Clinical trial results:
A 12-Month, Double-Blind, Placebo-Controlled, Parallel-Group Study to evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) in the reduction of Clinical Asthma Exacerbations in Patients (12-75 years of age) with Eosinophilic Asthma

Summary

EudraCT number	2010-024006-35
Trial protocol	SK DE GR
Global end of trial date	03 April 2014

Results information

Result version number	v1 (current)
This version publication date	09 July 2016
First version publication date	09 July 2016

Trial information

Trial identification

Sponsor protocol code	C38072/3083

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01285323
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products, R&D Inc.
Sponsor organisation address	41 Moores Road, Frazer, Pennsylvania, United States, 19355
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 215-591-3000, ustevatrials@tevapharm.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 215-591-3000, ustevatrials@tevapharm.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine whether reslizumab, at a dose of 3 mg/kg administered intravenously (iv) every 4 weeks over 12 months, is more effective than placebo in reducing the number of clinical asthma exacerbations (CAEs) in patients with eosinophilic asthma as assessed by the frequency of CAEs.
A CAE is defined by 1 of the following:
1) a hospitalization because of asthma,
2) emergency treatment because of asthma,
3) a decrease in forced expiratory volume in 1 second (FEV1) by 20% or more from baseline, or
4) If the peak expiratory flow rate (PEFR) drops below 30% from baseline on 2 consecutive days worsening of asthma will be assessed. If there is a prescribed increase in baseline oral corticosteroid (OCS) or inhaled corticosteroid (ICS) or if the symptoms warrant additional asthma treatment (OCS) this would be considered a CAE.

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Code of Federal Regulations [CFR] Title 21, Parts 50, 54, 56, 312, and 314; European Union (EU) Directive 2001/20/EC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use). Information regarding any investigational study centers participating in this study that could not comply with these standards was documented.
Written and/or oral information about the study was provided to all patients in a language understandable by the patients. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. For patients aged 12 through 17, a signed and dated informed consent form (ICF) was obtained from each parent/guardian and a signed and dated assent form was obtained from each patient before any study specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards were explained, according to local IEC/IRB requirements.
The patient’s willingness to participate in the study was documented in the assent form, which was signed by the patient with the date of that signature indicated. Each investigator kept the original consent/assent forms and copies were given to the patients. It was also explained to the patients that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 February 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 18

Country: Number of subjects enrolled	Slovakia: 30
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 64
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Argentina: 14
Country: Number of subjects enrolled	Brazil: 21
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Korea, Republic of: 34
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	Peru: 68
Country: Number of subjects enrolled	Russian Federation: 40
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Ukraine: 107
Country: Number of subjects enrolled	United States: 31
Worldwide total number of subjects	464
EEA total number of subjects	130

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	12
Adults (18-64 years)	415
From 65 to 84 years	37
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 1111 patients were screened for this study. Of the 1111 patients screened, 464 patients at 82 centers in 15 countries were randomly assigned to double-blind treatment.

Pre-assignment

Screening details:

Patients who continued to meet inclusion/exclusion criteria and who enrolled in the study were randomly assigned in a blinded fashion (1:1) to 1 of the following 2 treatment groups: reslizumab at 3 mg/kg or placebo, stratified by OCS use (yes or no) at study enrollment and by region (US or other).

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Patients were randomly assigned to treatment through an Interactive Response Technology (IRT). Using this system ensured a balance across treatment groups; no effort was made to maintain a balance among treatment groups, within a study center. To maintain the blinding to study drug in this 2 treatment group study, the volume of study drug (including active or placebo treatment) to be taken from each vial was assigned by IRT on the basis of the patient's body weight and assigned treatment group.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo administered intravenously once every 4 weeks (+-7 days) for a total of 13 doses.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Matching placebo (acetate sucrose buffer), administered intravenously (iv) once every 4 weeks for a total of 13 doses.

Arm title	Reslizumab 3.0 mg/kg

Arm description:

Reslizumab 3.0 mg/kg administered intravenously once every 4 weeks (+-7 days) for a total of 13 doses.

Arm type	Experimental
Investigational medicinal product name	Reslizumab
Investigational medicinal product code	
Other name	Cinquil, humanized monoclonal antibody, CEP-38072
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were administered intravenously over 15 to 30 minutes reslizumab at a dosage of 3.0 mg/kg at baseline and once every 4 weeks relative to baseline over 48 weeks for a total of 13 doses.

Number of subjects in period 1	Placebo	Reslizumab 3.0 mg/kg
Started	232	232
Full Analysis Set	232	232
Safety Analysis Set	232	232
Completed	199	202
Not completed	33	30
Consent withdrawn by subject	15	11
Adverse event, non-fatal	9	8
Not specified	1	3
Lost to follow-up	1	1
Lack of efficacy	4	2
Protocol deviation	1	2
Non-compliance with study procedures	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo administered intravenously once every 4 weeks (+-7 days) for a total of 13 doses.	
Reporting group title	Reslizumab 3.0 mg/kg
Reporting group description:	
Reslizumab 3.0 mg/kg administered intravenously once every 4 weeks (+-7 days) for a total of 13 doses.	

Reporting group values	Placebo	Reslizumab 3.0 mg/kg	Total
Number of subjects	232	232	464
Age categorical Units: Subjects			
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
Age continuous Units: years			
arithmetic mean	47.5	46.4	
standard deviation	± 13.75	± 13.79	-
Gender categorical Units: Subjects			
Female	150	144	294
Male	82	88	170
Race Units: Subjects			
White	169	168	337
Black	4	6	10
Asian	21	16	37
American Indian or Alaskan Native	4	7	11
Pacific Islander	1	0	1
Other	33	35	68
Oral Corticosteroid Use at Baseline			
Participants who were taking oral corticosteroids at baseline as recorded by interactive response technology. This was a stratification factor.			
Units: Subjects			
Yes	27	27	54
No	205	205	410
Participants in the United States			
This was a stratification factor as reported by the interactive response technology (IRT).			
Units: Subjects			
Yes	15	16	31
No	217	216	433
Weight Units: kg			
arithmetic mean	73.9	74.7	
standard deviation	± 15.93	± 15.72	-

Height			
Units: cm			
arithmetic mean	165.2	166.4	
standard deviation	± 9.81	± 9.56	-
Body Mass Index			
Units: kg/m^2			
arithmetic mean	27	27	
standard deviation	± 5.05	± 5.26	-
Asthma exacerbations in the previous 12 months			
One Reslizumab participant reported no asthma exacerbations in the past 12 months.			
Units: exacerbations			
arithmetic mean	2	1.9	
standard deviation	± 1.78	± 1.58	-
Forced Expiratory Volume in 1 second (FEV1)			
Units: liters			
arithmetic mean	2.004	2.129	
standard deviation	± 0.6682	± 0.7848	-
Asthma Control Questionnaire (ACQ)			
The ACQ is a 7-item instrument that measures asthma control (Juniper et al 1999). Six questions are self-assessments; the seventh item, completed by a member of the study staff, is the result of the patient's FEV1 measurement. Each item has 7 possible answers on a scale of 0 to 6, and the overall score is the mean of all responses. A higher score is an indication of poorer asthma control.			
Units: units on a scale			
arithmetic mean	2.605	2.57	
standard deviation	± 0.79	± 0.89	-
Asthma Quality of Life Questionnaire (AQLQ)			
The AQLQ is a 32-item instrument administered as a self-assessment (Juniper et al 1992). The questionnaire is divided into 4 domains: activity limitation, symptoms, emotional function, and environmental stimuli. Patients were asked to recall their experiences during the last 2 weeks and to respond to each question on a 7-point scale (1=severe impairment, 7=no impairment). The overall AQLQ score is the mean of all 32 responses.			
Units: units on a scale			
arithmetic mean	4.223	4.352	
standard deviation	± 1.0794	± 1.0229	-
Asthma Symptom Utility Index (ASUI)			
The ASUI is an 11-item instrument designed to assess the frequency and severity of asthma symptoms and side effects, weighted by patient preferences (Revicki et al 1998). ASUI is a utility score that ranges from 0 to 1, with higher values indicating better asthma control.			
Units: units on a scale			
arithmetic mean	0.649	0.664	
standard deviation	± 0.1919	± 0.2005	-
Blood Eosinophil Count			
Units: 10^9 blood eosinophil /L			
arithmetic mean	0.688	0.61	
standard deviation	± 0.6824	± 0.4115	-
Number of Short-Acting Beta-Agonist Puffs (SABA) Daily			
Based on patient-reported total number of SABA puffs over the past 3 days. N=201, 204			
Units: puffs/day			
arithmetic mean	2.7	2.9	
standard deviation	± 2.41	± 2.82	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo administered intravenously once every 4 weeks (+-7 days) for a total of 13 doses.	
Reporting group title	Reslizumab 3.0 mg/kg
Reporting group description:	
Reslizumab 3.0 mg/kg administered intravenously once every 4 weeks (+-7 days) for a total of 13 doses.	

Primary: Frequency of Clinical Asthma Exacerbations (CAEs) During 12 Months of Treatment

End point title	Frequency of Clinical Asthma Exacerbations (CAEs) During 12 Months of Treatment

End point description:

An exacerbation event was considered a CAE if the patient met either or both of the criteria listed below and this was corroborated with at least 1 other measurement to indicate the worsening of clinical signs and symptoms of asthma:

- use of systemic, or an increase in the use of inhaled, corticosteroid treatment for 3 or more days; or an increased 2 or more fold for at least 3 or more days for patient's already on corticosteroids.
- asthma-related emergency treatment, such as an unscheduled visit to the physician's office or emergency room for nebulizer treatment or other urgent treatment to prevent worsening of asthma symptoms, or an asthma-related hospitalization.

CAEs were adjudicated by committee to assure consistency. Adjusted CAE rate and confidence intervals were based on Negative Binomial regression model adjusted for stratification factors.
Results are offered as adjusted means.

End point type	Primary
End point timeframe:	
Day 1 to Month 12	

End point values	Placebo	Reslizumab 3.0 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	232[1]	232[2]		
Units: CAEs in 52 weeks				
arithmetic mean (confidence interval 95%)	2.115 (1.329 to 3.365)	0.859 (0.549 to 1.345)		

Notes:

[1] - Randomized set - patients assigned to a treatment group, regardless if they took study drug

[2] - Randomized set - patients assigned to a treatment group, regardless if they took study drug

Statistical analyses

Statistical analysis title	CAEs During 12 Months

Statistical analysis description:

The frequency of CAEs was analyzed using the generalized linear model (GLM) for data from the negative binomial distributions that is commonly referred to as the negative binomial (NB) regression model. The primary NB model included the treatment group and randomization stratification factors as model factors and the logarithm of follow up time excluding the summed duration of exacerbations in

the treatment period as an offset variable.

Comparison groups	Reslizumab 3.0 mg/kg v Placebo
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Chi-squared
Parameter estimate	CAE rate ratio (reslizumab vs placebo
Point estimate	0.4063
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2819
upper limit	0.5855

Notes:

[3] - The treatment effect was tested using the likelihood based Chi-square test at the 0.05 significance level.

Primary: Frequency of Each of the Two Criteria for Clinical Asthma Exacerbations (CAEs)

End point title	Frequency of Each of the Two Criteria for Clinical Asthma Exacerbations (CAEs)

End point description:

An exacerbation event was considered a CAE if the patient met either or both of the criteria listed below and this was corroborated with at least 1 other measurement to indicate the worsening of clinical signs and symptoms of asthma:

- use of systemic, or an increase in the use of inhaled, corticosteroid treatment for 3 or more days; or an increased 2 or more fold for at least 3 or more days for patient's already on corticosteroids.
- asthma-related emergency treatment, such as an unscheduled visit to the physician's office or emergency room for nebulizer treatment or other urgent treatment to prevent worsening of asthma symptoms, or an asthma-related hospitalization CAEs were adjudicated by committee to assure consistency.

Adjusted CAE rate and confidence intervals for the two criteria were based on Negative Binomial regression model adjusted for stratification factors.
Results are offered as adjusted means.

End point type	Primary

End point timeframe:

Day 1 to Month 12

End point values	Placebo	Reslizumab 3.0 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	232[4]	232[5]		
Units: CAEs in 52 weeks				
arithmetic mean (confidence interval 95%)				
Requiring systemic corticosteroids >3 days	1.66 (1.0005 to 2.744)	0.646 (0.397 to 1.053)		
Requiring hospitalization or ER visit	0.047 (0.013 to 0.168)	0.033 (0.009 to 0.12)		

Notes:

[4] - Randomized set - patients assigned to a treatment group, regardless if they took study drug

[5] - Randomized set - patients assigned to a treatment group, regardless if they took study drug

Statistical analyses

Statistical analysis title	CAEs requiring systemic corticosteroids >3 days

Statistical analysis description:

The frequency of CAEs was analyzed using the generalized linear model (GLM) for data from the negative binomial distributions that is commonly referred to as the negative binomial (NB) regression model. The primary NB model included the treatment group and randomization stratification factors as model factors and the logarithm of follow up time excluding the summed duration of exacerbations in the treatment period as an offset variable.

Comparison groups	Reslizumab 3.0 mg/kg v Placebo
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Chi-squared
Parameter estimate	CAE rate ratio (reslizumab vs placebo)
Point estimate	0.3893
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2621
upper limit	0.5782

Notes:

[6] - The treatment effect was tested using the likelihood based Chi-square test at the 0.05 significance level.

Statistical analysis title	CAEs requiring hospitalization or ER visit

Statistical analysis description:

The frequency of CAEs was analyzed using the generalized linear model (GLM) for data from the negative binomial distributions that is commonly referred to as the negative binomial (NB) regression model. The primary NB model included the treatment group and randomization stratification factors as model factors and the logarithm of follow up time excluding the summed duration of exacerbations in the treatment period as an offset variable.

Comparison groups	Reslizumab 3.0 mg/kg v Placebo
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.402 [7]
Method	Chi-squared
Parameter estimate	CAE rate ratio (reslizumab vs placebo)
Point estimate	0.6686
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2878
upper limit	1.6479

Notes:

[7] - The treatment effect was tested using the likelihood based Chi-square test at the 0.05 significance level.

Secondary: Change From Baseline in Forced Expiratory Volume in 1 Second (FEV1) At Week 16

End point title	Change From Baseline in Forced Expiratory Volume in 1 Second (FEV1) At Week 16

End point description:

FEV1 is a standard measurement of air movement in the lungs of patients with asthma obtained from pulmonary function tests. It is the volume of air expired in the first second of a forced expiration using a spirometer.
Positive change from baseline scores indicate improvement in asthma control.

End point type	Secondary

End point timeframe:

Day 1 (baseline, pre-dose), Week 16

End point values	Placebo	Reslizumab 3.0 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214[8]	214[9]		
Units: liters				
least squares mean (standard error)	0.122 (± 0.0447)	0.223 (± 0.0445)		

Notes:

[8] - Randomized set
Number analyzed reflects participants with both baseline and Week 16 assessments.
[9] - Randomized set
Number analyzed reflects participants with both baseline and Week 16 assessments.

Statistical analyses

Statistical analysis title	Change From Baseline FEV1 to Week 16

Statistical analysis description:

A pre-specified fixed sequence multiple testing procedure was implemented to test the secondary endpoints while controlling the overall Type I error rate at 0.05. At the point where p>0.05, no further comparisons were interpreted inferentially

Comparison groups	Reslizumab 3.0 mg/kg v Placebo
Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0109 [10]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.101
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.179
Variability estimate	Standard error of the mean
Dispersion value	0.0397

Notes:

[10] - Statistical significance at <=0.05. Fixed Factors: treatment, visit, trt by visit interaction, region, OCS at enrollment, sex. Random: covariates for height, baseline value and patient

Secondary: Change From Baseline in Forced Expiratory Volume in 1 Second (FEV1) Over 16 Weeks

End point title	Change From Baseline in Forced Expiratory Volume in 1 Second (FEV1) Over 16 Weeks

End point description:

FEV1 is a standard measurement of air movement in the lungs of patients with asthma obtained from pulmonary function tests. It is the volume of air expired in the first second of a forced expiration using a spirometer. During study values used a mixed effect model for repeated measures (MMRM) with treatment group, visit, treatment and visit interaction, and stratification factors as fixed effects and participant as a random effect. Covariates for baseline values were also included in the model; for pulmonary function test analyses, covariates for height and sex were included as well.
Positive change from baseline scores indicate improvement in asthma control.

End point type	Secondary

End point timeframe:

Day 1 (baseline, pre-dose), Weeks 4, 8, 12 and 16

End point values	Placebo	Reslizumab 3.0 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227[11]	230[12]		
Units: liters				
least squares mean (standard error)	0.094 (± 0.041)	0.187 (± 0.041)		

Notes:

[11] - Randomized set.
Includes participants who contributed at least once to the analysis.
[12] - Randomized set.
Includes participants who contributed at least once to the analysis.

Statistical analyses

Statistical analysis title	Change From Baseline FEV1 over 16 Weeks

Statistical analysis description:

A pre-specified fixed sequence multiple testing procedure was implemented to test the secondary endpoints while controlling the overall Type I error rate at 0.05. At the point where p>0.05, no further comparisons were interpreted inferentially.

Comparison groups	Reslizumab 3.0 mg/kg v Placebo
Number of subjects included in analysis	457
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0037 [13]
Method	Mixed model repeated measures (MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.093
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.155

Variability estimate	Standard error of the mean
Dispersion value	0.0317

Notes:

[13] - Statistical significance at <=0.05. Fixed Factors: treatment, visit, trt by visit interaction, region, OCS at enrollment, sex. Random: covariates for height, baseline value and patient

Secondary: Change From Baseline in Asthma Quality of Life Questionnaire (AQLQ) to Week 16

End point title	Change From Baseline in Asthma Quality of Life Questionnaire (AQLQ) to Week 16

End point description:

The AQLQ is a 32-item instrument administered as a self-assessment (Juniper et al 1992). The questionnaire is divided into 4 domains: activity limitation, symptoms, emotional function, and environmental stimuli. Patients were asked to recall their experiences during the last 2 weeks and to respond to each question on a 7-point scale (1=severe impairment, 7=no impairment). The overall AQLQ score is the mean of all 32 responses. Five of the activity questions were "patient-specific," which means that each patient identified and scored 5 activities in which the patient was limited by asthma; these 5 activities were identified at the first visit and retained for all subsequent follow-up visits. Positive change from baseline scores indicate improvement in quality of life.

End point type	Secondary

End point timeframe:

Day 1 (baseline, pre-dose), Week 16

End point values	Placebo	Reslizumab 3.0 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216[14]	213[15]		
Units: units on a scale				
least squares mean (standard error)	0.777 (± 0.1152)	0.987 (± 0.1158)		

Notes:

[14] - Randomized set of participants with assessments at each timepoint.

[15] - Randomized set of participants with assessments at each timepoint.

Statistical analyses

Statistical analysis title	Change From Baseline in AQLQ to Week 16

Statistical analysis description:

A pre-specified fixed sequence multiple testing procedure was implemented to test the secondary endpoints while controlling the overall Type I error rate at 0.05. At the point where p>0.05, no further comparisons were interpreted inferentially.

Comparison groups	Reslizumab 3.0 mg/kg v Placebo
Number of subjects included in analysis	429
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0259 [16]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.209

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.025
upper limit	0.393
Variability estimate	Standard error of the mean
Dispersion value	0.937

Notes:

[16] - Statistical significance at <=0.05. Fixed Factors: treatment, visit, trt by visit interaction, region, OCS at enrollment, sex. Random: covariates for height, baseline value and patient.

Secondary: Change From Baseline in Asthma Control Questionnaire (ACQ) Over 16 Weeks

End point title	Change From Baseline in Asthma Control Questionnaire (ACQ) Over 16 Weeks

End point description:

The ACQ is a 7-item instrument that measures asthma control (Juniper et al 1999). Six questions are self-assessments; the seventh item, completed by a member of the study staff, is the result of the patient's FEV1 measurement. Each item has 7 possible answers on a scale of 0 to 6, and the total score is the mean of all responses (the total scale is therefore 0-6). A higher score is an indication of poorer asthma control. The during treatment average ACQ was estimated using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.
Negative change from baseline scores indicate improvement in asthma control.

End point type	Secondary

End point timeframe:

Day 1 (baseline, pre-dose), Weeks 4, 8, 12, 16

End point values	Placebo	Reslizumab 3.0 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228[17]	230[18]		
Units: units on a scale				
least squares mean (standard error)	-0.66 (± 0.0875)	-0.857 (± 0.0872)		

Notes:

[17] - Randomized set, including participants who contributed at least once to the analysis.

[18] - Randomized set, including participants who contributed at least once to the analysis.

Statistical analyses

Statistical analysis title	Change From Baseline in ACQ Over 16 Weeks

Statistical analysis description:

A pre-specified fixed sequence multiple testing procedure was implemented to test the secondary endpoints while controlling the overall Type I error rate at 0.05. At the point where p>0.05, no further comparisons were interpreted inferentially.

Comparison groups	Reslizumab 3.0 mg/kg v Placebo

Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0032 [19]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	-0.196
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.327
upper limit	-0.066
Variability estimate	Standard error of the mean
Dispersion value	0.0664

Notes:

[19] - Statistical significance at <=0.05. Fixed Factors: treatment, visit, trt by visit interaction, region, OCS at enrollment, sex. Random: covariates for height, baseline value and patient

Secondary: Kaplan-Meier Estimates for Time to First Clinical Asthma Exacerbation (CAE)

End point title	Kaplan-Meier Estimates for Time to First Clinical Asthma Exacerbation (CAE)

End point description:

An exacerbation event was considered a CAE if the patient met either or both of the criteria listed below and this was corroborated with at least 1 other measurement to indicate the worsening of clinical signs and symptoms of asthma:

- use of systemic, or an increase in the use of inhaled, corticosteroid treatment for 3 or more days; or an increased 2 or more fold for at least 3 or more days for patient's already on corticosteroids.
- asthma-related emergency treatment, such as an unscheduled visit to the physician's office or emergency room for nebulizer treatment or other urgent treatment to prevent worsening of asthma symptoms, or an asthma-related hospitalization.

CAEs were adjudicated by committee to assure consistency. The distributions were compared by a log rank test stratified by baseline usage of oral corticosteroid (yes or no) and geographical region (U.S. or other).
Values of 9999 = Insufficient data to estimate time.

End point type	Secondary

End point timeframe:

Day 1 to Day 526 (longest treatment time plus 2 weeks)

End point values	Placebo	Reslizumab 3.0 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	232[20]	232[21]		
Units: weeks				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[20] - Randomized set

[21] - Randomized set

Statistical analyses

Statistical analysis title	Time to First CAE

Statistical analysis description:

Kaplan-Meier estimate of probability (%) of not experiencing a CAE by week 52. The first CAEs for each patient occurring after randomization and up to 2 weeks after the end of treatment period were analyzed. Patients without a CAE within this time frame were censored at two weeks after the treatment completion date or study discontinuation, whichever came first.

Comparison groups	Reslizumab 3.0 mg/kg v Placebo
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.486
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.353
upper limit	0.67

Notes:

[22] - Stratified by baseline usage of oral corticosteroid (yes or no) and geographical region (U.S. or other).

Secondary: Change From Baseline in Asthma Symptom Utility Index (ASUI) Over 16 Weeks

End point title	Change From Baseline in Asthma Symptom Utility Index (ASUI) Over 16 Weeks

End point description:

The ASUI is an 11-item instrument designed to assess the frequency and severity of asthma symptoms and side effects, weighted by patient preferences (Revicki et al 1998). ASUI is a utility score that ranges from 0 to 1, with higher values indicating better asthma control; info obtained from questionnaire about asthma symptoms.
The during treatment average ASUI was estimated using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements. Positive change from baseline values indicate improvement in asthma symptoms. Information was obtained from questionnaire about asthma symptoms.

End point type	Secondary

End point timeframe:

Day 1 (baseline, pre-dose), Weeks 4, 8, 12, 16

End point values	Placebo	Reslizumab 3.0 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224[23]	227[24]		
Units: units on a scale				
least squares mean (standard error)	0.08 (± 0.0161)	0.115 (± 0.0161)		

Notes:

[23] - Randomized set, including participants who contributed at least once to the analysis.

[24] - Randomized set, including participants who contributed at least once to the analysis.

Statistical analyses

Statistical analysis title	Change from Baseline in ASUI Over 16 Weeks

Statistical analysis description:

A pre-specified fixed sequence multiple testing procedure was implemented to test the secondary endpoints while controlling the overall Type I error rate at 0.05. At the point where p>0.05, no further comparisons were interpreted inferentially.

Comparison groups	Reslizumab 3.0 mg/kg v Placebo
Number of subjects included in analysis	451
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0037 [25]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.035
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.011
upper limit	0.059
Variability estimate	Standard error of the mean
Dispersion value	0.012

Notes:

[25] - Statistical significance at <=0.05.
Fixed Factors: treatment, visit, trt by visit interaction, region, OCS at enrollment, sex. Random: covariates for height, baseline value and patient

Secondary: Change From Baseline in Short-Acting Beta-Agonist (SABA) Use Over 16 Weeks

End point title	Change From Baseline in Short-Acting Beta-Agonist (SABA) Use Over 16 Weeks

End point description:

SABA are used for quick relief of asthma symptoms. To measure SABA use, at each clinical visit patients were asked to recall their usage of SABA therapy within the last 3 days of the scheduled visit. If usage was confirmed, the number of puffs used was recorded. For the purpose of summaries, an average daily usage was evaluated by dividing the total number of puffs recorded over 3 days by 3.
The during treatment SABA use was estimated using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements. Negative change from baseline scores indicate improvement in asthma control.

End point type	Secondary

End point timeframe:

Day 1 (baseline, pre-dose), Weeks 4, 8, 12, 16

End point values	Placebo	Reslizumab 3.0 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188[26]	180[27]		
Units: SABA puffs per day				
least squares mean (standard error)	-0.44 (± 0.233)	-0.5 (± 0.23)		

Notes:

[26] - Randomized set including patients who contributed at least once to the analysis.

[27] - Randomized set including patients who contributed at least once to the analysis.

Statistical analyses

Statistical analysis title	Change from Baseline in SABA use

Statistical analysis description:

A pre-specified fixed sequence multiple testing procedure was implemented to test the secondary endpoints while controlling the overall Type I error rate at 0.05. At the point where p>0.05, no further comparisons were interpreted inferentially.

Comparison groups	Reslizumab 3.0 mg/kg v Placebo
Number of subjects included in analysis	368
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7263 [28]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	-0.062
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.411
upper limit	0.287
Variability estimate	Standard error of the mean
Dispersion value	0.1775

Notes:

[28] - Statistical significance at <=0.05.
Fixed Factors: treatment, visit, trt by visit interaction, region, OCS at enrollment, sex. Random: covariates for height, baseline value and patient

Secondary: Change From Baseline in Blood Eosinophil Count Over 16 Weeks and 52 Weeks

End point title	Change From Baseline in Blood Eosinophil Count Over 16 Weeks and 52 Weeks

End point description:

The blood eosinophil counts were measured using a standard complete blood count (CBC) with differential blood test. Results of all differential blood tests conducted after randomization were blinded. The during-treatment average eosinophil count was estimated using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.
Negative change from baseline values correlate to reduced asthma severity.

End point type	Secondary

End point timeframe:

Day 1 (baseline, pre-dose), Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 or early withdrawal

End point values	Placebo	Reslizumab 3.0 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226[29]	230[30]		
Units: 10^9/L				
least squares mean (standard error)				
Over first 16 weeks	-0.076 (± 0.0268)	-0.555 (± 0.0266)		
Over 52 weeks	-0.076 (± 0.0233)	-0.565 (± 0.0231)		

Notes:

[29] - Randomized set including patients who contributed at least once to the analysis.

[30] - Randomized set including patients who contributed at least once to the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Participants With Treatment-Emergent Adverse Events TEAE)

End point title	Participants With Treatment-Emergent Adverse Events TEAE)

End point description:

An adverse event (AE) was defined in the protocol as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. Severity was rated by the investigator on a scale of mild, moderate and severe, with severe= an inability to carry out usual activities. Relation of AE to treatment was determined by the investigator. Serious AEs include death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, OR an important medical event that jeopardized the patient and required medical intervention to prevent the previously listed serious outcomes.

End point type	Secondary

End point timeframe:

Day 1 (post-dose) to Week 65. The endpoint for adverse events was the last postbaseline observation, which included the 90 day follow-up visit.

End point values	Placebo	Reslizumab 3.0 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	232[31]	232[32]		
Units: participants				
Any TEAE	201	177		
Mild TEAE	36	67		
Moderate TEAE	140	98		
Severe TEAE	25	12		
Treatment-related AE	27	34		
Mild treatment-related AE	14	22		
Moderate treatment-related AE	13	11		
Severe treatment-related AE	0	1		
TEAE causing patient discontinuation	9	8		
Deaths	0	0		
Serious AEs	23	18		

Notes:

[31] - Safety analysis set

[32] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Participants With Treatment-Emergent Potentially Clinically Significant (PCS) Abnormal Lab Values

End point title	Participants With Treatment-Emergent Potentially Clinically Significant (PCS) Abnormal Lab Values

End point description:

Data represents participants with potentially clinically significant (PCS) abnormal serum chemistry, hematology (except for eosinophil values), and urinalysis values.
Significance criteria:

- Blood urea nitrogen: >=10.71 mmol/L
- Creatinine: >=177 µmol/L
- Urate: M>=625, F>=506 µmol/L
- Aspartate aminotransferase (AST): >=3*upper limit of normal (ULN)
- Alanine aminotransferase (ALT): >=3*ULN
- GGT = gamma-glutamyl transpeptidase: >= 3*ULN
- Total bilirubin: >=34.2 µmol/L
- White blood cells (low): <=3.0*10^9/L
- White blood cells (high): >=20*10^9/L
- Hemoglobin (age >=18 years): M<=115, F<=95 g/dL
- Hematocrit (age >=18 years): M<0.37, F<0.32 L/L
- Eosinophils/leukocytes: >=10.0%
- Platelets: <=75*10^9/L
- Neutrophils: <=1.0*10^9/L
- Urinalysis: blood, ketones, glucose, and protein: >=2 unit increase from baseline

End point type	Secondary

End point timeframe:

Week 4 to Week 52

End point values	Placebo	Reslizumab 3.0 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227[33]	230[34]		
Units: participants				
Blood urea nitrogen	5	4		
Creatinine	0	1		
Urate	5	2		
AST	3	2		
ALT	7	3		
GGT	11	9		
Bilirubin	3	3		
Leukocytes (low)	3	10		
Leukocytes (high)	0	1		
Hemoglobin	5	6		

Hematocrit	10	8		
Eosinophils/leukocytes	168	10		
Platelets	1	1		
Neutrophils	14	9		
Urine blood (hemoglobin)	28	12		
Urine ketones	6	1		
Urine glucose	9	7		
Urine protein	28	28		

Notes:

[33] - Safety analysis set, including participants who contributed to the analysis

[34] - Safety analysis set, including participants who contributed to the analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Participants With Treatment-Emergent Potentially Clinically Significant (PCS) Vital Signs Values

End point title	Participants With Treatment-Emergent Potentially Clinically Significant (PCS) Vital Signs Values

End point description:

Data represents participants with potentially clinically significant (PCS) vital sign values.
Significance criteria

- Sitting pulse (high): >100 and increase of >= 30 beats/minute
- Sitting systolic blood pressure (low): <90 and decrease of >= 30 mmHg
- Sitting systolic blood pressure (high): >160 and increase of >= 30 mmHg
- Sitting diastolic blood pressure (low): <50 and decrease of >=12 mmHg (if 12-17 years old: <55 and decrease of >=12 mmHg 0
- Sitting diastolic blood pressure (high): >100 and increase of >=12 mmHg
- Respiratory rate (low): <6 breaths/minute
- Respiratory rate (high): >24 and increase of >=10 breaths/minute
- Body temperature (low): <35.8° Celsius
- Body temperature (high): >=38.1 and increase of >=1.1° Celsius

End point type	Secondary

End point timeframe:

Week 4 to Week 52

End point values	Placebo	Reslizumab 3.0 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[35]	230[36]		
Units: participants				
>=1 postbaseline vital sign abnormality	58	49		
Sitting pulse (high)	6	6		
Sitting systolic blood pressure (low)	2	1		
Sitting systolic blood pressure (high)	0	1		
Sitting diastolic blood pressure (low)	4	3		
Sitting diastolic blood pressure (high)	3	4		
Respiratory rate (low)	0	1		
Respiratory rate (high)	4	5		
Body temperature (low)	50	39		
Body temperature (high)	1	0		

Notes:

[35] - Safety analysis set including participants who contributed data to the analysis

[36] - Safety analysis set including participants who contributed data to the analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Participants With a Positive Anti-Reslizumab Antibody Status During Study

End point title	Participants With a Positive Anti-Reslizumab Antibody Status During Study

End point description:

Counts of participants with a positive anti-drug antibody (ADA) response during treatment is offered for the experimental treatment arm. Blood samples were collected for determination of ADAs before study drug infusion.

End point type	Secondary

End point timeframe:

Baseline visit (prior to reslizumab exposure), Weeks 16, 32, 48 and 52

End point values	Placebo	Reslizumab 3.0 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[37]	232[38]		
Units: participants				
Baseline		10		
Week 16		10		
Week 32		10		
Week 48		10		
Week 52		10		
>=1 positive test result		15		

Notes:

[37] - Test not reported for placebo arm

[38] - Safety Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 (post-dose) to Week 65. The endpoint for adverse events was the last postbaseline observation, which included the 90 day follow-up visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo administered intravenously once every 4 weeks (+-7 days) for a total of 13 doses.

Reporting group title	Reslizumab 3.0 mg/kg

Reporting group description:

Reslizumab 3.0 mg/kg administered intravenously once every 4 weeks (+-7 days) for a total of 13 doses.

Serious adverse events	Placebo	Reslizumab 3.0 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 232 (9.91%)	18 / 232 (7.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasmacytoma			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour benign			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	3 / 232 (1.29%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Contusion			
subjects affected / exposed	2 / 232 (0.86%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brachial plexus injury			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column injury			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post concussion syndrome			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus lesion			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			

subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			

subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 232 (0.00%)	2 / 232 (0.86%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	6 / 232 (2.59%)	3 / 232 (1.29%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory failure			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status asthmaticus			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial secretion retention			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Allergic sinusitis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Foot deformity			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 232 (2.59%)	2 / 232 (0.86%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 232 (0.43%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycobacterium fortuitum infection			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
subjects affected / exposed	1 / 232 (0.43%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Reslizumab 3.0 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	160 / 232 (68.97%)	123 / 232 (53.02%)	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 232 (6.90%)	33 / 232 (14.22%)	
occurrences (all)	20	55	
Respiratory, thoracic and mediastinal			

disorders Asthma subjects affected / exposed occurrences (all)	 118 / 232 (50.86%) 293	 66 / 232 (28.45%) 133	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 8 / 232 (3.45%) 8	 12 / 232 (5.17%) 13	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all)	 56 / 232 (24.14%) 88 16 / 232 (6.90%) 27 14 / 232 (6.03%) 15	 45 / 232 (19.40%) 71 8 / 232 (3.45%) 16 2 / 232 (0.86%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2011	Amendment 1 (dated 14 April 2011) to the protocol was issued when 1 patient had been enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: • change in sponsor's medical expert and pharmacovigilance representative • text was added to the study objectives to clarify the definition of emergency treatment for asthma • inclusion criterion (f) was revised to clearly state that baseline asthma therapy must be stable for 30 days prior to screening and continue without dosage changes throughout the study • exclusion criterion (c) was revised to clearly state that patients with pulmonary conditions with symptoms of asthma and blood eosinophilia (eg, Churg Strauss syndrome, allergic bronchopulmonary aspergillosis) were also to be excluded • exclusion criterion (n) was added to exclude patients who had the presence of or suspected parasitic infestation/infection • exclusion criterion (o) was added to exclude patients who have received any live attenuated vaccine within the 12 week period prior to screening • a 90-day follow-up evaluation was added for assessment of adverse events, blood eosinophils, and vital signs for patients who did not enroll in the available open-label extension study
19 April 2011	Amendment 2 (dated 19 April 2011) to the protocol was issued after 1 patient was enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: • a change was made to stipulate that blood samples were to be collected for pharmacokinetics evaluation, blood eosinophil determination, and anti reslizumab antibody assessment each time a patient experienced a serious adverse event, an adverse event leading to withdrawal, or an exacerbation of asthma symptoms • inclusion criterion (h) was revised to clarify acceptable contraceptive methods to be used during the study • exclusion criterion (e) was revised to include other prohibited biologics (ie, interferon-α and anti-TNF) • exclusion criterion (f) was revised to specifically exclude patients who had previously received anti IL 5 mAbs, whether within or outside of a clinical study • exclusion criterion (i) was revised to clarify that patients may not have participated in any investigative biologics study within 90 days prior to screening

11 August 2011	Amendment 3 (dated 11 August 2011) to the protocol was issued after 8 patients had been enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: • change in sponsor's authorized representative and therapeutic area head • the definition of CAE was changed: the criterion capturing a fall in peak expiratory flow was modified to mandate associated asthma symptomatology • the assessment of CAEs was changed to only the treatment period of the study • inclusion criterion (b) requiring use of corticosteroids for the treatmeant of a CAE within the previous 12 months was changed to include use of intramuscular corticosteroids • exclusion criterion (p) was added and stated: The patient has a history of allergic reactions to or hypersensitivity to any component of the study drug • the procedures for diagnosing a CAE were changed to agree with the new definition of a CAE • the exclusion of a patient using OCSs greater than 10 mg/day was removed as part of an administrative letter dated 26 July 2011 and was presented in revised exclusion criterion (e2). As a result of this revision, inclusion criterion (f2) was amended so that a patient's baseline asthma therapy regimen could now include OCSs up to a maximum dose of prednisone daily, or equivalent, and that they would be allowed into the study as long as they were stable for 30 days prior to screening and continued without dosage changes throughout the study.
16 August 2012	Amendment 4 (dated 16 August 2012) to the protocol was issued after 328 patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: • change in sponsor, medical expert, pharmacovigilance representative, and contact information • assessments at the time of 1st CAE was removed based on United States Food and Drug Administration (FDA) input • revisions were made to include language regarding withholding of SABAs before lung function testing because of their impact on spirometry • additional assessments performed at screening were added (12 lead ECG, physical examination, urinalysis, vital signs measurements, β-HCG serum pregnancy test for all females of childbearing potential) • independent DSMB information was added • revision was made to ensure that the study blind was maintained when pharmacokinetic analysis was performed during the study • the study sample size was increased and the expected study completion date, study duration, and number of study centers were revised because of the change in sample size • 2 ACQ scores required prior to randomization, both had to be 1.5 or greater • patients with recent infections requiring hospitalization or oral/iv antibiotic were excluded from entering the study • benralizumab was added as an excluded prior medication • the use of an adjudication committee to assess CAEs was added • a 48-hour window was added for evaluating patients with a CAE
19 April 2013	Amendment 5 (dated 19 April 2013) to the protocol was issued after 464 patients were enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: • change in sponsor's authorized representative, medical expert, pharmacovigilance representative, and contact information for serious adverse event reporting • pharmacokinetic and immunogenicity information was updated • the sample size was revised using an annualized exacerbation rate of 1.2, from more current global data • additional ECG assessments incorporated into the study • clarification of sampling times and assessments • clarification of exploratory endpoints and secondary endpoints

24 January 2014	Amendment 6 (dated 24 January 2014) to the protocol was issued after 464 patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: • change in sponsor's authorized representative and medical expert • the definition of a CAE was changed to the current, more stringent definition such that a decease in lung function (ie, a CRF decrease in FEV1 or PEFR) was now designated as supportive of a medical intervention for worsening asthma, and not definitive in an of itself. • secondary objectives were revised to more clearly define the variables to be analyzed and OCS use was deleted as a secondary variable because this is a subset of the primary objective • evaluation of sputum eosinophils and potential asthma biomarkers in sputum supernatants were added as exploratory objective • the filter size was changed to 0.20-micron size • statistical analyses were changed to agree with the new efficacy variables

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported