Clinical trial results:
An Open-Label Extension Study to evaluate the Long-Term Safety and Efficacy of Reslizumab (3.0 mg/kg) as Treatment for Patients with Eosinophilic Asthma who completed a priorTeva-Sponsored Study in Eosinophilic Asthma

Summary

EudraCT number	2010-024540-15
Trial protocol	BE DE SE CZ GR HU NL DK PL SK
Global end of trial date	16 January 2015

Results information

Result version number	v2 (current)
This version publication date	19 April 2019
First version publication date	09 July 2016
Version creation reason	• Correction of full data set To correct typo of country code Switzerland (CH) with Chile (CL) and correct the Philippines and Thailand patient counts (Philippines has 25 patients and Thailand 10 due to patient transfer).

Trial information

Trial identification

Sponsor protocol code	C38072/3085

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01290887
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	04 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 January 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the long-term safety of reslizumab at a dosage of 3.0 mg/kg every 4 weeks for approximately 24 months in pediatric and adult patients with eosinophilic asthma as assessed by adverse events, physical examination findings, vital sign measurements, and concomitant medication usage throughout the study (every 4 weeks), clinical laboratory test results, and measurement of antidrug antibodies.

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 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 of 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. Written informed consent was obtained from each patient before any study procedures or assessments were done. It was 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.
For patients aged 12 to 17 years, a signed and dated informed consent form was obtained from a parent/guardian and a signed and dated assent form was obtained from each patient before any study-specific procedures or assessments were done and after the aims, methods, anticipated benefits, and potential hazards were explained, according to local IRB/IEC requirements.
Each patient’s willingness to participate in the study was documented in writing in a consent/assent form that was signed by the patient and, in the case of patients aged 12 to 17 years, also signed by a parent/guardian, with the date of each signature indicated. Each investigator kept the original consent/assent forms, and copies were given to the patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 February 2012
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	Argentina: 52
Country: Number of subjects enrolled	Australia: 23
Country: Number of subjects enrolled	Brazil: 37
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Israel: 57
Country: Number of subjects enrolled	Korea, Republic of: 21
Country: Number of subjects enrolled	Mexico: 36
Country: Number of subjects enrolled	New Zealand: 16
Country: Number of subjects enrolled	Peru: 55
Country: Number of subjects enrolled	Philippines: 25
Country: Number of subjects enrolled	Russian Federation: 69
Country: Number of subjects enrolled	Thailand: 10
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Ukraine: 92
Country: Number of subjects enrolled	United States: 160
Country: Number of subjects enrolled	South Africa: 35
Country: Number of subjects enrolled	Colombia: 17
Country: Number of subjects enrolled	Malaysia: 17
Country: Number of subjects enrolled	Poland: 59
Country: Number of subjects enrolled	Romania: 16
Country: Number of subjects enrolled	Slovakia: 27
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	Belgium: 37
Country: Number of subjects enrolled	Czech Republic: 35
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 49
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Hungary: 46
Country: Number of subjects enrolled	Chile: 14
Worldwide total number of subjects	1052
EEA total number of subjects	298

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)	28
Adults (18-64 years)	921
From 65 to 84 years	103
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 1052 patients with eosinophilic asthma at 201 centers in 30 countries were enrolled in this study.

Pre-assignment

Screening details:

Four hundred-eighty (46%) patients received reslizumab for the first time in Study 3085, having previously received placebo in Studies 3081, 3082, or 3083.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Reslizumab 3.0 mg/kg

Arm description:

Reslizumab 3.0 mg/kg administered intravenously once every 4 weeks (+-7 days) for up to 24 months.

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:

Reslizumab (3.0 mg/kg) administered intravenously by infusion every 28 days (±7 days), for approximately 24 months

Number of subjects in period 1	Reslizumab 3.0 mg/kg
Started	1052
Safety Analysis Set	1051
Completed	50
Not completed	1002
Adverse event, serious fatal	3
Non-compliance to study medication	1
Consent withdrawn by subject	58
Non-compliance to study procedures	1
Adverse event, non-fatal	14
Sponsor closure of the study	896
Not specified	9
Lost to follow-up	8

Lack of efficacy	9
Protocol deviation	3

Baseline characteristics

Reporting groups	
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 up to 24 months.	

Reporting group values	Reslizumab 3.0 mg/kg	Total	
Number of subjects	1052	1052	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	47.2		
standard deviation	± 14.02	-	
Gender categorical Units: Subjects			
Female	646	646	
Male	406	406	
Race Units: Subjects			
White	808	808	
Black	44	44	
Asian	87	87	
American Indian or Alaskan Native	10	10	
Pacific Islander	2	2	
Other	101	101	
Ethnicity Units: Subjects			
Hispanic or Latino	201	201	
Non-Hispanic or Latino	365	365	
Non-Hispanic and non-Latino	480	480	
Unknown	6	6	
Used Beta Agonist in Past 3 Days			
Usage of inhaled corticosteroids/long-acting beta-agonists and usage of oral corticosteroids. n=1051, 480, 571			
Units: Subjects			
Yes	597	597	

No	454	454	
Not recorded	1	1	

Weight			
n=1021, 466, 555			
Units: kg			
arithmetic mean	76		
standard deviation	± 17.32	-	
Height			
n=1018, 463, 555			
Units: cm			
arithmetic mean	165.7		
standard deviation	± 9.99	-	
Body Mass Index			
n=1018, 463, 555			
Units: kg/m^2			
arithmetic mean	27.7		
standard deviation	± 5.77	-	
Forced Expiratory Volume in 1 Second (FEV1)			
Units: liters			
arithmetic mean	2.199		
standard deviation	± 0.8108	-	
% Predicted Expiratory Volume In 1 Second			
Units: percentage of predicted FEV1			
arithmetic mean	73.115		
standard deviation	± 19.9664	-	
Forced Vital Capacity (FVC)			
Units: liters			
arithmetic mean	3.273		
standard deviation	± 1.0632	-	
Forced Expiratory Flow at 25% to 75% Forced Vital Capacity (FEF 25%-75%)			
n=1046, 478, 568			
Units: liters/second			
arithmetic mean	1.558		
standard deviation	± 0.9009	-	
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 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. n=1051, 480, 571			
Units: units on a scale			
arithmetic mean	1.624		
standard deviation	± 1.0527	-	
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. n=1045, 476, 569			

Units: units on a scale			
arithmetic mean	5.347		
standard deviation	± 1.1875	-	
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. n=377, 186, 191			
Units: units on a scale			
arithmetic mean	0.832		
standard deviation	± 0.1728	-	
Blood Eosinophil Count			
Units: 10^9/liter			
arithmetic mean	0.284		
standard deviation	± 0.3577	-	
Daily average number of puffs in past 3 days			
n=1029, 475, 554			
Units: puffs			
arithmetic mean	1.827		
standard deviation	± 2.4604	-	

Subject analysis sets

Subject analysis set title	Previous Placebo-Treated Subpopulation
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The subpopulation of participants who were treated with placebo in the previous double-blind studies. These participants were treated with resllizumab 3.0 mg/kg intravenously once every 4 weeks (+-7 days) for up to 24 months in this study.

Subject analysis set title	Previous Reslizumab-Treated Subpopulation
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The subpopulation of participants who were treated with reslizumab at a variety of dosages in the previous double-blind studies. These participants were treated with resllizumab 3.0 mg/kg intravenously once every 4 weeks (+-7 days) for up to 24 months in this study.

Reporting group values	Previous Placebo-Treated Subpopulation	Previous Reslizumab-Treated Subpopulation	
Number of subjects	481	571	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			

Age continuous Units: years			
arithmetic mean	47.4	47.1	
standard deviation	± 14.53	± 13.58	
Gender categorical Units: Subjects			
Female	314	332	
Male	167	239	
Race Units: Subjects			
White	371	437	
Black	22	22	
Asian	39	48	
American Indian or Alaskan Native	4	6	
Pacific Islander	1	1	
Other	44	57	
Ethnicity Units: Subjects			
Hispanic or Latino	83	118	
Non-Hispanic or Latino	187	178	
Non-Hispanic and non-Latino	208	272	
Unknown	3	3	
Used Beta Agonist in Past 3 Days			
Usage of inhaled corticosteroids/long-acting beta-agonists and usage of oral corticosteroids. n=1051, 480, 571			
Units: Subjects			
Yes	300	297	
No	180	274	
Not recorded	1	1	
Weight			
n=1021, 466, 555			
Units: kg			
arithmetic mean	75.4	76.5	
standard deviation	± 16.67	± 17.85	
Height			
n=1018, 463, 555			
Units: cm			
arithmetic mean	165.3	166	
standard deviation	± 10.03	± 9.96	
Body Mass Index			
n=1018, 463, 555			
Units: kg/m^2			
arithmetic mean	27.6	27.7	
standard deviation	± 5.42	± 6.04	
Forced Expiratory Volume in 1 Second (FEV1) Units: liters			
arithmetic mean	2.096	2.285	
standard deviation	± 0.7856	± 0.8222	
% Predicted Expiratory Volume In 1 Second Units: percentage of predicted FEV1			

arithmetic mean	70.739	75.116	
standard deviation	± 19.756	± 19.9404	
Forced Vital Capacity (FVC)			
Units: liters			
arithmetic mean	3.163	3.366	
standard deviation	± 1.0357	± 1.0779	
Forced Expiratory Flow at 25% to 75% Forced Vital Capacity (FEF 25%-75%)			
n=1046, 478, 568			
Units: liters/second			
arithmetic mean	1.467	1.634	
standard deviation	± 0.889	± 0.9045	
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 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. n=1051, 480, 571			
Units: units on a scale			
arithmetic mean	1.832	1.45	
standard deviation	± 1.0912	± 0.987	
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. n=1045, 476, 569			
Units: units on a scale			
arithmetic mean	5.17	5.496	
standard deviation	± 1.216	± 1.1431	
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. n=377, 186, 191			
Units: units on a scale			
arithmetic mean	0.803	0.861	
standard deviation	± 0.191	± 0.1479	
Blood Eosinophil Count			
Units: 10^9/liter			
arithmetic mean	0.528	0.078	
standard deviation	± 0.3792	± 0.148	
Daily average number of puffs in past 3 days			
n=1029, 475, 554			
Units: puffs			
arithmetic mean	2.13	1.568	
standard deviation	± 2.4996	± 2.3982	

End points

End points reporting groups

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 up to 24 months.	
Subject analysis set title	Previous Placebo-Treated Subpopulation
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The subpopulation of participants who were treated with placebo in the previous double-blind studies. These participants were treated with resllizumab 3.0 mg/kg intravenously once every 4 weeks (+-7 days) for up to 24 months in this study.	
Subject analysis set title	Previous Reslizumab-Treated Subpopulation
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The subpopulation of participants who were treated with reslizumab at a variety of dosages in the previous double-blind studies. These participants were treated with resllizumab 3.0 mg/kg intravenously once every 4 weeks (+-7 days) for up to 24 months in this study.	

Primary: Participants With Treatment-Emergent Adverse Events

End point title	Participants With Treatment-Emergent Adverse Events[1]
End point description:	
An adverse event 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	Primary
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.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Single treatment arm study. No analysis was planned to compare the subpopulations.

End point values	Reslizumab 3.0 mg/kg	Previous Placebo-Treated Subpopulation	Previous Reslizumab-Treated Subpopulation	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1051[2]	480[3]	571[4]	
Units: participants				
At least 1 AE	744	359	385	
Severe AE	78	31	47	
Treatment-related AE	90	49	41	
AE causing patient discontinuation	18	6	12	
Serious AE	78	33	45	
Death	3	1	2	
AE up to follow-up period	711	344	367	
AE during follow-up period	160	78	82	

Notes:

[2] - Safety analysis set

[3] - Safety analysis set

[4] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Primary: 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[5]

End point description:

Participants with potentially clinically significant (PCS) abnormal serum chemistry, hematology, and urinalysis values on any of the during treatment lab analyses.
Significance criteria:

- Blood urea nitrogen: >=10.71 mmol/L
- Creatinine: >=177 µmol/L
- Uric acid: M>=625, F>=506 µmol/L
- Aspartate aminotransferase: >=3*upper limit of normal (ULN). Normal range is 10-43 U/L
- Alanine aminotransferase: >=3*ULN. Normal range is 10-40 U/L
- GGT = gamma-glutamyl transpeptidase: >= 3*upper limit of normal. Normal range is 5-49 U/L.
- Total bilirubin: >=34.2 µmol/L
- White blood cells- low: <=3.0*10^9/L
- White blood cells-high: >=20*10^9/L
- Hemoglobin: M<=115, F<=95 g/dL
- Hematocrit: M<0.37, F<0.32 L/L
- Platelets: >=700*10^9/L
- Absolute neutrophil count: <=1.0*10^9/L
- Eosinophils: >=10
- Urinalysis: ketones, blood, glucose, and total protein: >=2 unit increase from baseline

End point type	Primary

End point timeframe:

Weeks 4, 8, 24 and 48

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Single treatment arm study. No analysis was planned to compare the subpopulations.

End point values	Reslizumab 3.0 mg/kg	Previous Placebo-Treated Subpopulation	Previous Reslizumab-Treated Subpopulation	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1044[6]	477[7]	567[8]	
Units: participants				
Blood urea nitrogen	23	13	10	
Creatinine	5	3	2	
Uric acid	13	8	5	
Aspartate aminotransferase	11	6	5	
Alanine aminotransferase	14	7	7	
GGT	39	24	15	
Total bilirubin	6	3	3	
White blood cells- low	18	10	8	
White blood cells- high	3	2	1	

Hemoglobin	19	10	9	
Hematocrit	26	13	13	
Platelets	2	1	1	
Absolute neutrophil count	14	7	7	
Eosinophils	51	24	27	
Ketones in urine	24	15	9	
Blood (hemoglobin) in urine	107	52	55	
Glucose in urine	54	22	32	
Total protein in urine	156	71	85	

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Primary: 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[9]

End point description:

Significance criteria

- Sitting heart rate-high: >100 and increase of >= 30 beats/min (all ages)
- Sitting heart rate-low: <50 and decrease of >=30 beats/min
- Systolic blood pressure (BP)-high: >130 and increase of >=30 mmHg (ages 12-17)
- Systolic BP-low: <90 and decrease of >=30 mmHg (ages >=18)
- Systolic BP-high: >160 and increase of >=30 mmHg (ages >=18)
- Diastolic BP-low: <55 and decrease of >=12 mmHg (ages 12-17)
- Diastolic BP-high: >85 and increase of >=12 mmHg (ages 12-17)
- Diastolic BP-low: <50 and decrease of >=12 mmHg (ages >=18)
- Diastolic BP-high: >100 and increase of >=12 mmHg (ages >=18)
- Respiration rate: >20 and increase of >=10 breaths/minute (ages 12-17)
- Respiration rate: >24 and increase of >=10 breaths/minute (ages >=18)
- Body temperature-low: <96.5° Fahrenheit (all ages)
- Body temp-high: >100.5° F (all ages)

End point type	Primary

End point timeframe:

Week 4 to Week 65 (treatment and follow-up visits)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Single treatment arm study. No analysis was planned to compare the subpopulations.

End point values	Reslizumab 3.0 mg/kg	Previous Placebo-Treated Subpopulation	Previous Reslizumab-Treated Subpopulation	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1047[10]	478[11]	571[12]	
Units: participants				
Heart rate - high (ages 12-17)	3	1	2	
Heart rate - low (ages >=18)	3	2	1	
Heart rate - high (ages >=18)	16	8	8	
Systolic BP - high (ages 12-17)	1	0	1	

Systolic BP - low (ages >=18)	1	1	0	
Systolic BP - high (ages >=18)	16	8	8	
Diastolic BP - low (ages 12-17)	2	1	1	
Diastolic BP - high (ages 12-17)	3	2	1	
Diastolic BP - low (ages >=18)	6	2	4	
Diastolic - high (ages >=18)	25	13	12	
Respiration rate - high (ages 12-17)	1	0	1	
Respiration rate - high (ages >=18)	8	6	2	
Body temperature - low (ages 12-17)	6	3	3	
Body temperature - high (ages 12-17)	1	0	1	
Body temperature - low (ages >=18)	223	102	121	
Body temperature - high (ages >=18)	4	3	1	

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Forced Expiratory Volume In 1 Second (FEV1) at Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, End of Study and Endpoint

End point title	Forced Expiratory Volume In 1 Second (FEV1) at Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, End of Study and Endpoint

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.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, end of study and endpoint

End point values	Reslizumab 3.0 mg/kg	Previous Placebo-Treated Subpopulation	Previous Reslizumab-Treated Subpopulation	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1051[13]	480[14]	571[15]	
Units: liters				
arithmetic mean (standard deviation)				
Week 4 (n=1009, 457, 552)	2.222 (± 0.7857)	2.155 (± 0.7636)	2.277 (± 0.7999)	
Week 8 (n=955, 437, 518)	2.22 (± 0.8096)	2.162 (± 0.7966)	2.27 (± 0.8179)	
Week 12 (n=925, 426, 499)	2.223 (± 0.7932)	2.171 (± 0.769)	2.267 (± 0.8114)	
Week 16 (n=906, 418, 488)	2.222 (± 0.7957)	2.169 (± 0.7761)	2.267 (± 0.8101)	
Week 24 (n=844, 386, 458)	2.243 (± 0.8013)	2.188 (± 0.7966)	2.289 (± 0.8032)	

Week 36 (n=645, 291, 354)	2.258 (± 0.8178)	2.234 (± 0.824)	2.278 (± 0.8133)	
Week 48 (n=448, 198, 250)	2.261 (± 0.8099)	2.167 (± 0.7905)	2.336 (± 0.8189)	
Week 60 (n=244, 101, 143)	2.308 (± 0.8689)	2.234 (± 0.9214)	2.36 (± 0.8292)	
Week 72 (n=161, 56, 105)	2.387 (± 0.8466)	2.424 (± 0.9093)	2.367 (± 0.815)	
Week 84 (n=133, 45, 88)	2.422 (± 0.8425)	2.496 (± 0.8496)	2.384 (± 0.8411)	
Week 96 (n=69, 23, 46)	2.505 (± 0.8283)	2.748 (± 0.8963)	2.383 (± 0.7737)	
End of study (n=82, 28, 54)	2.329 (± 0.8997)	2.505 (± 0.9386)	2.237 (± 0.8736)	
Endpoint (n=1047, 478, 569)	2.228 (± 0.7989)	2.174 (± 0.7798)	2.273 (± 0.8127)	

Notes:

[13] - Safety analysis set of participants with assessments at stated timeframes

[14] - Safety analysis set of participants with assessments at stated timeframes

[15] - Safety analysis set of participants with assessments at stated timeframes

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Predicted Forced Expiratory Volume In 1 Second (% Predicted FEV1) at Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, End of Study and Endpoint

End point title	Percent Predicted Forced Expiratory Volume In 1 Second (% Predicted FEV1) at Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, End of Study and Endpoint

End point description:

The percent predicted FEV1 is the ratio of the volume of air expired in the first second of a forced expiration to the patient's predicted FEV based on a similar population without asthma. Percent predicted lung function values were transcribed directly from the lung function report to the CRF, without any calculation by Teva.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, end of study and endpoint

End point values	Reslizumab 3.0 mg/kg	Previous Placebo-Treated Subpopulation	Previous Reslizumab-Treated Subpopulation	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1051[16]	480[17]	571[18]	
Units: percentage of predicted FEV1				
arithmetic mean (standard deviation)				
Week 4 (n=1009, 457, 552)	74.123 (± 19.4521)	73.295 (± 19.7933)	74.808 (± 19.156)	
Week 8 (n=955, 437, 518)	73.983 (± 20.1949)	73.056 (± 19.9848)	74.765 (± 20.357)	
Week 12 (n=925, 426, 499)	74.279 (± 19.6002)	73.797 (± 19.2586)	74.69 (± 19.8973)	
Week 16 (n=906, 418, 488)	74.266 (± 19.9188)	73.797 (± 19.5962)	74.668 (± 20.2025)	

Week 24 (n=844, 386, 458)	74.785 (± 19.7729)	74.284 (± 19.5601)	75.208 (± 19.9621)	
Week 36 (n=645, 291, 354)	75.179 (± 20.493)	74.805 (± 20.5634)	75.487 (± 20.4589)	
Week 48 (n=448, 198, 250)	75.313 (± 19.95)	73.654 (± 19.9535)	76.627 (± 19.889)	
Week 60 (n=244, 101, 143)	75.743 (± 21.195)	74.511 (± 22.5211)	76.613 (± 20.2416)	
Week 72 (n=161, 56, 105)	76.827 (± 18.2256)	76.856 (± 20.1821)	76.812 (± 17.1937)	
Week 84 (n=133, 45, 88)	78.308 (± 18.4011)	79.017 (± 18.5149)	77.945 (± 18.4383)	
Week 96 (n=69, 23, 46)	78.912 (± 15.9949)	83.245 (± 14.9074)	76.746 (± 16.2345)	
End of study (n=82, 28, 54)	73.719 (± 20.0902)	79.672 (± 18.6997)	70.633 (± 20.2554)	
Endpoint (n=1047, 478, 569)	74.69 (± 19.8307)	74.195 (± 19.8134)	75.107 (± 19.853)	

Notes:

[16] - Safety analysis set of participants with assessments at stated timeframes

[17] - Safety analysis set of participants with assessments at stated timeframes

[18] - Safety analysis set of participants with assessments at stated timeframes

Statistical analyses

No statistical analyses for this end point

Secondary: Forced Vital Capacity (FVC) at Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, End of Study and Endpoint

End point title	Forced Vital Capacity (FVC) at Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, End of Study and Endpoint

End point description:

The FVC is the volume of air that can be forcibly blown out after full inspiration, measured in liters.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, end of study and endpoint

End point values	Reslizumab 3.0 mg/kg	Previous Placebo-Treated Subpopulation	Previous Reslizumab-Treated Subpopulation	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1051[19]	480[20]	571[21]	
Units: liters				
arithmetic mean (standard deviation)				
Week 4 (n=1009, 457, 552)	3.304 (± 1.0334)	3.222 (± 0.9929)	3.372 (± 1.0619)	
Week 8 (n=955, 437, 518)	3.297 (± 1.0577)	3.226 (± 1.0228)	3.358 (± 1.0836)	
Week 12 (n=925, 426, 499)	3.292 (± 1.0232)	3.238 (± 0.9788)	3.339 (± 1.0584)	
Week 16 (n=906, 418, 488)	3.298 (± 1.0444)	3.238 (± 0.9949)	3.349 (± 1.0835)	
Week 24 (n=844, 386, 458)	3.307 (± 1.0449)	3.233 (± 1.0095)	3.369 (± 1.0709)	

Week 36 (n=644, 291, 353)	3.336 (± 1.0479)	3.324 (± 1.0571)	3.346 (± 1.0416)	
Week 48 (n=448, 198, 250)	3.332 (± 1.0371)	3.229 (± 1.0334)	3.414 (± 1.0348)	
Week 60 (n=244, 101, 143)	3.381 (± 1.1037)	3.323 (± 1.1874)	3.422 (± 1.0428)	
Week 72 (n=161, 56, 105)	3.434 (± 1.1143)	3.5 (± 1.1839)	3.398 (± 1.0795)	
Week 84 (n=133, 45, 88)	3.474 (± 1.1487)	3.606 (± 1.1403)	3.406 (± 1.1535)	
Week 96 (n=69, 23, 46)	3.537 (± 1.168)	3.849 (± 1.2342)	3.381 (± 1.1145)	
End of study (n=82, 28, 54)	3.39 (± 1.2206)	3.524 (± 1.1842)	3.321 (± 1.2443)	
Endpoint (n=1047, 478, 569)	3.307 (± 1.0466)	3.25 (± 1.0194)	3.355 (± 1.0675)	

Notes:

[19] - Safety analysis set of participants with assessments at stated timeframes

[20] - Safety analysis set of participants with assessments at stated timeframes

[21] - Safety analysis set of participants with assessments at stated timeframes

Statistical analyses

No statistical analyses for this end point

Secondary: Forced Expiratory Flow at 25% to 75% Forced Vital Capacity (FEF 25%-75%) at Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, End of Study and Endpoint

End point title	Forced Expiratory Flow at 25% to 75% Forced Vital Capacity (FEF 25%-75%) at Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, End of Study and Endpoint

End point description:

The FEF 25%-75% is the force expiratory flow at 25% to 75% of the Forced Vital Capacity (FVC), measured in liters/second.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, end of study and endpoint

End point values	Reslizumab 3.0 mg/kg	Previous Placebo-Treated Subpopulation	Previous Reslizumab-Treated Subpopulation	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1051[22]	480[23]	571[24]	
Units: liters/second				
arithmetic mean (standard deviation)				
Week 4 (n=991, 446, 545)	1.589 (± 0.9195)	1.558 (± 0.9363)	1.614 (± 0.9055)	
Week 8 (n=942, 429, 513)	1.585 (± 0.9268)	1.546 (± 0.9279)	1.618 (± 0.9255)	
Week 12 (n=912, 418, 494)	1.607 (± 0.958)	1.587 (± 0.9833)	1.624 (± 0.9367)	
Week 16 (n=891, 408, 483)	1.593 (± 0.9234)	1.561 (± 0.9427)	1.62 (± 0.9068)	
Week 24 (n=830, 377, 453)	1.629 (± 0.9565)	1.619 (± 0.9967)	1.637 (± 0.9227)	

Week 36 (n=634, 285, 349)	1.646 (± 1.008)	1.642 (± 1.1087)	1.65 (± 0.9193)	
Week 48 (n=440, 191, 249)	1.664 (± 0.9871)	1.628 (± 1.0408)	1.691 (± 0.945)	
Week 60 (n=242, 99, 143)	1.715 (± 1.1265)	1.605 (± 1.0869)	1.791 (± 1.1508)	
Week 72 (n=161, 56, 105)	1.781 (± 1.0276)	1.81 (± 1.0239)	1.766 (± 1.0341)	
Week 84 (n=133, 45, 88)	1.877 (± 1.07)	1.848 (± 0.9047)	1.892 (± 1.1499)	
Week 96 (n=69, 23, 46)	2.001 (± 1.0457)	2.12 (± 1.0597)	1.942 (± 1.0453)	
End of study (n=82, 28, 54)	1.741 (± 0.9854)	1.939 (± 1.1105)	1.639 (± 0.9079)	
Endpoint (n=1031, 468, 563)	1.592 (± 0.9188)	1.546 (± 0.9041)	1.629 (± 0.93)	

Notes:

[22] - Safety analysis set of participants with assessments at stated timeframes

[23] - Safety analysis set of participants with assessments at stated timeframes

[24] - Safety analysis set of participants with assessments at stated timeframes

Statistical analyses

No statistical analyses for this end point

Secondary: Average Daily Use of Short-Acting Beta-Agonist (SABA)Therapy at Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, End of Study and Endpoint

End point title	Average Daily Use of Short-Acting Beta-Agonist (SABA)Therapy at Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, End of Study and Endpoint

End point description:

SABA are used for quick relief of asthma symptoms. To measure SABA use, at each clinical visit participants 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.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, end of study and endpoint

End point values	Reslizumab 3.0 mg/kg	Previous Placebo-Treated Subpopulation	Previous Reslizumab-Treated Subpopulation	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1051[25]	480[26]	571[27]	
Units: # puffs/day				
arithmetic mean (standard deviation)				
Week 4 (n=599, 276, 323)	2.5 (± 2.43)	2.5 (± 2.42)	2.4 (± 2.45)	
Week 8 (n=560, 258, 302)	2.4 (± 2.46)	2.4 (± 2.28)	2.4 (± 2.62)	
Week 12 (n=529, 251, 278)	2.5 (± 2.3)	2.6 (± 2.07)	2.4 (± 2.5)	
Week 16 (n=505, 244, 261)	2.4 (± 2.3)	2.5 (± 2.3)	2.2 (± 2.29)	
Week 24 (n=454, 211, 243)	2.4 (± 2.51)	2.6 (± 2.55)	2.3 (± 2.46)	
Week 36 (n=334, 160, 174)	2.3 (± 2.47)	2.4 (± 2.27)	2.3 (± 2.64)	
Week 48 (n=232, 111, 121)	2.3 (± 2.42)	2.2 (± 2.28)	2.4 (± 2.54)	

Week 60 (n=114, 50, 64)	2.3 (± 2.86)	2.1 (± 2.19)	2.5 (± 3.3)	
Week 72 (n=76, 29, 47)	1.9 (± 1.99)	2.1 (± 2.19)	1.8 (± 1.88)	
Week 84 (n=54, 19, 35)	2.2 (± 2.12)	2 (± 1.57)	2.4 (± 2.38)	
Week 96 (n=40, 14, 26)	1.8 (± 1.5)	1.8 (± 1.41)	1.7 (± 1.57)	
End of study (n=39, 16, 23)	2.4 (± 1.9)	2.1 (± 1.76)	2.7 (± 1.99)	
Endpoint (n=843, 390, 453)	2.2 (± 3.35)	2.2 (± 2.2)	2.2 (± 4.09)	

Notes:

[25] - Safety analysis set of participants with assessments at stated timeframes

[26] - Safety analysis set of participants with assessments at stated timeframes

[27] - Safety analysis set of participants with assessments at stated timeframes

Statistical analyses

No statistical analyses for this end point

Secondary: Asthma Symptom Utility Index (ASUI) Score at Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, End of Study and Endpoint

End point title	Asthma Symptom Utility Index (ASUI) Score at Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, End of Study and Endpoint

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.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, end of study and endpoint

End point values	Reslizumab 3.0 mg/kg	Previous Placebo-Treated Subpopulation	Previous Reslizumab-Treated Subpopulation	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1051[28]	480[29]	571[30]	
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=1008, 456, 552)	0.838 (± 0.1724)	0.831 (± 0.1829)	0.844 (± 0.1631)	
Week 8 (n=950, 436, 514)	0.847 (± 0.1626)	0.843 (± 0.1663)	0.851 (± 0.1596)	
Week 12 (n=926, 426, 500)	0.847 (± 0.1661)	0.839 (± 0.1752)	0.854 (± 0.1578)	
Week 16 (n=902, 416, 486)	0.851 (± 0.1673)	0.845 (± 0.169)	0.856 (± 0.1659)	
Week 24 (n=844, 386, 458)	0.852 (± 0.1658)	0.844 (± 0.172)	0.859 (± 0.1602)	
Week 36 (n=645, 291, 354)	0.857 (± 0.1673)	0.844 (± 0.1821)	0.867 (± 0.1536)	
Week 48 (n=449, 198, 251)	0.854 (± 0.1701)	0.851 (± 0.1699)	0.856 (± 0.1705)	
Week 60 (n=246, 100, 146)	0.866 (± 0.1534)	0.869 (± 0.1573)	0.865 (± 0.1513)	
Week 72 (n=161, 56, 105)	0.865 (± 0.1453)	0.876 (± 0.1346)	0.858 (± 0.1509)	

Week 84 (n=132, 45, 87)	0.873 (± 0.151)	0.884 (± 0.146)	0.868 (± 0.1541)	
Week 96 (n=69, 23, 46)	0.832 (± 0.1823)	0.822 (± 0.2036)	0.836 (± 0.1729)	
End of study (n=83, 28, 55)	0.853 (± 0.1767)	0.877 (± 0.0979)	0.84 (± 0.2053)	
Endpoint (n=1047, 478, 569)	0.847 (± 0.1669)	0.843 (± 0.1679)	0.85 (± 0.1661)	

Notes:

[28] - Safety analysis set of participants with assessments at stated timeframes

[29] - Safety analysis set of participants with assessments at stated timeframes

[30] - Safety analysis set of participants with assessments at stated timeframes

Statistical analyses

No statistical analyses for this end point

Secondary: Asthma Control Questionnaire (ACQ) at Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, End of Study and Endpoint

End point title	Asthma Control Questionnaire (ACQ) at Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, End of Study and Endpoint

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.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, end of study and endpoint

End point values	Reslizumab 3.0 mg/kg	Previous Placebo-Treated Subpopulation	Previous Reslizumab-Treated Subpopulation	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1051[31]	480[32]	571[33]	
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=1008, 456, 552)	1.482 (± 0.9852)	1.546 (± 1.0154)	1.429 (± 0.9573)	
Week 8 (n=954, 437, 517)	1.417 (± 0.9762)	1.446 (± 0.9805)	1.392 (± 0.9729)	
Week 12 (n=926, 426, 500)	1.405 (± 0.9648)	1.459 (± 1.0004)	1.36 (± 0.932)	
Week 16 (n=903, 416, 487)	1.369 (± 0.9655)	1.444 (± 1.0016)	1.305 (± 0.9299)	
Week 24 (n=844, 386, 458)	1.362 (± 0.9812)	1.436 (± 1.0135)	1.299 (± 0.9497)	
Week 36 (n=644, 291, 353)	1.347 (± 0.9746)	1.425 (± 1.0189)	1.282 (± 0.9331)	
Week 48 (n=448, 198, 250)	1.346 (± 0.9766)	1.408 (± 0.9699)	1.297 (± 0.981)	
Week 60 (n=243, 100, 143)	1.292 (± 0.954)	1.284 (± 0.9739)	1.297 (± 0.9432)	

Week 72 (n=161, 56, 105)	1.249 (± 0.8587)	1.283 (± 0.9176)	1.231 (± 0.8295)	
Week 84 (n=132, 45, 87)	1.186 (± 0.91)	1.143 (± 0.902)	1.209 (± 0.9186)	
Week 96 (n=69, 23, 46)	1.369 (± 0.9594)	1.323 (± 0.9862)	1.391 (± 0.9559)	
End of study (n=82, 28, 54)	1.308 (± 0.9216)	1.061 (± 0.7653)	1.437 (± 0.975)	
Endpoint (n=1047, 478, 569)	1.417 (± 0.9759)	1.45 (± 0.9901)	1.389 (± 0.9637)	

Notes:

[31] - Safety analysis set of participants with assessments at stated timeframes

[32] - Safety analysis set of participants with assessments at stated timeframes

[33] - Safety analysis set of participants with assessments at stated timeframes

Statistical analyses

No statistical analyses for this end point

Secondary: Asthma Quality of Life Questionnaire (AQLQ) Total Score at Weeks 24, 48, 72, 96, End of Study and Endpoint

End point title	Asthma Quality of Life Questionnaire (AQLQ) Total Score at Weeks 24, 48, 72, 96, End of Study and Endpoint

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.

End point type	Secondary

End point timeframe:

Weeks 24, 48, 72, 96, End of Study and Endpoint

End point values	Reslizumab 3.0 mg/kg	Previous Placebo-Treated Subpopulation	Previous Reslizumab-Treated Subpopulation	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1051[34]	480[35]	571[36]	
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 24 (n=834, 382, 452)	5.627 (± 1.1091)	5.551 (± 1.1558)	5.691 (± 1.0651)	
Week 48 (n=442, 193, 249)	5.672 (± 1.0982)	5.602 (± 1.118)	5.725 (± 1.0818)	
Week 72 (n=162, 56, 106)	5.809 (± 1.0124)	5.808 (± 1.0002)	5.809 (± 1.0235)	
Week 96 (n=69, 23, 46)	5.734 (± 1.1333)	5.585 (± 1.1422)	5.809 (± 1.134)	
End of study (n=83, 28, 55)	5.829 (± 1.1434)	5.956 (± 0.9431)	5.765 (± 1.2361)	
Endpoint (n=1030, 472, 558)	5.587 (± 1.1503)	5.535 (± 1.169)	5.631 (± 1.1334)	

Notes:

[34] - Safety analysis set of participants with assessments at stated timeframes

[35] - Safety analysis set of participants with assessments at stated timeframes

[36] - Safety analysis set of participants with assessments at stated timeframes

Statistical analyses

No statistical analyses for this end point

Secondary: Participants With a Positive Anti-Reslizumab Antibody Status at Baseline, Weeks 24, 48, 72, 96, End of Study, Endpoint and Overall

End point title	Participants With a Positive Anti-Reslizumab Antibody Status at Baseline, Weeks 24, 48, 72, 96, End of Study, Endpoint and Overall

End point description:

Blood samples were collected for the determination of anti-drug antibody (ADAs) before study drug infusion at baseline and every 24 weeks until end of treatment visit or early withdrawal. Serum samples were analyzed by Teva (Teva Biopharmaceuticals USA, Rockville, Maryland, USA) using a validated homogeneous solution based bridging enzyme linked immune sorbent assay (Mikulsis et al 2011, Qui et al 2010). The analysis of anti-reslizumab antibody in patient serum consists of 3 tiers of assays for screening, confirmation, and titer analysis. If a participant had a treatment-emergent ADA response (ie, ADA positive at any of the postdose time points but negative at the predose time point) or if there was a treatment-boosted ADA response (defined as a greater than 4-fold increase from a positive baseline ADA response (Shankar et at 2014), the participant was classified as overall ADA positive.
Predose samples for the reslizumab-experienced participants came from the previous studies.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 48, 72, 96, End of Study, Endpoint and Overall

End point values	Previous Placebo-Treated Subpopulation	Previous Reslizumab-Treated Subpopulation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	480[37]	571[38]		
Units: participants				
Overall (n=466, 548)	24	25		
Baseline (n=442, 541)	16	24		
Week 24 (n=382, 445)	12	13		
Week 48 (n=187, 247)	9	7		
Week 72 (n=56, 104)	4	4		
Week 96 (n=24, 48)	3	1		
End of study (n=142, 52)	4	1		
Endpoint (n=466, 545)	12	17		

Notes:

[37] - Safety analysis set of participants with assessments at stated timeframes

[38] - Safety analysis set of participants with assessments at stated timeframes

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 post-baseline 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	Reslizumab 3.0 mg/kg

Reporting group description:

Reslizumab 3.0 mg/kg administered intravenously once every 4 weeks (+-7 days) for up to 24 months.

Serious adverse events	Reslizumab 3.0 mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	78 / 1051 (7.42%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	3 / 1051 (0.29%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	2 / 1051 (0.19%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Ovarian epithelial cancer			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Metastases to lung				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma in situ				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphoma				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Borderline ovarian tumour				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anal cancer				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Vascular disorders				
Hypovolaemic shock				
subjects affected / exposed	2 / 1051 (0.19%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Shock haemorrhagic				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Suprapubic pain				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Adverse drug reaction				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hernia				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Endometrial hyperplasia				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Asthma				
subjects affected / exposed	18 / 1051 (1.71%)			
occurrences causally related to treatment / all	3 / 24			
deaths causally related to treatment / all	0 / 0			
Nasal polyps				
subjects affected / exposed	2 / 1051 (0.19%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pleural effusion				

subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasal septum deviation			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemothorax			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Asthmatic crisis			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	2 / 1051 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Aggression			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Investigations			
Liver function tests abnormal			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural			

complications				
Spinal compression fracture				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Skull fractured base				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hand fracture				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Contusion				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Myocardial infarction				
subjects affected / exposed	2 / 1051 (0.19%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Cardio-respiratory arrest			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Tachycardia			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular extrasystoles			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery occlusion			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Coronary artery stenosis			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Transient ischaemic attack				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorder				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Carpal tunnel syndrome				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Amaurosis fugax				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Pneumoperitoneum				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Megacolon				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 1051 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Pancreatitis			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 1051 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dermatitis atopic			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Actinic keratosis			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urethral stenosis			

subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Stress urinary incontinence			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 1051 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Otitis media acute			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Peritonitis			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mastoiditis			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infective exacerbation of bronchiectasis			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis pneumococcal			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infectious pleural effusion			

subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			
subjects affected / exposed	1 / 1051 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Reslizumab 3.0 mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	519 / 1051 (49.38%)		
Nervous system disorders			
Headache			
subjects affected / exposed	73 / 1051 (6.95%)		
occurrences (all)	106		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	301 / 1051 (28.64%)		
occurrences (all)	563		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	107 / 1051 (10.18%)		
occurrences (all)	141		

Nasopharyngitis			
subjects affected / exposed	150 / 1051 (14.27%)		
occurrences (all)	226		
Sinusitis			
subjects affected / exposed	77 / 1051 (7.33%)		
occurrences (all)	114		
Bronchitis			
subjects affected / exposed	62 / 1051 (5.90%)		
occurrences (all)	77		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2011	The following major changes (not all inclusive) were made to the protocol: • the original title of the protocol "A 24 Month Open Label Extension Study to Evaluate the Long Term Safety and Efficacy of Reslizumab (3.0 mg/kg) as Treatment for Patients (12 Through 75 Years of Age) With Eosinophilic Asthma Who Completed a Prior Cephalon Sponsored Study in Eosinophilic Asthma" was changed, because study treatment could be as long as 104 weeks (26 months) and the age range was already specified in the protocol • clinical laboratory tests were added at weeks 4 and 8, and all objectives and endpoints relative to these measures were revised to include the data collected • text was revised to clarify that the reslizumab dose is based on baseline body weight • footnote "o" was added for vital signs measurements at visit 1 • text regarding informed consent for minors was revised to reflect that only 1 parent was required to sign the informed consent form • the word "rescue" was deleted when used regarding SABA use review • the administration rate for reslizumab was corrected from 2 mg/min to 2 mL/min • text was revised to clarify that the investigator may adjust the dose for concomitant medications taken for asthma based on best clinical practices • the time for refraining from SABA use before study visits was changed from 4 to 6 hours • text regarding monitoring of adverse events during any washout phase of the study was deleted since this open label study did not have a washout phase • text regarding safety variables and analysis was revised to reflect additional analysis of clinical laboratory test results at weeks 4 and 8
14 April 2011	The following major changes (not all inclusive) were made to the protocol: • administrative changes were documented • a 90 day follow up evaluation was added for the assessment of adverse events, blood eosinophils, and vital signs to allow for additional safety monitoring • in addition to standard safety monitoring by the sponsor, an independent DSMB was implemented to oversee the safety of the patients
19 April 2011	The following major changes (not all inclusive) were made to the protocol: • a change was made to stipulate that blood samples were to be collected for pharmacokinetic 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 criteria (a) and (b) were changed for clarification of country specific age requirements • exclusion criterion (f) was revised to clarify acceptable contraceptive methods to be used during the study

19 April 2013	Amendment 4 (dated 19 April 2013) to the protocol was issued after 627 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 changes (not all inclusive) were made to the protocol: • Cephalon was acquired and became an affiliate of Teva Branded Pharmaceutical Products R&D, Inc; administrative changes due to the acquisition were reflected, where appropriate, in the study protocol • clinical laboratory information was revised to encompass appropriate countries • background information was clarified/restated and a table with completed clinical studies of reslizumab was added for harmonization with other reslizumab study protocols • pharmacokinetic, pharmacodynamic, and immunogenicity content was added for clarification • patient population with eosinophilic asthma qualified as "moderate to severe" • added to 90 day follow up evaluation: (±7 days) • immunogenicity (from anti reslizumab antibody assessment) was removed as a safety evaluation in the study • text for emergency treatment was added to include: unscheduled visits to the physician's office for nebulizer treatment or other urgent treatment to prevent worsening of asthma symptoms, or a visit to the emergency room for treatment, regardless of subsequent admission • beta agonist use was qualified as "short acting" and % FEV1 as % "predicted" • text was added to specify who was required to have a urine β HCG test • IRT registration was added to the procedure and assessment schedule • baseline body weight was specified to be used throughout the study to determine dose
14 April 2014	Teva communicated its intent to terminate Study C38072/3085 to all investigators involved with the trial on 09 January 2014. The rationale for the termination was that the primary study objective, in terms of open label events for patient exposure to an investigational product without confirmed benefit/risk, had been sufficiently met. This was primarily based on substantial over-enrollment from the originally planned sample size (approximately 740 patients) and is consistent with the Stopping Rules and Discontinuation Criteria in Section 3.6 of the original protocol. The decision to terminate the study was not due to any new or emerging safety concerns at that time. Following study termination, protocol amendment 5 was developed and issued on 14 April 2014 in countries within the European Union to comply with applicable EU legislation in this particular circumstance. This revised protocol was submitted and approved in all EU countries. The following major procedural changes (not all inclusive) were made to the protocol: • change in signatory and administration of the study • purpose of the study was redefined to align with changes to the primary objective, ie, obtaining additional safety data for reslizumab • planned enrollment increased from 740 to 1000 patients, as actual enrollment exceeded initial predictions • decision to terminate the study early (duration "up to 24 months") as exposure to study drug had been met with no new or emerging safety or efficacy concerns • duration of patient participation was corrected to include 90 day follow up visit • study was defined as being complete when the last patient completed his/her last study visit

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported