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

Summary

EudraCT number	2015-000865-29
Trial protocol	CZ ES HU BE PL DE
Global end of trial date	31 January 2018

Results information

Result version number	v1 (current)
This version publication date	16 December 2018
First version publication date	16 December 2018

Trial information

Trial identification

Sponsor protocol code	C38072-AS-30025

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02452190
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products, R&D Inc
Sponsor organisation address	41 Moores Road, Frazer, United States, 19355
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 001 2155913000, ustevatrials@tevapharm.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 001 2155913000, ustevatrials@tevapharm.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001202-PIP02-13
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 January 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to establish the safety and efficacy of the subcutaneous formulation of reslizumab in participants with uncontrolled asthma and elevated blood eosinophils.

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 Title 21, Parts 11, 50, 54, 56, 312, and 314; European Union Directive 2001/20/EC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical studies on medicinal products for human use).
Written and/or oral information about the study was provided to all participants in a language understandable by the participants. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from each participant before any study procedures or assessments were done. It was explained to the participants 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	12 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 27
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Hungary: 35
Country: Number of subjects enrolled	Israel: 34
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Romania: 18

Country: Number of subjects enrolled	Russian Federation: 45
Country: Number of subjects enrolled	Turkey: 4
Country: Number of subjects enrolled	Ukraine: 76
Country: Number of subjects enrolled	United States: 105
Country: Number of subjects enrolled	South Africa: 12
Worldwide total number of subjects	468
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)	53
Adults (18-64 years)	348
From 65 to 84 years	67
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1159 participants were screened, of whom 468 participants were eligible and enrolled in a 3-week run-in period for self-monitoring. All 468 enrolled participants were then randomized at 201 centers in 20 countries.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching placebo administered subcutaneously 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 injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo administered once every 4 weeks (+/-7 days)

Arm title	Reslizumab 110 mg

Arm description:

Reslizumab 110 milligrams (mg) administered subcutaneously once every 4 weeks (+/-7 days) for a total of 13 doses.

Arm type	Experimental
Investigational medicinal product name	Resizumab
Investigational medicinal product code	CEP-38072
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Reslizumab 110 mg once every 4 weeks (+/-7 days)

Number of subjects in period 1	Placebo	Reslizumab 110 mg
Started	232	236
Intent to Treat (ITT) Population	230	234
Completed	197	212
Not completed	35	24
Consent withdrawn by subject	20	11
Investigator's Decision	2	-
Withdrawal by Sponsor	1	3
Adverse event (non-fatal)	2	5
Death	-	1
Pregnancy	1	-
Noncompliance with study drug	1	-
Lost to follow-up	4	3
Lack of efficacy	3	1
Participant traveled abroad	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching placebo administered subcutaneously once every 4 weeks (+/-7 days) for a total of 13 doses.	
Reporting group title	Reslizumab 110 mg
Reporting group description:	
Reslizumab 110 milligrams (mg) administered subcutaneously once every 4 weeks (+/-7 days) for a total of 13 doses.	

Reporting group values	Placebo	Reslizumab 110 mg	Total
Number of subjects	232	236	468
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	25	28	53
Adults (18-64 years)	176	172	348
From 65-84 years	31	36	67
Age Continuous			
Units: years			
arithmetic mean	45.03	47.08	
standard deviation	± 17.748	± 17.695	-
Sex: Female, Male			
Units: Subjects			
Female	130	145	275
Male	102	91	193
Region of Enrollment			
Units: Subjects			
United States and Canada|	58	52	110
Europe|	127	137	264
Rest of World|	47	47	94
Race/Ethnicity, Customized			
Units: Subjects			
Not Hispanic or Latino|	203	218	421
Hispanic or Latino|	26	17	43
Unknown|	3	1	4
Blood Eosinophil Category at Baseline			
Units: Subjects			
less than (<)300 per (/) microliter (mcl)|	0	1	1
300 to <400/mcl	42	48	90
greater than or equal to (≥)400/mcl	190	187	377
Race/Ethnicity, Customized			
Units: Subjects			
White	201	207	408
Black or African American	11	15	26
Asian	11	6	17
American Indian or Alaska Native	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0

Other	8	8	16

Pre-bronchodilator Forced Expiratory Volume in 1 Second (FEV1)			
Number of participants analyzed N=Participants in the ITT population with pre-bronchodilator FEV1 at baseline measures available. (N=229 and 234 for Placebo and Reslizumab arm, respectively)			
Units: liters			
arithmetic mean	2.102	1.988	
standard deviation	± 0.870	± 0.780	-
Asthma Quality of Life Questionnaire for Participants 12 Years and Older (AQLQ+12) Score			
AQLQ is a 32-item self-assessment. AQLQ+12 is modified version of AQLQ to measure functional impairments of participants 12-70 years. It is divided into 4 domains: activity limitation, symptoms, emotional function, environmental stimuli. Participants were asked to recall experiences during the last 2 weeks and respond to each question on a 7-point scale (1=severe impairment, 7=no impairment), where higher scores indicate better quality of life. Overall AQLQ+12 score is the mean of all 32 responses. N=ITT population with baseline AQLQ+12 scores available. N=215, 217 for Pla, Res, respectively			
Units: units on a scale			
arithmetic mean	4.39	4.28	
standard deviation	± 0.995	± 1.048	-
Asthma Control Questionnaire (ACQ-6) Score			
The ACQ-6 is a validated 6-item asthma assessment tool that has been widely used. Six questions are self-assessments (completed by the participant), 5 questions assessing asthma symptoms: night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and 1 question for short-acting bronchodilator use. Each item on the ACQ has a possible score ranging from 0 to 6, and the total score is the mean of all responses. The total score ranging from 0-6 (0=totally controlled and 6=severely uncontrolled). ITT population (N= 230 and 234 for Pla and Res, respectively)			
Units: units on a scale			
arithmetic mean	2.42	2.48	
standard deviation	± 0.812	± 0.88	-
Total Asthma Symptom Scores			
Asthma symptoms were recorded by participants in an asthma control diary. Night score was assessed on a 5-point scale where 0=no symptoms, slept through night, to 4=bad night, no sleep. Day score was assessed on a 6-point scale where 0=very well, no symptoms, to 5=asthma very severe, unable to carry out daily activities. Total asthma symptom score was calculated by taking the sum of the night and day asthma symptom scores recorded each day, ranging from 0 (no symptom) to 9 (severe symptom). N=ITT population with asthma symptom scores at baseline. (N= 222 and 224 for Pla and Res, respectively)			
Units: units on a scale			
arithmetic mean	2.6	2.5	
standard deviation	± 1.62	± 1.53	-
Number of Clinical Asthma Exacerbation (CAE) Events in the Previous 12 Months			
CAE at baseline were defined as asthma exacerbations requiring systemic corticosteroids within last 12 months. ITT population N=230 and 234 for placebo and reslizumab arms, respectively.			
Units: Count of Events			
arithmetic mean	2.30	2.35	
standard deviation	± 0.843	± 1.043	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Matching placebo administered subcutaneously once every 4 weeks (+/-7 days) for a total of 13 doses.	
Reporting group title	Reslizumab 110 mg
Reporting group description:	
Reslizumab 110 milligrams (mg) administered subcutaneously once every 4 weeks (+/-7 days) for a total of 13 doses.	

Primary: Frequency of Clinical Asthma Exacerbations (CAEs) During 52 Weeks of Treatment

End point title	Frequency of Clinical Asthma Exacerbations (CAEs) During 52 Weeks of Treatment
End point description:	
CAE is deterioration in asthma control, determined by investigator and evidenced by new/worsening symptoms based on history, asthma control diary, physical examination, and/or ambulatory or clinic visit assessment of lung function and that resulted in a medical intervention, including at least 1 of the following: use of systemic corticosteroids or at least a doubling from a stable maintenance oral corticosteroid dose for at least 3 days; asthma-specific hospital admission; asthma-specific ER department visit. Adjusted CAE rate and CIs were based on Negative Binomial regression model adjusted for stratification factors. Offset variable calculated as the logarithm of treatment duration minus the summed duration of exacerbations during treatment period. ITT population included all randomized participants, excluding participants from the site terminated due to GCP issues. Treatment based on to which participants were randomized, regardless of which treatment they received	
End point type	Primary
End point timeframe:	
Day 1 to Week 52	

End point values	Placebo	Reslizumab 110 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	234		
Units: CAEs in 52 weeks				
number (confidence interval 95%)	0.52 (0.347 to 0.773)	0.41 (0.279 to 0.607)		

Statistical analyses

Statistical analysis title	Difference between Reslizumab and Placebo
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, randomization stratification factors, and number of prior exacerbations as model factors and the logarithm of treatment duration excluding the summed duration of exacerbations in the treatment period as an offset variable.	
Comparison groups	Placebo v Reslizumab 110 mg

Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.194 [2]
Method	Chi-squared
Parameter estimate	CAE rate ratio (reslizumab vs placebo)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.562
upper limit	1.124

Notes:

[1] - A fixed-sequence multiple testing procedure was implemented to test the primary and 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.

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

Secondary: Change from Baseline to Week 52 in Pre-bronchodilator Forced Expiratory Volume in 1 Second (FEV1)

End point title	Change from Baseline to Week 52 in Pre-bronchodilator Forced Expiratory Volume in 1 Second (FEV1)

End point description:

Change in pre-bronchodilator FEV1 from baseline to week 52 is presented. FEV1 is a standard measurement of air movement in the lungs of participants 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. Analysis of the change from baseline to each visit was performed using a mixed effect model for repeated measures (MMRM) including fixed effects for treatment, visit, treatment by visit interaction, age group, blood eosinophil counts at enrollment, and sex, height and baseline value as covariates, and participant as a random effect. ITT includes all randomized participants, excluding participants from the site terminated due to GCP issues. Treatment was based on the treatment to which participants were randomized, regardless of which treatment they received. Overall number of participants analyzed=participants with both baseline and Week 52 FEV1 values available.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo	Reslizumab 110 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	211		
Units: liters				
least squares mean (standard error)	0.225 (± 0.040)	0.368 (± 0.039)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in Asthma Quality of Life

Questionnaire for Participants 12 Years and Older (AQLQ+12) Score

End point title	Change from Baseline to Week 52 in Asthma Quality of Life Questionnaire for Participants 12 Years and Older (AQLQ+12) Score

End point description:

AQLQ is a 32-item instrument administered as a self-assessment. AQLQ+12 is a modified version of AQLQ developed to measure functional impairments of participants aged 12-70 years. It is divided into 4 domains: activity limitation, symptoms, emotional function, and environmental stimuli. Participants were asked to recall their experiences during the last 2 weeks and respond to each question on a 7-point scale (1=severe impairment, 7=no impairment), where higher scores indicated "better quality of life." Overall AQLQ+12 score is the mean of all 32 responses. Analysis of the change from baseline to each visit was performed using a MMRM including fixed effects for treatment, visit, treatment by visit interaction, age group, blood eosinophil counts at enrollment, and sex, height and baseline value as covariates, and participant as a random effect. ITT population aged 12-70 years. Overall number of participants analyzed=participants with both baseline and Week 52 AQLQ+12 score available.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo	Reslizumab 110 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	197		
Units: units on a scale				
least squares mean (standard error)	1.06 (± 0.089)	1.14 (± 0.087)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in 6-item Asthma Control Questionnaire (ACQ-6) Score

End point title	Change from Baseline to Week 52 in 6-item Asthma Control Questionnaire (ACQ-6) Score

End point description:

ACQ-6 is a 6-item asthma assessment tool. 6 questions are self-assessments, 5 assessing asthma symptoms: night waking, symptoms on waking, activity limits, shortness of breath, wheezing, and 1 question for short-acting bronchodilator use. Each item has possible score ranges from 0-6, and total score is mean of all responses. Total score range from 0-6 (0=totally controlled, 6=severely uncontrolled). Higher score=poorer asthma control. Analysis of change from baseline to each visit performed using a MMRM including fixed effects for treatment, visit, treatment by visit interaction, age group, eosinophil count at enrollment, and sex, height and baseline value as covariates, and participant as a random effect. ITT includes all randomized participants, excluding the site terminated due to GCP issues. Treatment based on what participants were randomized to, regardless of which they received. Number of participants analyzed=participants with both baseline and Week 52 ACQ-6 score available.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo	Reslizumab 110 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	212		
Units: units on a scale				
least squares mean (standard error)	-1.14 (± 0.080)	-1.22 (± 0.078)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in Total Asthma Symptom Scores (Day and Night)

End point title	Change from Baseline to Week 52 in Total Asthma Symptom Scores (Day and Night)

End point description:

Asthma symptoms recorded by participant each day and night in an asthma diary. Night score assessed on 5-point scale: 0=no symptoms to 4=bad night. Day score assessed on 6-point scale where 0=very well to 5=asthma very severe. Total symptom score calculated by taking the sum of the night and day symptom scores recorded ranging from 0 (no symptom) to 9 (severe symptom). Lower symptom score indicated better outcome. Analysis of the change from baseline to each visit was performed using a MMRM including fixed effects for treatment, visit, treatment by visit interaction, age group, eosinophil count at enrollment, and sex, height and baseline value as covariate, and participant as a random effect. ITT=all randomized participants, excluding from site terminated due to GCP issues. Treatment based on treatment to which participants were randomized, regardless of treatment received. Overall number of participants analyzed=participants with both baseline and Week 52 total asthma symptom score.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo	Reslizumab 110 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	143		
Units: units on a scale				
least squares mean (standard error)	-1.4 (± 0.12)	-1.5 (± 0.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Percentage of Asthma Control Days

End point title	Change from Baseline in Percentage of Asthma Control Days

End point description:

The percentage of asthma control days over 52 weeks of treatment is presented. An asthma control day was defined as a day on which the participant used less than or equal to 2 puffs of inhaled short-acting beta-agonist, had no nighttime awakenings, and experienced no asthma exacerbations. Analysis of the

change from baseline to each visit was performed using a mixed effect MMRM including fixed effects for treatment, visit, treatment by visit interaction, age group, blood eosinophil counts at enrollment, and sex, height and baseline value as covariates, and participant as a random effect. ITT population includes all randomized participants, excluding participants from the site terminated due to GCP issues. Treatment was based on the treatment to which participants were randomized, regardless of which treatment they actually received.

End point type	Secondary

End point timeframe:

Day 1 to Week 52

End point values	Placebo	Reslizumab 110 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	234		
Units: percentage of days				
least squares mean (standard error)	7.1 (± 1.27)	8.0 (± 1.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 32 in St. George's Respiratory Questionnaire (SGRQ) Total Score

End point title	Change from Baseline to Week 32 in St. George's Respiratory Questionnaire (SGRQ) Total Score

End point description:

SGRQ is 17-item questionnaire with 50 weighted responses that provides total score and 3 component scores: Symptoms (distress caused by respiratory symptoms), Activity (physical activities cause/limited by breathlessness), and Impacts (social/psychological effects). Total score and each of the SGRQ subscores are from 0-100 where 0=best, 100=worst health. Increase in score indicates worsening health. Analysis of the change from baseline to each visit was performed using a MMRM including fixed effects for treatment, visit, treatment by visit interaction, age group, eosinophil counts at enrollment, and sex, height and baseline value as covariates, and participant as a random effect. ITT=all randomized participants, excluding site terminated due to GCP issues. Treatment was based on treatment to which participants were randomized, regardless of which treatment they received. Overall number of participants analyzed=participants with both baseline and Week 32 SGRQ total scores available.

End point type	Secondary

End point timeframe:

Baseline, Week 32

End point values	Placebo	Reslizumab 110 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	222		
Units: units on a scale				
least squares mean (standard error)	-13.1 (± 1.38)	-16.4 (± 1.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier (K-M) Estimate of Probability (Percent [%]) of Not Experiencing a CAE by Week 52

End point title	Kaplan-Meier (K-M) Estimate of Probability (Percent [%]) of Not Experiencing a CAE by Week 52

End point description:

CAE defined as deterioration in asthma control, as determined by investigator and new or worsening asthma symptoms based on history, asthma control diary, physical examination, and/or ambulatory/clinic visit assessment of lung function and that resulted in a medical intervention, including 1 of the following: use of systemic corticosteroids or at least a doubling from a stable maintenance oral corticosteroid dose for at least 3 days; asthma-specific hospital admission; asthma-specific ER visit. KM method used to estimate/compare the distributions of time to first CAE between groups. Participants without event during treatment period were censored at either the date of the end of treatment visit for participants who completed treatment or at date of last dose for participants who discontinued. ITT=all randomized participants, excluding site terminated due to GCP issues. Treatment based on treatment to which participants were randomized regardless of which treatment they received.

End point type	Secondary

End point timeframe:

Day 1 to Week 52

End point values	Placebo	Reslizumab 110 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	234		
Units: percent probability				
number (confidence interval 95%)	0.66 (0.59 to 0.72)	0.66 (0.59 to 0.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of CAEs Requiring Hospitalization and/or Emergency Department Visits During 52 weeks of Treatment

End point title	Frequency of CAEs Requiring Hospitalization and/or Emergency Department Visits During 52 weeks of Treatment

End point description:

CAE defined as deterioration in asthma control, as determined by investigator and new or worsening asthma symptoms based on history, asthma control diary, physical examination, and/or ambulatory/clinic visit assessment of lung function and that resulted in a medical intervention, including 1 of the following: use of systemic corticosteroids or at least a doubling from a stable maintenance oral corticosteroid dose for at least 3 days; asthma-specific hospital admission; asthma-specific ER visit.

Frequency of CAEs over treatment period expressed as adjusted CAEs rate in 52 weeks. Adjusted CAE rate and CIs based on Negative Binomial regression model adjusted for stratification factors (age group, blood eosinophil group) and number of prior exacerbations, and an offset variable. ITT=all randomized participants, excluding site terminated due to GCP issues. Treatment based on treatment to which participants were randomized regardless of which treatment they received.

End point type	Secondary

End point timeframe:

Day 1 to Week 52

End point values	Placebo	Reslizumab 110 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	234		
Units: CAEs in 52 weeks				
number (confidence interval 95%)	0.05 (0.016 to 0.169)	0.05 (0.015 to 0.158)		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Moderate Exacerbations During 52 Weeks of Treatment

End point title	Frequency of Moderate Exacerbations During 52 Weeks of Treatment

End point description:

Moderate exacerbation defined as deterioration in asthma control determined by investigator and new/worsening symptoms based on history, asthma diary, physical exam, and/or ambulatory or clinic visit assessment of lung function and that resulted in a medical intervention requiring additional asthma controller medication that was not a systemic corticosteroid and did not result in an asthma-specific hospitalization or ER visit (that is, a medical intervention that did not meet criteria for primary endpoint). Frequency of moderate exacerbations over treatment period expressed as adjusted exacerbation rate in 52 weeks. Adjusted exacerbation rate and CIs based on Negative Binomial regression model adjusted for stratification factors (age group, eosinophil group) and number of prior exacerbations, and offset variable. ITT=all randomized participants, excluding site terminated due to GCP issues. Treatment based on treatment participants were randomized to, regardless of what was received.

End point type	Secondary

End point timeframe:

Day 1 to Week 52

End point values	Placebo	Reslizumab 110 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	234		
Units: Number of moderate exacerbations				
number (confidence interval 95%)	0.15 (0.082 to 0.290)	0.14 (0.074 to 0.250)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug to the end of treatment visit (Week 52) for completed participants and between the first dose of study drug and 4 weeks after the last dose of study drug for participants who discontinued treatment early.

Adverse event reporting additional description:

1 participant randomized to the placebo group was treated with reslizumab 110 mg at 1 study visit and counted in the reslizumab 110 mg arm for safety.There were no deaths during the treatment period. 1 death in the reslizumab group occurred 48 days after the participant's last dose.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Reslizumab 110 mg

Reporting group description:

Reslizumab 110 milligrams (mg) administered subcutaneously once every 4 weeks (+/-7 days) for a total of 13 doses.

Reporting group title	Placebo

Reporting group description:

Matching placebo administered subcutaneously once every 4 weeks (+/-7 days) for a total of 13 doses.

Serious adverse events	Reslizumab 110 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 237 (8.02%)	19 / 231 (8.23%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign tracheal neoplasm	Additional description: The events of Bronchial neoplasm benign and Benign tracheal neoplasm were reported for the same participant.		
subjects affected / exposed	1 / 237 (0.42%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial neoplasm benign	Additional description: The events of Bronchial neoplasm benign and Benign tracheal neoplasm were reported for the same participant.		
subjects affected / exposed	1 / 237 (0.42%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			

subjects affected / exposed	1 / 237 (0.42%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 237 (0.42%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 237 (0.42%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Lumbar radiculopathy			
subjects affected / exposed	1 / 237 (0.42%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 237 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 237 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reaction to food colouring			
subjects affected / exposed	0 / 237 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			

subjects affected / exposed	0 / 237 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 237 (0.42%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 237 (0.42%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary cirrhosis primary			
subjects affected / exposed	1 / 237 (0.42%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 237 (0.00%)	4 / 231 (1.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 237 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	4 / 237 (1.69%)	5 / 231 (2.16%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 237 (0.42%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eosinophilic pneumonia			
subjects affected / exposed	0 / 237 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	1 / 237 (0.42%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 237 (0.42%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis noninfective			
subjects affected / exposed	0 / 237 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 237 (0.00%)	1 / 231 (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			
Rhabdomyolysis			
subjects affected / exposed	1 / 237 (0.42%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 237 (0.42%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			

subjects affected / exposed	1 / 237 (0.42%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	1 / 237 (0.42%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	1 / 237 (0.42%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 237 (0.84%)	4 / 231 (1.73%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 237 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 237 (0.42%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 237 (0.00%)	1 / 231 (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	Reslizumab 110 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	102 / 237 (43.04%)	97 / 231 (41.99%)	
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 237 (5.91%)	10 / 231 (4.33%)	
occurrences (all)	28	19	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	13 / 237 (5.49%)	7 / 231 (3.03%)	
occurrences (all)	35	13	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	9 / 237 (3.80%)	18 / 231 (7.79%)	
occurrences (all)	15	25	
Rhinitis allergic			
subjects affected / exposed	16 / 237 (6.75%)	12 / 231 (5.19%)	
occurrences (all)	16	12	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	14 / 237 (5.91%)	15 / 231 (6.49%)	
occurrences (all)	16	19	
Bronchitis			
subjects affected / exposed	13 / 237 (5.49%)	17 / 231 (7.36%)	
occurrences (all)	14	23	
Upper respiratory tract infection			
subjects affected / exposed	28 / 237 (11.81%)	19 / 231 (8.23%)	
occurrences (all)	37	26	
Viral upper respiratory tract infection			
subjects affected / exposed	27 / 237 (11.39%)	31 / 231 (13.42%)	
occurrences (all)	45	42	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2015	Amendment 1 (04 May 2015) was issued before any participants were enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: 1) The total blood volume was corrected. 2) The AQLQ questionnaire was replaced by the AQLQ+12 Questionnaire.
25 January 2016	Amendment 2 (25 January 2016) to the protocol was issued after 24 participants were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of the participants already enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: 1) Methods of recording adverse events on the CRF were clarified. 2) SABA therapy was changed to asthma rescue medication. 3) Procedures on discontinuation of study treatment were clarified. 4) The inclusion criteria were amended to encompass a medium and higher daily dose range of ICS per GINA 2015.
25 July 2016	Amendment 3 (25 July 2016) to the protocol was issued after 368 participants were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of the participants already enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: 1) The total enrollment of the study was increased in order to ensure adequate adolescent enrollment. 2) CPK assessments were added based on a request by Health Authorities. 3) Opportunistic infections were added to the list of protocol-defined adverse events for expedited reporting to Teva; an appendix on opportunistic infections was added.
24 October 2016	Amendment 4 (24 October 2016) to the protocol was issued after 468 participants were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of the participants already enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: 1) The follow-up visit was changed from 8 to 12 weeks after the EOT as requested by the European Medicines Agency. 2) Adolescents were required to complete the early follow-up visit before starting an open-label extension study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported