they are submitting historical reversibility or methacholine provocation results to support inclusion criterion e. Reversibility testing may be repeated once, within the 2-week screening period.

[g] βHCG serum pregnancy tests will be performed at screening; urine pregnancy testing will be performed every 4 weeks thereafter until week 24 or early withdrawal (female patients who are not 2 years postmenopausal or surgically sterile) and at the early follow-up visit (V20).
[h] The patient must have had a blood eosinophil count ≥300/μL in the 12 months before ICF or ≥300/μL during screening or during OCS optimization or at the week -2 visit. A CBC with differential need not be repeated at every visit during the optimization period and should be done at the investigator's discretion if the eosinophil criteria were not met at screening.
[i] 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 7.1.7.3.2.
[j] CPK measurement only. CPK will be collected with PK sample.
[k] Physical examination, vital signs, and ECG should be obtained before spirometry procedures and IP administration.
[l] For adults, height will be measured at screening only. For patients <18 years of age, height will be measured at screening, DoR, and EOT. Use of a stadiometer is preferable, if available, or use a cloth tape securely attached to the wall that will allow reproducible results. Height should be measured in centimeters, without shoes.
[m] Pre-bronchodilator spirometry assessments should only be performed after withholding short-acting bronchodilators (ie, inhaled short-acting beta-agonists and/or short acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled LABAs 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.
[n] Optional at visits 2-11.
[o] For post-bronchodilatory spirometry, short-acting beta-agonists, such as salbutamol or albuterol, administered via a metered dose inhaler should be used. Four separate doses (eg, albuterol 360 μg or salbutamol 100 μg ex-valve) should be given by a metered dose inhaler as tolerated. Post-bronchodilator spirometry should be completed a minimum of 15 minutes after dosing of short-acting beta-agonist.
[p] Blood samples for PK and ADA analysis will be drawn before administration of study drug.
[q] If possible, a blood sample for measurement of serum reslizumab concentrations will be obtained from patients experiencing an adverse event leading to withdrawal, a serious adverse event, an observation of any severe hypersensitivity reaction (eg, anaphylaxis), or an exacerbation of asthma symptoms.
[r] 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. Procedures and assessments to be performed if an unscheduled visit occurs are described in Protocol Section 3.16.5.
[s] Based on investigator's assessment.
[t] 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).

ACQ-6=6-item Asthma Control Questionnaire; ADA=anti-drug antibody; AQLQ=Asthma Quality of Life Questionnaire; βHCG=beta human chorionic gonadotropin; CAE=clinical asthma exacerbation; CBC=complete blood count; CPK=creatine phosphokinase; CRF = case report form; DoR=date of randomization; ECG=electrocardiogram; eDiary = electronic diary; EOT=end of treatment; EQ-5D=European Quality of Life 5-dimension health state utility index; FEV_1=forced expiratory volume in 1 second; [redacted] HCU=health care utilizations; HIV=human immunodeficiency virus; ICF=Informed Consent Form; IP=Investigational Product; LABA=long-acting beta-agonist; OCS=oral corticosteroid; PEF=peak expiratory flow; PK=pharmacokinetic; [redacted] ULN = upper limit of normal V=visit; W=wee

2.2. Primary and Secondary Measures and Endpoints

2.2.1. Primary Efficacy Endpoint

The primary efficacy variable and endpoint for this study is the categorized percent reduction in the daily OCS dose during weeks 20 to 24 as compared with the dose at the end of the optimization phase. Percent reduction will be categorized as follows:

- 90% to 100%
- 75% to <90%
- 50% to <75%
- >0% to <50%
- No decrease in OCS, or loss of baseline asthma control during weeks 20 through 24, or discontinuation from study drug

Loss of baseline asthma control will be defined as FEV_1 value of less than 80% of baseline at the week 24 visit, or clinically significant worsening in ACQ-6 score (change in score of 0.5) at the week 24 visit compared with baseline, and/or CAE during weeks 20 through 24 (CAE defined in Section 6.3.3.1).

2.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study are as follows:

- Proportion of patients achieving ≥50% reduction in OCS dose at weeks 20 to 24 relative to the OCS dose at the date of randomization (DoR)/baseline, while maintaining asthma control
- Proportion of patients achieving dose reduction to ≤5 mg daily dose at weeks 20 to 24, while maintaining asthma control
- Percent change from DoR/baseline in OCS dose at weeks 20 to 24
- Proportion of patients achieving less than 5 mg decrement in OCS dose (ie, the minimal and non-responders) at weeks 20 to 24 compared with the OCS dose at DoR/baseline, while maintaining asthma control
- Clinical asthma exacerbation related:
  - Annualized rate of CAEs requiring a burst of systemic corticosteroid (injection, or if oral, at least a doubling from the current OCS dose for at least 3 days); an asthma-specific hospital admission; or an asthma-specific emergency department visit during the treatment period (weeks 0 to 24)
- Proportion of patients discontinuing OCS at weeks 20 to 24, while maintaining asthma control

2.2.3. Other Efficacy Endpoints

The other efficacy endpoints are as follows:

- Time to first clinical asthma exacerbation
- Other clinic lung functions including the following:
  - Pre-bronchodilator FEV_1: change from DoR/baseline to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
  - Post-bronchodilator FEV_1: change from DoR/baseline to weeks 4, 12, 20, and 24 or early withdrawal
- Ambulatory lung function: change in morning (AM) and evening (PM) peak expiratory flow (PEF) from run-in baseline at each week through week 24 or early withdrawal
- Asthma Quality of Life (AQLQ) + 12 score: change from DoR/baseline to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- ACQ-6 score: change from DoR/baseline to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- Change in total inhalations of reliever bronchodilator medication (eg, SABA) (number of inhalations per 24 hours: day+night) from run-in baseline at each week through week 24 or early withdrawal
- Number of nighttime awakenings due to asthma over the 24-week treatment period
- Change in total asthma symptom score from run-in baseline at each week through week 24 or early withdrawal
- European Quality of Life 5-dimension health state utility index (EQ-5D) score: change from DoR/baseline to week 24 or early withdrawal
- St. George's Respiratory Questionnaire (SGRQ) score: change from DoR/baseline to weeks 12 and 24 or early withdrawal

2.2.4. Target Biomarker Endpoint

The target biomarker endpoints are the blood eosinophil counts at DoR/baseline; weeks 4, 8, 12, 16, 20, and 24 or early withdrawal; and at the follow-up visit (approximately week 32).

2.2.5. Immunogenicity Endpoint

The immunogenicity endpoints are the immunogenicity incidence and the impact of ADA on clinical outcomes. The drug-emergent ADA response will be identified by analyzing ADA test results for serum samples obtained before the administration of study drug at DoR/baseline; prior to study drug administration at weeks 4, 8, 12, and 24 or early withdrawal; and at the follow-up visit (approximately week 32). An additional sample will be obtained at the late follow-up visit (approximately week 48).

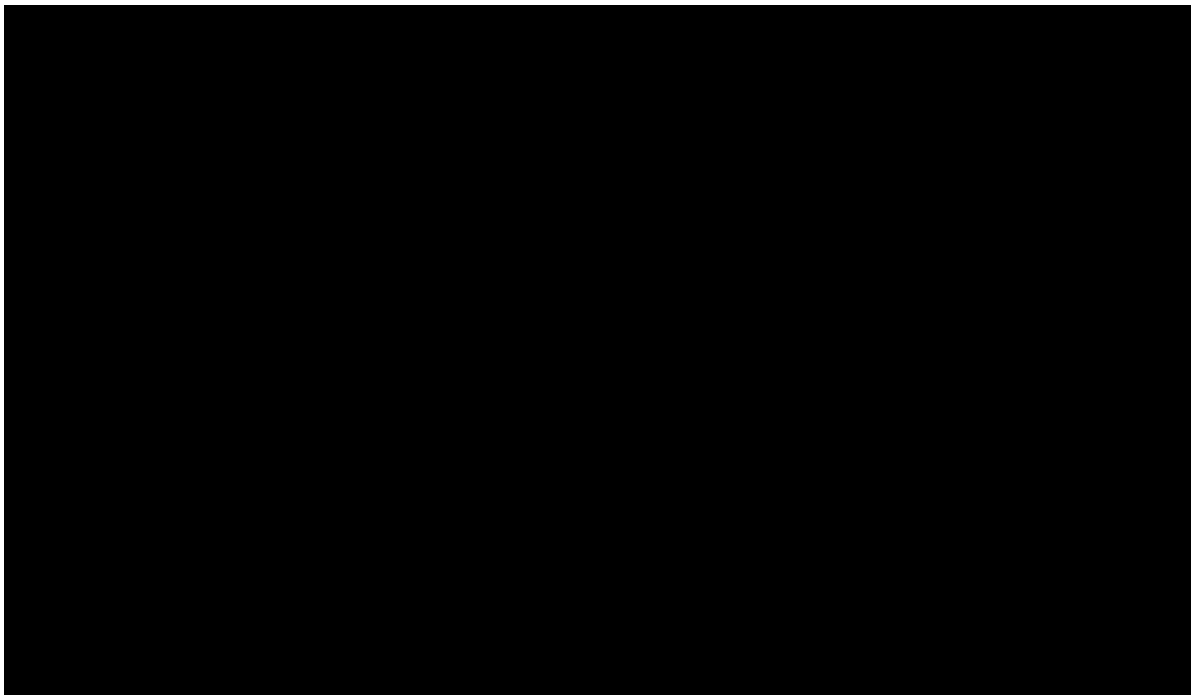
2.2.6. Pharmacokinetic Endpoint

There are no specific endpoints related to PK. Measured concentrations will be used to characterize the PK of sc reslizumab in the studied population and to explore exposure-response relationships. Serum reslizumab concentrations will be determined from blood samples collected

from each patient at DoR/baseline; and prior to study drug administration at weeks 4, 8 12, and 24 or early withdrawal; and at the follow-up visit (approximately week 32). An additional PK sample will be obtained at the late follow-up visit (approximately week 48).

2.2.7. Exploratory Endpoints

The exploratory endpoints are as follows:



2.2.8. Safety Endpoints

Safety endpoints will include the following:

- Occurrence of adverse events throughout the study, including the week 32 follow-up visit
- Clinical laboratory evaluations of serum chemistry at screening, DoR, and periodically throughout the study
- Clinical laboratory evaluations of hematology throughout the study
- Vital signs (pulse, body temperature, respiratory rate, and blood pressure) measurements throughout the study
- ECG evaluation at screening and at week 24 or early withdrawal
- Physical examination findings, including body weight measurements, throughout the study
- Signs and/or symptoms of adrenal insufficiency (OCS withdrawal effects) throughout the study
- Concomitant medication usage throughout the study, including the week 32 follow-up visit

2.3. Sample Size and Power Considerations

The primary efficacy variable and endpoint for this study is the percent reduction in the daily OCS dose during weeks 20 to 24 as compared with the dose at the end of the optimization phase. The study will be considered positive if the measure meets statistical significance at the respective predefined significance level. A statistically significant effect of reslizumab over placebo, as measured by the primary efficacy variable, is required to establish the efficacy of reslizumab treatment.

The sample size was calculated based on the following assumptions:

- Categorical reduction in OCS dose after 24 weeks of treatment will have the following distribution for the placebo group (based on Bel et al 2014):
  - 10.9% percent of subjects will have 90% to 100% reduction
  - 7.9% percent of subjects will have 75% to <90% reduction
  - 14.8% percent of subjects will have 50% to <75% reduction
  - 10.8% percent of subjects will have 0% to <50% reduction
  - 55.6% percent of subjects will have no reduction, loss of asthma control, or discontinuation from study drug
- The overall odds ratio between reslizumab and placebo based on proportional odds model will be 2.63
- Alpha level of 0.05

Based on the above assumptions, a sample size of 76 subjects per group will provide 90% power to detect a significant effect of reslizumab over placebo on the probability for a higher categorical reduction of OCS dose.

2.4. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. In order to achieve balance between treatment groups with regard to average daily OCS use/requirement and age, randomization will be stratified by optimized, average daily OCS dose (>10 mg or ≤10 mg) and age at baseline (12 to <18 years or ≥18 years). Within each stratum, patients will be randomly assigned to receive treatment with sc reslizumab at a dosage of 110 mg every 4 weeks or a matching placebo in a 1:1 ratio. This system is used to ensure a balance across treatment groups.

The randomization list and treatment will be assigned to the relevant treatment groups through a qualified contract research organization (CRO), eg, via Interactive Web Response System (IWRS). Generation of the medication list and management of the interactive response technology (IRT) system will be done by a qualified CRO under the oversight of Teva's Clinical Supply Chain.

The sponsor's 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 (Global Bioassays and Technology), who will not be blinded in order 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 removing the blind.

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

3.1. Intent to Treat Analysis Set

The intent to treat (ITT) analysis set will include all randomized patients. 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 24) 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 all efficacy endpoints, the on-treatment approach will be utilized as the main approach to analysis. However, it should be noted that all patients will be included in the analysis of the primary and secondary endpoints related to OCS dose reduction by incorporating missing data (due to dropout) as nonresponders. The analytic approach including all data collected from patients will additionally be conducted as sensitivity analyses for the primary endpoint.

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 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. 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 24) 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 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 5 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 5: Major Protocol Violations

Violation	Approach to identifying protocol violations
Patient was not on a daily maintenance dose of OCS prior to screening	Inclusion criteria (c); disposition CRF Medication CRF Protocol violation CRF
Patient does not have a documented blood eosinophil ≥300/μL	Inclusion criteria (d); disposition CRF Laboratory data (for eosinophils obtained during the screening and optimization periods) Subject status CRF (for historical eosinophils) Protocol violation CRF
Patient was not on ICS (at least 880 μg of inhaled fluticasone propionate or equivalent) plus another controller at baseline (eg, LABA, LAMA, LTRA, or theophylline). For patients 12 through <18 years, ICS dose must correspond to at least a medium total daily ICS dose.	Inclusion criteria (e); disposition CRF Medication CRF 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.
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 OCS dose (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. OCS Strata

Selected efficacy endpoints including OCS dose (primary), pre-bronchodilator FEV_1, AQLQ+12, ACQ-6, and blood eosinophils will be analyzed separately for patients taking an optimized baseline dose of OCS ≤10 mg and >10 mg. OCS strata will be defined based on the optimized baseline dose of OCS recorded in the clinical database.

3.4.3. Other Subgroups

Selected efficacy endpoints including OCS dose (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)
- Duration of OCS use (<5, ≥5 years)
- 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. Oral Corticosteroid Dose

The baseline value is the prescribed optimized OCS dose following the optimization period and will be defined as the OCS dose reported on the day of first dose of study drug.

4.2.2. 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 6 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.

4.2.3. 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.

4.2.4. Patient Reported Outcomes

The baseline value for patient reported variables (eg, ACQ-6, AQLQ +12, SGRQ, EQ-5D) will be the last observed value prior to the first dose of study drug.

4.2.5. Biomarkers

The baseline value for blood eosinophil levels will be the maximum value of the observed assessments from the screening visit to Week -2 (inclusive).

4.2.6. 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

Analysis of the primary and secondary variables related to categorical OCS dose reduction will incorporate missing data as nonresponders, as described in Section 6.2.2 and Section 6.3.2. The primary variable will also be assessed including multiple imputations for missing data as a sensitivity analysis, as described in Section 6.2.3 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 24) 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 24) 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 6. Weekly average data will be generated using 7-day window intervals derived based on these analysis days.

Table 6: Definition of Analysis Days for Diary Data

Study Period	Diary Day	Study Day[a]	Time Point
Baseline	Day -7	-7	PM
		-6	AM
	Day -6	-6	PM
		-5	AM
	Day -5	-5	PM
		-4	AM
	Day -4	-4	PM
		-3	AM
	Day -3	-3	PM
		-2	AM
	Day -2	-2	PM
		-1	AM
	Day -1	-1	PM
		1 (pre-dose)	AM
Treatment	Day 1	1	PM
		2	AM
	Day 2	2	PM
		3	AM
	…	..	PM
		..	AM
	Day 167	167	PM
		168	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 in the safety analysis set, patients in the PP analysis set, patients who completed treatment (all 24 weeks while on study treatment), patients who completed the planned treatment phase (remained active in the study for the full 24 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 32, for patients not participating in the LTE study) or up to and including end of treatment (Week 24, 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 optimized OCS dose) 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 medical history, duration of oral corticosteroid use for asthma, and [redacted] will be collected and reported.

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 7: 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

6.2.1. Variable Definition

The primary efficacy variable for this study is the categorized percent reduction in the daily OCS dose during weeks 20 to 24 as compared with the OCS dose at the end of the optimization phase.

The week 20 to 24 maintenance dose and corresponding values for absolute and percent change (reduction) from baseline will be calculated as follows:

- **Baseline dose** = the prescribed optimized OCS dose following the OCS optimization period (Table 8)
- **Maintenance dose** = mean of all daily OCS doses during the maintenance period extending from Week 20 to Week 24 (Table 8)
- **Absolute reduction** = maintenance dose – baseline dose
- **Percent reduction** = 100 x (**absolute reduction** / baseline dose)

For both the primary and secondary efficacy analyses, OCS dose will refer to the total daily dose of oral prednisone prescribed for asthma (as per CRF), unless otherwise noted.

The 5 categories for the primary analysis of percent reduction during weeks 20 to 24 are:

- 90% to 100% reduction
- 75% to <90% reduction
- 50% to <75% reduction
- >0% to <50% reduction
- No decrease in OCS, or loss of baseline asthma control during weeks 20 through 24, or discontinuation from study drug

Loss of baseline asthma control will be defined as FEV_1 value of <80% of baseline at the week 24 visit, or clinically significant worsening in ACQ-6 score (increase ≥0.5) at the week 24 visit compared with baseline, and/or clinical asthma exacerbation during weeks 20 through 24 (CAE defined in Section 6.3.3.1).

6.2.2. Primary Analysis

The primary endpoint is the 5-level categorical percent reduction in OCS dose during weeks 20 to 24, compared to the optimized dose at baseline. The primary analysis will incorporate data from all randomized patients. Patients who are unable to maintain asthma control or who

withdraw treatment prematurely will be analyzed as part of the lowest category of response. The primary endpoint will be analyzed using a proportional odds model including factors for treatment group and the randomization strata (age and OCS dose, as defined in Section 2.4); baseline OCS dose and duration of OCS use prior to study entry will also be included as covariates. Age and OCS dose will be based on data recorded in the clinical database.

The proportional odds ratio (reslizumab/placebo) will be estimated from this model, representing the ratio of the odds of a patient outcome being in a higher OCS dose reduction category for reslizumab compared to placebo. The estimated odds ratio, 95% CI, and p-value will be reported. A frequency distribution bar graph will be provided for the number of patients in each of the 5 categories by treatment group.

The following sample Statistical Analysis Software (SAS®) code pertains to the primary efficacy analysis of categorical dose reduction; 'treatment' is the randomized group ('0'=placebo) and 'out_cat5' is the 5-level response category (1=worst category, …, 5=best category):

```
proc genmod data=<<>> order=internal descending;
    class treatment (param=ref ref='0') strata1 strata2;
    model out_cat5 = treatment strata1 strata2 ocsbase ocsdur
                    / dist=mult link=cumlogit aggregate=treatment type3;
    estimate "odds ratio" treatment 1 -1 / exp;
    ods output parameterestimates=<<>>;
run;
```

Note that multicollinearity occurs when there is a high degree of correlation among two or more of the independent variables included within a linear model; it can lead to unstable and unreliable estimates of the regression coefficients. It is recognized that, in the model described above for the primary endpoint (and for the models described subsequently in Section 6.3.2.2 for the related secondary endpoints), the categorical variable for OCS dose randomization strata is expected to be correlated to the continuous variable for OCS dose at baseline. The presence of collinearity between these variables will tend to make the estimates for each of these coefficients unstable, as well as increase the standard errors of their estimated coefficients. However, since the variable of interest in these models is the effect of treatment, and OCS dose at baseline has been included in the model as a control variable, estimation of the regression coefficient for treatment should be unaffected by the presence of this collinearity and the performance of OCS dose as a control variable in the model should not be impaired.

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 control variables (age and OCS dose) 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).
- Per-protocol: analysis of the primary endpoint, based on the PP analysis set.
- Additional analysis including data collected after early withdrawal from treatment.

  - If a patient elects to withdraw from treatment (or is discontinued from treatment by the investigator), every attempt will be made to continue the assessments subsequent to his/her withdrawal from the study. If the patients agrees to remain in the study, they will continue to receive study prednisone treatment for the remainder of their participation in the study.
  - In this analysis, patients will be categorized according to the percent dose reduction at 24 weeks regardless of whether they withdrew early from treatment or completed treatment. For patients who withdraw early and for whom the sponsor fails to retrieve data after withdrawal despite all attempts to contact the patients, multiple imputation will be performed to determine the categorization according to the percent dose reduction at 24 weeks. The multiple imputations will use 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 will be detailed in Appendix A.

- "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. Subgroup Analyses 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 analysis described for the primary endpoint (Section 6.2.2). An interaction p-value will be derived from a separate proportional odds 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.

6.3. 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 24) visit for patients who completed treatment and from the first dose of study drug to the last dose of study drug (+4 weeks) for patient 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 for this study are as follows:

- Proportion of patients achieving ≥50% reduction in OCS dose at weeks 20 to 24 relative to the OCS dose at the date of randomization (DoR)/baseline, while maintaining asthma control

- Proportion of patients achieving dose reduction to ≤5 mg daily dose at weeks 20 to 24, while maintaining asthma control
- Percent change from DoR/baseline in OCS dose at weeks 20 to 24
- Proportion of patients achieving less than 5 mg decrement in OCS dose (ie, the minimal and non-responders) at weeks 20 to 24 compared with the OCS dose at DoR/baseline, while maintaining asthma control
- Annualized rate of clinical asthma exacerbations requiring a burst of systemic corticosteroid (injection, or if oral, at least a doubling from the current OCS dose for at least 3 days); an asthma-specific hospital admission; or an asthma-specific emergency department visit during the treatment period (weeks 0 to 24)
- Proportion of patients discontinuing OCS at weeks 20 to 24, while maintaining asthma control

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

6.3.2. OCS Dose

Note: All analyses related to OCS dose will be discussed within this section; this will include the planned analyses related to the list of secondary variables (in Section 6.3.1), as well as additional planned analyses related to OCS dose that have not otherwise been specified. The analysis of OCS dose as a continuous variable will be discussed separately from the analysis of OCS dose as a categorical variable.

6.3.2.1. Variable Definition

6.3.2.1.1. Continuous Variable

The post-baseline values for OCS dose and corresponding values for absolute and percent change from baseline will be calculated as follows:

- **Baseline dose** = the prescribed optimized OCS dose following the OCS optimization period (Table 8)
- **Post-baseline dose** = mean of all daily OCS doses during each defined analysis period (Table 8)
- **Absolute reduction** = post-baseline dose – baseline dose
- **Percent reduction** = 100 x (**absolute reduction** / baseline dose)

Table 8: Definition of Analysis Days for OCS Dose

Analysis period	Start day	Stop day
Baseline Dose	Day of first dose of study drug	N/A
Baseline to Week 4	Day of first dose of study drug + 1 day	Day of W4 Visit
Week 4 to Week 8	Day of W4 Visit + 1 day	Day of W8 Visit
Week 8 to Week 12	Day of W8 Visit + 1 day	Day of W12 Visit
Week 12 to Week 16	Day of W12 Visit + 1 day	Day of W16 Visit
Week 16 to Week 20	Day of W16 Visit + 1 day	Day of W20 Visit
Week 20 to Week 24 (Maintenance Dose)	Day of W20 Visit + 1 day	Day of W24 Visit

DoR=Day of Randomization

6.3.2.1.2. Categorical Variable

The proportion of patients achieving a 50% or greater reduction in OCS dose at weeks 20 to 24 will be based on the percent reduction from baseline to weeks 20 to 24. The categories for this analysis are:

- 50-100% reduction
- <50% reduction, or loss of baseline asthma control during weeks 20 through 24, or discontinuation from study drug

The proportion of patients who achieve a reduction of their OCS dose to less than or equal to 5 mg at weeks 20 to 24 will be based on the observed post-baseline value during weeks 20 to 24. The categories for this analysis are:

- ≤5 mg
- >5 mg, or loss of baseline asthma control during weeks 20 through 24, or discontinuation from study drug

The proportion of patients who achieve a total reduction (discontinuation) of their OCS dose at weeks 20 to 24 will be based on the observed post-baseline value during weeks 20 to 24. The categories for this analysis are:

- =0 mg
- >0 mg, or loss of baseline asthma control during weeks 20 through 24, or discontinuation from study drug

  Note: Total reduction implies no OCS use during the entire period (weeks 20 to 24).

The proportion of patients achieving less than a 5 mg reduction in OCS dose at weeks 20 to 24 will be based on the absolute reduction from baseline to weeks 20 to 24. The categories for this analysis are:

- ≥5 mg reduction

- <5 mg reduction, or loss of baseline asthma control during weeks 20 through 24, or discontinuation from study drug

6.3.2.2. Analysis

6.3.2.2.1. Continuous Variable

Summary statistics for OCS dose and change from baseline (percent and absolute) 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 (12 to <18 years and ≥18 years), OCS dose at baseline (>10 mg and ≤10 mg); baseline OCS dose and duration of OCS use prior to study entry as covariates, and patient as a random effect (see Section 6.4.3.2 for sample SAS® code for the MMRM model). Age and OCS dose at baseline 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.

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. A line graph presenting the LS mean change from baseline over time (at each visit) will be provided for OCS dose by treatment group.

6.3.2.2.2. Categorical Variable

Each of the categorical secondary endpoints will be analyzed using a binary logistic regression model, incorporating the same covariates as the primary endpoint. The estimated odds ratio, 95% CI, and p-value will be presented. Patients who are unable to maintain asthma control or who withdraw treatment prematurely will be counted as nonresponders and analyzed as part of the lowest category of response. A frequency distribution bar graph will be provided for the number of patients in each of the categories by treatment group.

The following sample SAS® code pertains to the secondary efficacy analysis of categorical dose reduction; ‘treatment’ is the randomized group (‘0’=placebo) and ‘out_cat2’ is the 2-level response category (1=worst category, 2=best category):

```
proc logistic data=<<>>;
    class treatment (param=ref ref='0') strata1 strata2;
    model out_cat2 (desc) = treatment strata1 strata2 ocsbase ocsdur / expb;
    contrast "odds ratio" treatment 1 -1 / estimate;
    ods output contrastestimate=<<>>;
run;
```

6.3.2.2.3. Other Sensitivity Analyses

Change from baseline to weeks 20 to 24 will additionally be analyzed using a non-parametric (Wilcoxon rank-sum) test in which the patient's rank is analyzed rather than the actual observed percent reduction. For patients who withdraw early or do not maintain asthma control between weeks 20 to 24, a rank corresponding to a value less than the smallest observed reduction among all patients will be imputed. The median and 95% CI will be calculated with the use of the Hodges-Lehmann estimate. The p-value will be based on the Wilcoxon rank-sum test.

To further assess corticosteroid burden, the total number of days corticosteroids are taken for exacerbations (defined in Section 6.3.3.1) and the total cumulative dose of corticosteroids taken during the entire study will be summarized separately by treatment group. Corticosteroids taken for exacerbations will be based on medication use, as per the CAE CRF. Cumulative dose will be the sum of the corticosteroid doses (prescribed for either asthma or CAE, as per the medication CRF) multiplied by the duration of corticosteroid treatment, taking dose frequency into account.

- If 5mg is prescribed once daily for 10 days, the cumulative dose is 5*10 = 50.
- If 5mg is prescribed once every other day for 10 days, the cumulative dose is 5*5=25.

The analyses of corticosteroid burden will include all oral, iv, and im corticosteroid preparations. Non-prednisone treatments will be converted to a prednisone equivalent dose using the conversion factors in Table 9. The list of medications will be reviewed and updated, if necessary, prior to unblinding. The final table will be documented in the minutes from the final Statistical Data Review meeting.

Table 9: Conversion of Corticosteroid to Prednisone-Equivalent Doses

Medication Type	Medication	Conversion Factor
Short-acting:	Cortisone	0.2
	Hydrocortisone	0.25
Intermediate-acting:	Methylprednisolone	1.25
	Meprednisone	1.25
	Prednisolone	1
	Prednisone	1
	Triamcinolone	1.25
Long-acting:	Betamethasone	8.33
	Dexamethasone	6.67

Analysis of the total cumulative dose of corticosteroids will be performed using an ANCOVA model with fixed effects for treatment, age group, OCS dose group, and baseline OCS dose as a covariate. Similarly, analysis of the total number of days corticosteroids taken for exacerbations will be performed using an ANOVA model with fixed effects for treatment, age group, and OCS dose group.

6.3.3. Clinical Asthma Exacerbations

6.3.3.1. Variable Definition

A clinical asthma exacerbation (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 (injection, or if oral, at least a doubling from the current OCS 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 [injection, or if oral at least a doubling from the current OCS 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 (injectable), or for those with a doubling of the OCS dose, the stop date is when the return to their baseline dose (dose prior to exacerbation), or the last day of an asthma-specific hospitalization or emergency department visit, whichever is later. For patients receiving at least a doubling from their current dose of OCS for at least 3 days that did not return to baseline (dose prior to exacerbation), the CAE stop date will be the day that they have been on a new stable dose for at least 10 days.

6.3.3.2. Analysis

The annualized rate of CAEs will be analyzed using the generalized linear model (GLM) for data from the negative binomial distributions, commonly referred to as the negative binomial (NB) regression model. The NB model will include factors for treatment group, randomization strata (age and OCS dose as defined in Section 2.4), number of exacerbations in the previous year, 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 OCS dose will be based on data recorded in the clinical database.

The ratio of CAE rate between the treatment groups and its 95% CI will be estimated from the NB model. Treatment effect will be evaluated using the likelihood based chi-square test. The analysis of clinical asthma exacerbations will be on-treatment, excluding exacerbations observed after stopping study 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 24) 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. Analyses will only be performed if a sufficient number of patients have exacerbations for the model to converge satisfactorily.

The following sample SAS® code pertains to the 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;
```

6.4. Other (and Exploratory) 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 24) 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.

[redacted]

6.4.1. Other (and Exploratory) Efficacy Variable(s)

The other (and exploratory) efficacy endpoints are:

- Time to first clinical asthma exacerbation
- Other clinic lung functions including the following:
  - Pre-bronchodilator FEV_1: change from DoR/baseline to weeks 4, 8, 12, 16, 20, 24 or early withdrawal; [redacted]
  - Post-bronchodilator FEV_1: change from DoR/baseline to weeks 4, 12, 20, 24 or early withdrawal; [redacted]
- Ambulatory lung function: change in morning (AM) and evening (PM) peak expiratory flow (PEF) from run-in baseline at each week through week 24 or early withdrawal

- Asthma Quality of Life (AQLQ) + 12 score: change from DoR/baseline to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- ACQ-6 score: change from DoR/baseline to weeks 4, 8, 12, 16, 20, 24 or early withdrawal; [redacted]
- Change in total inhalations of reliever bronchodilator medication (number of inhalations per 24 hours: day+night) from run-in baseline at each week through week 24 or early withdrawal
- Number of nighttime awakenings due to asthma over the 24-week treatment period
- Change in total asthma symptom score from run-in baseline at each week through week 24 or early withdrawal
- European Quality of Life 5-dimension health state utility index (EQ-5D) score: change from DoR/baseline to week 24 or early withdrawal
- St. George's Respiratory Questionnaire (SGRQ) score: change from DoR/baseline to weeks 12 and 24 or early withdrawal
- [redacted]

6.4.2. Time to First Clinical Asthma Exacerbation

6.4.2.1. Variable Definition

Refer to Section 6.3.3.1 for the definition of a clinical asthma exacerbation.

6.4.2.2. Analysis

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 24) 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 this time frame will be censored at either the date of the end of treatment (week 24) 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.

6.4.3. Pulmonary Function Tests

6.4.3.1. 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 4, 8, 12, 16, 20, 24, and 32 (follow-up) and post-bronchodilator assessments (FEV_1) are measured at weeks 4, 12, 20, 24, and 32 (follow-up).

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).

6.4.3.2. Analysis

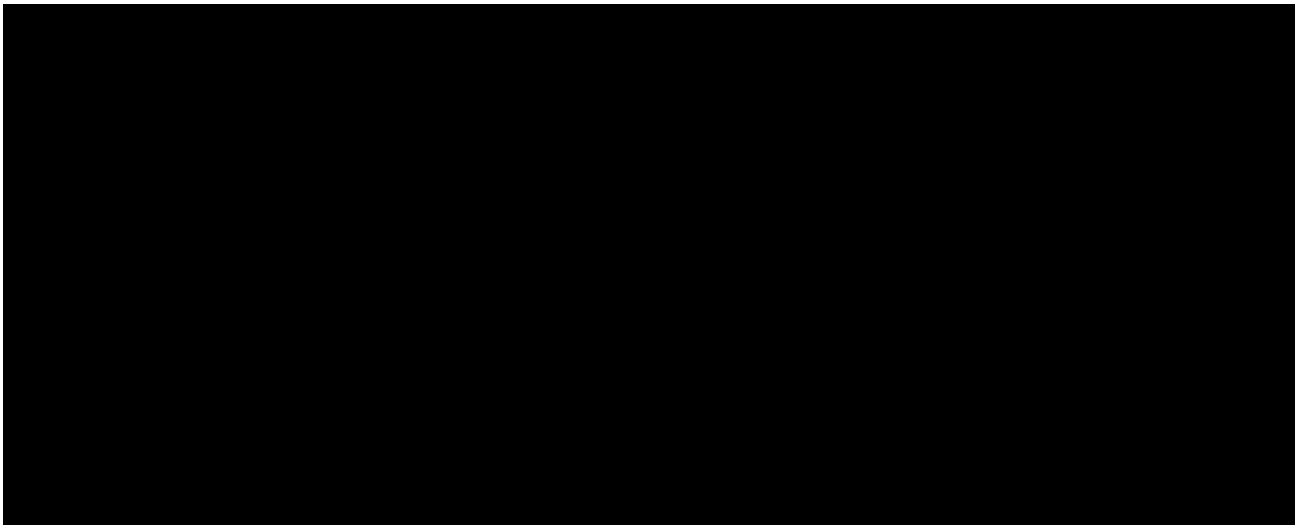
Summary statistics of actual values and change from baseline to each scheduled visit will be provided by treatment group.

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), OCS dose at baseline (>10 mg and ≤10 mg), and sex, height and baseline value as covariates, and patient as a random effect. Age and OCS dose at baseline 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, FVC, $FEF_{25\%-75\%}$ by treatment group.

Pre-bronchodilator FEV_1 at Week 24 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 24.

6.4.4. AQLQ +12

6.4.4.1. 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, 20, and 24. 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

6.4.4.1.1. 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.

6.4.4.2. 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 6.4.3.2 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 24 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 24.

6.4.5. ACQ-6

6.4.5.1. 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 4, 8, 12, 16, 20, 24, and 32 (follow-up), the patient answers each of the 6 questions, identifying the response that best describes how the patient has been during the past week.

6.4.5.1.1. 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.

6.4.5.2. 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 6.4.3.2 with the exception of inclusion of sex and height in the model. [redacted] A line graph will be provided for the LS mean change from baseline over time (at each visit).

ACQ-6 at Week 24 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 24.

6.4.6. SGRQ

6.4.6.1. 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 12 and 24.

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.

6.4.6.1.1. 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.

6.4.6.2. 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 6.4.3.2 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 24.

6.4.7. EQ-5D

6.4.7.1. Variable Definition

The EQ-5D consists of the descriptive system and the visual analogue scale (VAS). The descriptive system is comprised of 5 health domains (mobility, self care, usual activities, pain/discomfort, anxiety/depression) and each domain has 3 levels of response (1=no problems, 2=some problems, 3=major problems). For the VAS component, the response is indicated on the

visual analogue scale provided and the value corresponding to the scale is recorded in the designated box (0=worst imaginable health state, 100=best imaginable health state). The EQ-5D is administered as a self assessment at week 24.

6.4.7.1.1. Missing data handling and total score calculation

For the descriptive system, there should be only one response recorded for each domain. If multiple responses are indicated for a single domain, the response will be treated as missing.

A unique health state is defined by a 5-digit code, combining levels across each of the 5 domains. For example, 11111 would indicate no problem in any domain and 33333 would indicate major problems in all domains.

6.4.7.2. Analysis

For the descriptive system, the number and percentage of patients at each of the levels 1-3 will be summarized descriptively for each domain.

For the VAS component, summary statistics of actual values and change from baseline to Week 24 will be provided by treatment group. Analysis of the change from baseline to Week 24 will be performed using an analysis of covariance (ANCOVA) model with fixed effects for treatment, age group, OCS dose at baseline, and baseline value as covariate.

6.4.9. Asthma Control Diary

6.4.9.1. Variable Definition

6.4.9.1.1. 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.

6.4.9.1.2. 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.

6.4.9.1.3. 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.

6.4.9.1.4. 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.

6.4.9.2. 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, AM/PM reliever use, AM/PM PEF, and nighttime awakenings. 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).

PEF measurements collected in the morning and in the evening will be summarized separately. Asthma symptoms collected in the morning and in the evening will be summed to derive a total

daily symptom score. Total reliever use will be derived as the sum of the morning and evening counts.

A weekly average of the daily diary measures (AM/PM PEF, total asthma symptom score, and total reliever use) will be derived (see Table 6 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.

Nighttime awakenings will be derived and analyzed as a percentage over the treatment period, derived as:

> Awakening-free nights (%) = 100 x (total number of awakening-free nights / total number of days during the treatment period)

The treatment period is defined in Section 6.4. Note that missing data will be treated as non-responders in this analysis (eg, if response for nighttime awakenings is missing for a given day, then the day will not be counted as an awakening-free night).

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 6.4.3.2 with the exception of inclusion of sex and height in the model.

Analysis of the percentage of awakening-free nights will be performed using an analysis of variance (ANOVA) model with fixed effects for treatment, age group, and OCS dose at baseline.

A line graph presenting the LS mean change from baseline over time (at each week) will be provided for morning PEF, evening PEF, total asthma symptom score, and total reliever use 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 24) 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 24) 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 10. 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 10: List of Search 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)	

Term	Code	Level	FDA term (if applicable)	If LLT- under which PT
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)	

Term	Code	Level	FDA term (if applicable)	If LLT- under which PT
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	

Term	Code	Level	FDA term (if applicable)	If LLT- under which PT
Nocardiosis	10029444	PT	Nocardiosis	
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

7.3.1.7. OCS Use and OCS Withdrawal

Adverse events associated with oral corticosteroid use and oral corticosteroid withdrawal (investigator-assessed) will be recorded on the Adverse Event CRF and summarized separately.

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

- Patients with at least one AE related to OCS withdrawal
- Patients with at least one AE related to OCS use

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 andat 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 11; 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 11: 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 11: 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

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 12 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 12: 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 24 will be summarized using patient counts. Summary statistics for ECG variables will be presented at week 24. Actual values and changes from baseline to week 24 will be summarized.

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

- Absolute value at week 24
  - QTc interval >450 msec
  - QTc interval >500 msec
- Change from baseline to week 24
  - QTc interval increase >30 msec
  - QTc interval increase >60 msec
- Combined absolute value and change from baseline to week 24
  - 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.

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).

Oral corticosteroid medications will be summarized separately.

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; and prior to study drug administration at weeks 4, 8, 12, 24 or early withdrawal; and at the follow up visit (approximately week 32). An additional PK sample will be taken at the late follow-up visit (approximately week 48).

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 4, 8, 12, 16, 20, 24 or early withdrawal; and at the follow-up visit (approximately week 32).

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.

8.4. Immunogenicity

Samples for immunogenicity assessment for development of anti-drug antibodies will be obtained before the administration of study drug at baseline/DoR; weeks 4, 8, 12, 24 or early withdrawal; and at the follow-up visit (approximately week 32). An additional sample will be obtained at the late follow-up visit (approximately week 48). 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

Table 13 presents changes to the analyses specified in the CSP, Amendment 02.

Table 13: Changes to the Protocol Specified Analyses

Protocol Section	Protocol Description	Change/Rationale
9.5.6.3	The NB model will include the treatment group and randomization stratification factors as model factors and an offset variable.	The number of exacerbations in the previous year has been added as a covariate in the NB model. This variable has been shown to be influential in previous studies of reslizumab iv.

Table 14 summarizes the key changes that have been implemented since the original approved SAP. Only substantive changes have been included; editorial and/or administrative changes are generally not listed.

Table 14: Key Changes to the Statistical Analysis Plan, Amendment 01

SAP Section	SAP Description	Change	Rationale
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 24) 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 all efficacy endpoints, the on-treatment approach will be utilized as the main approach to analysis. However, it should be noted that all patients will be included in the analysis of the primary and secondary	Clarification

SAP Section	SAP Description	Change	Rationale
		endpoints related to OCS dose reduction by incorporating missing data (due to dropout) as nonresponders. The analytic approach including all data collected from patients will additionally be conducted as sensitivity analyses for the primary endpoint.	
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 24) 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 OCS dose (primary), pre-bronchodilator FEV1, and blood eosinophils will be analyzed separately for patients aged 12 to <18 years and ≥18 years.	Selected efficacy endpoints including OCS dose (primary), pre-bronchodilator FEV1, 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	Inclusion of 2 additional efficacy endpoints and clarification regarding definition of age strata

SAP Section	SAP Description	Change	Rationale
		the age recorded in the clinical database.	
3.4.2	Selected efficacy endpoints including OCS dose (primary), pre-bronchodilator FEV1, and blood eosinophils will be analyzed separately for patients taking an optimized baseline dose of OCS ≤10 mg and >10 mg.	Selected efficacy endpoints including OCS dose (primary), pre-bronchodilator FEV1, AQLQ+12, ACQ-6, and blood eosinophils will be analyzed separately for patients taking an optimized baseline dose of OCS ≤10 mg and >10 mg. OCS strata will be defined based on the optimized baseline dose of OCS recorded in the clinical database.	Inclusion of 2 additional efficacy endpoints and clarification regarding definition of OCS strata
3.4.3	Selected efficacy endpoints including OCS dose (primary), pre-bronchodilator FEV1, and blood eosinophils will also be examined for the following demographic subgroups:	Selected efficacy endpoints including OCS dose (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.
4.2.1 6.3.2.1.1 (Table 8)	The baseline value is the prescribed optimized OCS dose following the optimization period and will be defined as the OCS dose reported on the day of randomization. Start day for "Baseline Dose" equal to DoR Start day for "Baseline to Week 4" equal to DoR + 1 day	The baseline value is the prescribed optimized OCS dose following the optimization period and will be defined as the OCS dose reported on the day of first dose of study drug. Start day for "Baseline Dose" equal to Day of first dose of study drug Start day for "Baseline to Week 4" equal to Day of first dose of study drug + 1 day	Reference start date changed from day of randomization to day of first dose of study drug administration
4.5, 6.3, 6.3.3.2, 6.4, 6.4.2.2, 6.4.9.2	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 24) visit. For patients who prematurely discontinue treatment, the treatment period will be	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 24) visit. For patients who prematurely discontinue treatment, the treatment period will be	Reference start date changed from day of randomization to day of first dose of study drug administration

SAP Section	SAP Description	Change	Rationale
	defined from the day of randomization to the last dose of study drug + 4 weeks.	defined from the first dose of study drug to the last dose of study drug + 4 weeks.	
5.2	<<null>>	Patients will be categorized as completed the study if they either complete the study visits up to and including follow-up (Week 32, for patients not participating in the LTE study) or up to and including end of treatment (Week 24, for patients participating in the LTE study).	Clarification, based on inclusion of the long term extension study
	<<null>>	KM plots will be provided for time to discontinuation from treatment to identify if there is a differential dropout pattern between the treatment groups.	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
6.2.1	Percent reduction in OCS dose will be calculated as: • 100 x ((baseline dose – maintenance dose) / baseline dose) In this calculation, the maintenance dose is defined as the mean of all daily OCS doses during the maintenance period extending from	The week 20 to 24 maintenance dose and corresponding values for absolute and percent change (reduction) from baseline will be calculated as follows: • **Baseline dose** = the prescribed optimized OCS dose following the OCS optimization period (Table 8)	Clarification

SAP Section	SAP Description	Change	Rationale
	the Week 20 visit to the Week 24 visit, and baseline dose is the prescribed optimized OCS dose following the OCS optimization run-in period.	• **Maintenance dose** = mean of all daily OCS doses during the maintenance period extending from Week 20 to Week 24 (Table 8) • **Absolute reduction** = maintenance dose – baseline dose • **Percent reduction** = 100 x (**absolute reduction** / baseline dose)	
6.2.2, 6.3.2.2.1, 6.3.3.2, 6.4.3.2	<<null>>	Age and OCS dose will be based on data recorded in the clinical database.	Clarification
6.2.3	<<null>>	The primary analysis with control variables (age and OCS dose) 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	If a patient elects to withdraw from treatment (or is discontinued from treatment by the investigator), every attempt will be made to continue the assessments subsequent to his/her withdrawal from the study. If the patients agrees to remain in the study, they will continue to receive study	If a patient elects to withdraw from treatment (or is discontinued from treatment by the investigator), every attempt will be made to continue the assessments subsequent to his/her withdrawal from the study. If the patients agrees to remain in the study, they will continue to receive study prednisone treatment for the remainder of	Correction

SAP Section	SAP Description	Change	Rationale
	prednisone treatment ~~according to the OCS dose reduction algorithm~~ for the remainder of their participation in the study.	their participation in the study.	
6.2.4	An interaction p-value will be derived from a separate proportional odds model including terms for treatment, subgroup, and treatment by subgroup interaction.	An interaction p-value will be derived from a separate proportional odds model including additional terms for subgroup and treatment by subgroup interaction.	Clarification
6.4.2.2	<<null>>	The hazard ratio (95% CI) and p-value will be estimated using a Cox proportional hazards regression model adjusting for the stratification factors.	New analysis added
6.4.3.2	<<null>>	The proportion of patients achieving an increase of ≥100 mL in FEV1 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 FEV1 from baseline to Week 24.	New analysis added
6.4.4.2	<<null>>	AQLQ +12 at Week 24 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
6.4.5.2	<<null>>	ACQ-6 at Week 24 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	New analysis added

SAP Section	SAP Description	Change	Rationale
		be presented graphically using forest plots.	
7.3.1.6	<<null>>	Opportunistic Infections	New section added
7.5	Table 11	Table 11	PCS (potentially clinically significant) criteria for CPK changed to Grades 3-4
8.2.2	[redacted]		

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APPENDIX A. IMPUTATION AND ANALYSIS STEPS FOR SENSITIVITY ANALYSIS OF THE PRIMARY VARIABLE

The following represents an outline of the planned methodology for the multiple imputation procedure for the sensitivity analysis of the primary OCS response 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 (49476) that will be used in the analysis after unblinding.

```
data 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 24 weeks of treatment
2. ET1; patients who withdrew early from treatment but remained in the study contributing post-treatment follow-up data through week 24
3. ET2; patients who withdrew early from treatment but elected not to remain in the study through week 24

Step 3: Imputation of missing data.

Missing values for OCS dose (continuous) at week 24 and at visits in which earlier OCS doses were missing will be imputed. The missing OCS dose will be imputed based on measurements observed at previous visits and treatment group, assuming data are missing at random (MAR). The resulting observations at week 24 will be categorized as per the primary endpoint.

If the pattern of missing data is monotonic, the MONOTONE method in PROC MI will be used for imputation with a linear regression technique.

```
proc mi data=&indata out=&outdata nimpute=10 seed=&seed;
  class treatment;
  monotone regression (week4=treatment base /details);
  monotone regression (week8=treatment base week4 /details);
  monotone regression (week12=treatment base week4 week8 /details);
  monotone regression (week16=treatment base week4 week8 week12 /details);
  monotone regression (week20=treatment base week4 week8 week12 week16/details);
  monotone regression (week24=treatment base week4 week8 week12 week16 week20/details);
  var treatment base week4 week8 week12 week16 week20 week24;
run;
```

If the pattern of missing data is not monotonic, the MCMC MONOTONE method can be selected to transform the missing data pattern to a monotonic missing data structure by filling in missing values for earlier visits that have lower rates of missing data (ie, MCMC MONOTONE as a preliminary step, to be followed by application of the MONOTONE method in PROC MI).

```
proc mi data=&indata out=&outdata nimpute=10 seed=&seed;
  mcmc impute=monotone NBIter=2000 NIter=10000;
  var base week4 week8 week12 week16 week20 week24;
  by treatment;
run;

proc mi data=&outdata out=&outdata2 nimpute=1 seed=&seed;
  class treatment;
  monotone regression (week4=treatment base /details);
  monotone regression (week8=treatment base week4 /details);
  monotone regression (week12=treatment base week4 week8 /details);
  monotone regression (week16=treatment base week4 week8 week12 /details);
  monotone regression (week20=treatment base week4 week8 week12 week16/details);
  monotone regression (week24=treatment base week4 week8 week12 week16 week20/details);
  var treatment base week4 week8 week12 week16 week20 week24;
  by _imputation_;
run;
```

After this step, 10 datasets with complete data have been created.

Step 4: Re-run the primary analysis model.

Percent change from baseline and the corresponding 5-level response variable will be computed based on the imputed dose values at week 24. The proportional odds model will be fitted to the complete set of data for each of the 10 imputed datasets using the same covariates that were used for the primary analysis.

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 odds ratio.

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 primary response variable (OCS dose). 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.

Imputations will be performed for the missing OCS dose at week 24 and the resulting observations will be categorized as per the primary endpoint. OCS dose 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 OCS dose in the control group will be imputed assuming that missing data are MAR. For the treatment group, the OCS dose will be imputed in the same manner, but then a constant shift (>0) will be added to the imputed values to allow for MNAR. In the treatment group, this shift will be progressively increased and the process repeated until the treatment effect is no longer significant at the 5% level. The value of the shift 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. Missing values will be imputed assuming MAR in both treatment groups using the multiple imputation 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 shift parameter will be used to adjust imputed values for OCS dose, by adding the shift parameter to the imputed values. The following pseudo-code is provided to demonstrate this concept, where OUTMI is the output dataset(s) from Step 1, COMPLETER identifies the patients who discontinued treatment early with incomplete follow-up, week24 is the OCS dose at week 24, and δ is the shift parameter.

```
data outmi;
   set outmi;
   if armcd='RESLIZUMAB' and COMPLETER='N' then week24=week24+δ;
run;
```

   After this step, 10 datasets with complete data have been created.

3. The proportional odds 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 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 shift parameter resulting in estimates of the odds ratio and p-values for each shift parameter.

The odds ratio and associated p-value will be summarized corresponding to each selected shift value until the tipping point is achieved.

APPENDIX C. SGRQ – ITEM WEIGHTS FOR PROGRAMMING