



Clinical trial results:

A 16-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Reslizumab (0.3 or 3.0 mg/kg) as Treatment for Patients (12-75 Years of Age) with Eosinophilic Asthma

Summary

EudraCT number	2010-023342-67
Trial protocol	BE SE HU NL PL
Global end of trial date	12 September 2013

Results information

Result version number	v2 (current)
This version publication date	23 July 2016
First version publication date	23 July 2015
Version creation reason	• Correction of full data set QC'd

Trial information

Trial identification

Sponsor protocol code	C38072/3081
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01270464
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Global Branded Pharmaceutical Products R&D, Inc.
Sponsor organisation address	41 Moores Road, Frazer, Pennsylvania, United States, 19355
Public contact	Director, Clinical Research, Teva Global Branded Pharmaceutical Products R&D, Inc., 1 215-591-3000, ustevatrials@tevapharm.com
Scientific contact	Director, Clinical Research, Teva Global Branded Pharmaceutical Products R&D, Inc., 1 215-591-3000, 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	29 January 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine whether reslizumab, at a dosage of 0.3 or 3.0 mg/kg administered once every 4 weeks for a total of 4 doses, is more effective than placebo in improving lung function in patients with eosinophilic asthma as assessed by the overall change from baseline in forced expiratory volume in 1 second (FEV1).

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Code of Federal Regulations [CFR] Title 21, Parts 50, 54, 56, 312, and 314; EU Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical

practice in the conduct of clinical studies of medicinal products for human use).

Each investigator was responsible for performing the study in accordance with the protocol, ICH guidelines, and GCP, and for collecting, recording, and reporting the data accurately and properly.

Agreement of each investigator to conduct and administer this study in accordance with the protocol was documented in separate study agreements with the sponsor and other forms as required by national authorities in the country where the study center is located.

Written and/or oral information about the study in a language understandable by the patient was provided to all 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-specific procedures or assessments were done. For patients aged 12 to 17 years, a signed and dated informed consent form was obtained from a parent/guardian. It was explained to all 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.

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	07 February 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Belgium: 13

Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Argentina: 43
Country: Number of subjects enrolled	Brazil: 19
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Colombia: 6
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Mexico: 26
Country: Number of subjects enrolled	United States: 115
Worldwide total number of subjects	315
EEA total number of subjects	75

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)	15
Adults (18-64 years)	283
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 1025 patients screened at 80 centers in 12 countries (Argentina, Belgium, Brazil, Canada, Colombia, Hungary, Israel, Mexico, Netherlands, Poland, Sweden, and the US), 315 patients met entry criteria at 68 centers and were considered to be eligible for enrollment.

Period 1

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

Blinding implementation details:

To maintain the blinding in this 3-group study, each patient was to receive a specific volume of study drug (including active or placebo) on the basis of the patient's body weight and assigned treatment group. Interactive response technology (IRT) was used to randomly assign a patient to 1 of 3 treatment groups. To maintain blinding to eosinophil counts during the study, eosinophil count data were redacted from hematology results during the treatment period.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo administered intravenously (iv) once every 4 weeks, for a total of 4 doses.

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

Dosage and administration details:

Placebo administered by iv infusion by qualified study personnel every 4 weeks for a total of 4 doses.

Arm title	Reslizumab - 0.3 mg/kg
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Arm description:

0.3 mg/kg, administered intravenously (iv) once every 4 weeks, for a total of 4 doses

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

Dosage and administration details:

3.0 mg/kg or 0.3 mg/kg doses administered intravenously (iv) by qualified site personnel once every 4 weeks, for a total of 4 doses.

Arm title	Reslizumab - 3.0 mg/kg
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Arm description:

3.0 mg/kg, administered intravenously (iv) once every 4 weeks, for a total of 4 doses.

Arm type	Experimental
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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:

3.0 mg/kg or 0.3 mg/kg doses administered intravenously (iv) by qualified site personnel once every 4 weeks, for a total of 4 doses.

Number of subjects in period 1	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg
Started	105	104	106
Safety analysis set	105	103	103
Full analysis set	105	103	103
Pharmacokinetic analysis set	105	103	103
Completed	85	92	88
Not completed	20	12	18
Consent withdrawn by subject	2	1	4
Adverse event, non-fatal	9	1	7
Lost to follow-up	2	3	1
unspecified	1	1	3
Lack of efficacy	2	3	1
Protocol deviation	4	3	2

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Placebo administered intravenously (iv) once every 4 weeks, for a total of 4 doses.	
Reporting group title	Reslizumab - 0.3 mg/kg
Reporting group description: 0.3 mg/kg, administered intravenously (iv) once every 4 weeks, for a total of 4 doses	
Reporting group title	Reslizumab - 3.0 mg/kg
Reporting group description: 3.0 mg/kg, administered intravenously (iv) once every 4 weeks, for a total of 4 doses.	

Reporting group values	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg
Number of subjects	105	104	106
Age categorical			
Stratification factor with data as reported in the case report form: 1) 12-17 years 2) >= 18 years			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	5	5	5
Adults (18-64 years)	93	91	99
From 65-84 years	7	8	2
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	44.2	44.5	43
standard deviation	± 14.89	± 14.03	± 14.41
Gender categorical			
Units: Subjects			
Female	62	59	62
Male	43	45	44
Race			
Units: Subjects			
White	85	80	90
Black	7	6	5
Asian	0	2	2
American Indian or Alaskan Native	1	0	0
Pacific Islander	1	0	0
Other	11	16	9
Ethnicity			
Units: Subjects			
Hispanic or Latino	29	29	31
Non-Hispanic and non-Latino	74	73	75

Unknown	2	2	0
Asthma Exacerbation Within the Last 12 Months			
A stratification factor with data as reported in the case report form			
Units: Subjects			
Yes	57	58	60
No	48	46	46
Weight			
Units: kg			
arithmetic mean	77	75.9	75.7
standard deviation	± 20.1	± 18.8	± 20.3
Height			
Units: cm			
arithmetic mean	166.4	166.2	165.9
standard deviation	± 10.93	± 12.21	± 10.24
Body Mass Index			
Units: kg/m ²			
arithmetic mean	27.7	27.6	27.4
standard deviation	± 6.01	± 6.68	± 6.87
In Forced Expiratory Volume In 1 Second (FEV1)			
Respiratory baseline values offered for the Full Analysis Set (n=105, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			
Units: liters			
arithmetic mean	2.222	2.157	2.169
standard deviation	± 0.8125	± 0.8506	± 0.7815
Forced Vital Capacity (FVC)			
Respiratory baseline values offered for the Full Analysis Set (n=105, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			
Units: liters			
arithmetic mean	3.288	3.289	3.199
standard deviation	± 1.0503	± 1.1232	± 1.0097
Forced Expiratory Flow at 25% to 75% Forced Vital Capacity (FEF 25%-75%)			
Respiratory baseline values offered for the Full Analysis Set (n=105, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			
Units: liter/second			
arithmetic mean	1.657	2.337	1.705
standard deviation	± 0.9201	± 8.9642	± 1.5396
% Predicted Expiratory Volume In 1 Second (FEV1)			
Respiratory baseline values offered for the Full Analysis Set (n=105, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			
Units: % predicted FEV1			
arithmetic mean	71.1	68.8	70
standard deviation	± 19.84	± 18.48	± 18.31
Asthma Control Questionnaire (ACQ)			
Respiratory baseline values offered for the Full Analysis Set (n=105, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			
Units: units on a scale			
arithmetic mean	2.471	2.499	2.591
standard deviation	± 0.8301	± 0.8903	± 0.8861
Asthma Quality of Life Questionnaire			
Respiratory baseline values offered for the Full Analysis Set (n=105, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			

Units: units on a scale			
arithmetic mean	4.374	4.479	4.164
standard deviation	± 1.2047	± 1.2266	± 1.2233
Asthma Symptom Utility Index (ASUI)			
Respiratory baseline values offered for the Full Analysis Set (n=105, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			
Units: units on a scale			
arithmetic mean	0.674	0.675	0.657
standard deviation	± 0.1897	± 0.2061	± 0.1913
Average Daily Use of Short-Acting Beta-Agonist (SABA) Use			
SABA use values offered for the Full Analysis Set (n=104, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			
Units: SABA puffs per day			
arithmetic mean	2.3	1.9	2.3
standard deviation	± 2.2	± 2.45	± 2.58
Blood Eosinophil Count			
Blood eosinophil baseline values offered for the Full Analysis Set (n=105, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			
Units: 10 ⁹ / L			
arithmetic mean	0.601	0.644	0.595
standard deviation	± 0.4331	± 0.4926	± 0.3931

Reporting group values	Total		
Number of subjects	315		
Age categorical			
Stratification factor with data as reported in the case report form: 1) 12-17 years 2) >= 18 years			
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)	15		
Adults (18-64 years)	283		
From 65-84 years	17		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	183		
Male	132		
Race			
Units: Subjects			
White	255		
Black	18		
Asian	4		
American Indian or Alaskan Native	1		

Pacific Islander	1		
Other	36		
Ethnicity			
Units: Subjects			
Hispanic or Latino	89		
Non-Hispanic and non-Latino	222		
Unknown	4		
Asthma Exacerbation Within the Last 12 Months			
A stratification factor with data as reported in the case report form			
Units: Subjects			
Yes	175		
No	140		
Weight			
Units: kg			
arithmetic mean			
standard deviation	-		
Height			
Units: cm			
arithmetic mean			
standard deviation	-		
Body Mass Index			
Units: kg/m ²			
arithmetic mean			
standard deviation	-		
In Forced Expiratory Volume In 1 Second (FEV1)			
Respiratory baseline values offered for the Full Analysis Set (n=105, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			
Units: liters			
arithmetic mean			
standard deviation	-		
Forced Vital Capacity (FVC)			
Respiratory baseline values offered for the Full Analysis Set (n=105, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			
Units: liters			
arithmetic mean			
standard deviation	-		
Forced Expiratory Flow at 25% to 75% Forced Vital Capacity (FEF 25%-75%)			
Respiratory baseline values offered for the Full Analysis Set (n=105, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			
Units: liter/second			
arithmetic mean			
standard deviation	-		
% Predicted Expiratory Volume In 1 Second (FEV1)			
Respiratory baseline values offered for the Full Analysis Set (n=105, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			
Units: % predicted FEV1			
arithmetic mean			
standard deviation	-		
Asthma Control Questionnaire (ACQ)			
Respiratory baseline values offered for the Full Analysis Set (n=105, 103, 103) so that comparisons can			

be made with endpoint "Change from Baseline...." results.			
Units: units on a scale arithmetic mean standard deviation	-		
Asthma Quality of Life Questionnaire			
Respiratory baseline values offered for the Full Analysis Set (n=105, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			
Units: units on a scale arithmetic mean standard deviation	-		
Asthma Symptom Utility Index (ASUI)			
Respiratory baseline values offered for the Full Analysis Set (n=105, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			
Units: units on a scale arithmetic mean standard deviation	-		
Average Daily Use of Short-Acting Beta-Agonist (SABA) Use			
SABA use values offered for the Full Analysis Set (n=104, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			
Units: SABA puffs per day arithmetic mean standard deviation	-		
Blood Eosinophil Count			
Blood eosinophil baseline values offered for the Full Analysis Set (n=105, 103, 103) so that comparisons can be made with endpoint "Change from Baseline...." results.			
Units: 10^9 / L arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo administered intravenously (iv) once every 4 weeks, for a total of 4 doses.	
Reporting group title	Reslizumab - 0.3 mg/kg
Reporting group description: 0.3 mg/kg, administered intravenously (iv) once every 4 weeks, for a total of 4 doses	
Reporting group title	Reslizumab - 3.0 mg/kg
Reporting group description: 3.0 mg/kg, administered intravenously (iv) once every 4 weeks, for a total of 4 doses.	

Primary: Change From Baseline In Forced Expiratory Volume In 1 Second (FEV1) over 16 weeks

End point title	Change From Baseline In Forced Expiratory Volume In 1 Second (FEV1) over 16 weeks
End point description: FEV1 is a standard measurement of air movement in the lungs of patients with asthma obtained from pulmonary function tests. It is the volume of air expired in the first second of a forced expiration using a spirometer.	
End point type	Primary
End point timeframe: Day 0 (baseline, pre-dose), Weeks 4, 8, 12 and 16	

End point values	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103 ^[1]	101 ^[2]	102 ^[3]	
Units: liters				
least squares mean (standard error)	0.126 (± 0.0549)	0.242 (± 0.0556)	0.286 (± 0.0548)	

Notes:

[1] - Full analysis set-all patients randomly assigned to treatment and treated 1+ doses of study drug

[2] - Full analysis set

[3] - Full analysis set

Statistical analyses

Statistical analysis title	Placebo to Reslizumab 3.0 mg/kg
Statistical analysis description: The primary variable was analyzed using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.	
Comparison groups	Placebo v Reslizumab - 3.0 mg/kg

Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0018 ^[4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.259
Variability estimate	Standard error of the mean
Dispersion value	0.0507

Notes:

[4] - The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the a priori significance level of 0.05.

Statistical analysis title	Placebo to Reslizumab 0.3 mg/kg
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Statistical analysis description:

The primary variable was analyzed using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.

Comparison groups	Placebo v Reslizumab - 0.3 mg/kg
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0237 ^[5]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.115
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.215
Variability estimate	Standard error of the mean
Dispersion value	0.0508

Notes:

[5] - The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the a priori significance level of 0.05.

Secondary: Change From Baseline in Forced Vital Capacity (FVC) over 16 Weeks

End point title	Change From Baseline in Forced Vital Capacity (FVC) over 16 Weeks
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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
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End point timeframe:

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

End point values	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103 ^[6]	101 ^[7]	102 ^[8]	
Units: liters				
least squares mean (standard error)	0.172 (± 0.0614)	0.22 (± 0.0623)	0.301 (± 0.0613)	

Notes:

[6] - Full analysis set

[7] - Full analysis set

[8] - Full analysis set

Statistical analyses

Statistical analysis title	Placebo to Reslizumab 3.0 mg/kg
Statistical analysis description:	
As with the primary outcome, this respiratory test outcome was analyzed using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.	
Comparison groups	Placebo v Reslizumab - 3.0 mg/kg
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0174 ^[9]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.237
Variability estimate	Standard error of the mean
Dispersion value	0.0543

Notes:

[9] - The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the a priori significance level of 0.05.

Statistical analysis title	Placebo to Reslizumab 0.3 mg/kg
Statistical analysis description:	
As with the primary outcome, this respiratory test outcome was analyzed using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.	
Comparison groups	Placebo v Reslizumab - 0.3 mg/kg

Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3731 ^[10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.058
upper limit	0.155
Variability estimate	Standard error of the mean
Dispersion value	0.0543

Notes:

[10] - The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the a priori significance level of 0.05.

Secondary: Change From Baseline in Forced Expiratory Flow at 25% to 75% Forced Vital Capacity (FEF 25%-75%) over 16 Weeks

End point title	Change From Baseline in Forced Expiratory Flow at 25% to 75% Forced Vital Capacity (FEF 25%-75%) over 16 Weeks
End point description:	The FEF 25%-75% is the force expiratory flow at 25% to 75% of the Forced Vital Capacity (FVC).
End point type	Secondary
End point timeframe:	Day 1 (baseline, pre-dose), Weeks 4, 8, 12, 16

End point values	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103 ^[11]	101 ^[12]	102 ^[13]	
Units: liters/second				
least squares mean (standard error)	-0.145 (± 0.1342)	-0.114 (± 0.1361)	0.089 (± 0.1342)	

Notes:

[11] - Full analysis set

[12] - Full analysis set

[13] - Full analysis set

Statistical analyses

Statistical analysis title	Placebo to Reslizumab 3.0 mg/kg
Statistical analysis description:	As with the primary outcome, this respiratory test outcome was analyzed using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.
Comparison groups	Placebo v Reslizumab - 3.0 mg/kg

Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0552 ^[14]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.233
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.472
Variability estimate	Standard error of the mean
Dispersion value	0.1212

Notes:

[14] - The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the a priori significance level of 0.05.

Statistical analysis title	Placebo to Reslizumab 0.3 mg/kg
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Statistical analysis description:

As with the primary outcome, this respiratory test outcome was analyzed using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.

Comparison groups	Placebo v Reslizumab - 0.3 mg/kg
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.802 ^[15]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.209
upper limit	0.27
Variability estimate	Standard error of the mean
Dispersion value	0.1215

Notes:

[15] - The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the a priori significance level of 0.05.

Secondary: Change From Baseline in % Predicted Expiratory Volume In 1 Second (FEV1) at Week 16 and at Endpoint

End point title	Change From Baseline in % Predicted Expiratory Volume In 1 Second (FEV1) at Week 16 and at Endpoint
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End point description:

The % predicted FEV1 is the ratio of the volume of air expired in the first second of a forced expiration to the FVC.

End point type	Secondary
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End point timeframe:

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

End point values	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105 ^[16]	103 ^[17]	103 ^[18]	
Units: % predicted FEV1				
arithmetic mean (standard deviation)				
Week 16 (n=84, 92, 91)	0.8 (± 11.92)	4.9 (± 15.06)	7.5 (± 14.74)	
Endpoint (n=103, 101, 102)	0.8 (± 13.83)	5.5 (± 15.16)	6.7 (± 15.01)	

Notes:

[16] - Full analysis set.

[17] - Full analysis set

[18] - Full analysis set

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Asthma Control Questionnaire (ACQ) over 16 Weeks
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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. A higher score is an indication of poorer asthma control. Negative change from baseline scores indicate improvement.

End point type	Secondary
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End point timeframe:

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

End point values	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103 ^[19]	101 ^[20]	101 ^[21]	
Units: units on a scale				
least squares mean (standard error)	-0.494 (± 0.1231)	-0.732 (± 0.125)	-0.853 (± 0.1233)	

Notes:

[19] - Full analysis set, including patients who contributed at least once to the analysis.

[20] - Full analysis set, including patients who contributed at least once to the analysis.

[21] - Full analysis set, including patients who contributed at least once to the analysis.

Statistical analyses

Statistical analysis title	Placebo to Resizumab 3.0 mg/kg
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Statistical analysis description:

As with the primary outcome, this respiratory test outcome was analyzed using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of

treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.

Comparison groups	Placebo v Reslizumab - 3.0 mg/kg
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014 ^[22]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.359
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.577
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.111

Notes:

[22] - The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the a priori significance level of 0.05.

Statistical analysis title	Copy of Placebo to Resizumab 0.3 mg/kg
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Statistical analysis description:

As with the primary outcome, this respiratory test outcome was analyzed using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.

Comparison groups	Placebo v Reslizumab - 0.3 mg/kg
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0329 ^[23]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.238
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.456
upper limit	-0.019
Variability estimate	Standard error of the mean
Dispersion value	0.1108

Notes:

[23] - The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the a priori significance level of 0.05.

Secondary: Change From Baseline in Asthma Quality of Life Questionnaire (AQLQ) at Week 16 or at Last Observed Value

End point title	Change From Baseline in Asthma Quality of Life Questionnaire (AQLQ) at Week 16 or at Last Observed Value
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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) for a total scale

of 32-224. Five of the activity questions were “patient-specific,” which means that each patient identified and scored 5 activities in which the patient was limited by asthma; these 5 activities were identified at the first visit and retained for all subsequent follow-up visits. Positive change from baseline scores indicate improvement in quality of life.

The AQLQ score was only assessed once during the study at week 16 or at early withdrawal if it met endpoint criteria for efficacy assessments: ie, last postbaseline assessment if within 3 to 5 weeks of the last dose of study drug.

End point type	Secondary
End point timeframe:	
Day 1 (baseline, pre-dose), Week 16 or last observed value	

End point values	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101 ^[24]	96 ^[25]	99 ^[26]	
Units: units on a scale				
least squares mean (standard error)	0.779 (± 0.1817)	1.057 (± 0.1881)	1.138 (± 0.1829)	

Notes:

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

[25] - Full analysis set, including patients who contributed at least once to the analysis.

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

Statistical analyses

Statistical analysis title	Placebo to Reslizumab 3.0 mg/kg
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Statistical analysis description:

As with the primary outcome, this respiratory test outcome was analyzed using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.

Comparison groups	Placebo v Reslizumab - 3.0 mg/kg
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0241 ^[27]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.359
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.047
upper limit	0.67
Variability estimate	Standard error of the mean
Dispersion value	0.1582

Notes:

[27] - The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the a priori significance level of 0.05.

Statistical analysis title	Copy of Placebo to Reslizumab 0.3 mg/kg
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Statistical analysis description:

As with the primary outcome, this respiratory test outcome was analyzed using a mixed-effect model for

repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.

Comparison groups	Placebo v Reslizumab - 0.3 mg/kg
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0822 ^[28]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.278
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.036
upper limit	0.591
Variability estimate	Standard error of the mean
Dispersion value	0.1591

Notes:

[28] - The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the a priori significance level of 0.05.

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

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

The ASUI is an 11-item instrument designed to assess the frequency and severity of asthma symptoms and side effects, weighted by patient preferences (Revicki et al 1998). ASUI is a utility score that ranges from 0 to 1, with higher values indicating better asthma control; info obtained from questionnaire about asthma symptoms.

End point type	Secondary
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End point timeframe:

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

End point values	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103 ^[29]	101 ^[30]	101 ^[31]	
Units: units on a scale				
least squares mean (standard error)	0.082 (± 0.0218)	0.132 (± 0.0221)	0.129 (± 0.0218)	

Notes:

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

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

[31] - Full analysis set, including patients who contributed at least once to the analysis.

Statistical analyses

Statistical analysis title	Placebo to Reslizumab 3.0 mg/kg
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Statistical analysis description:

As with the primary outcome, this respiratory test outcome was analyzed using a mixed-effect model for

repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.

Comparison groups	Placebo v Reslizumab - 3.0 mg/kg
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016 ^[32]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.085
Variability estimate	Standard error of the mean
Dispersion value	0.0193

Notes:

[32] - The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the a priori significance level of 0.05.

Statistical analysis title	Copy of Placebo to Resizumab 0.3 mg/kg
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Statistical analysis description:

As with the primary outcome, this respiratory test outcome was analyzed using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.

Comparison groups	Placebo v Reslizumab - 0.3 mg/kg
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0094 ^[33]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.012
upper limit	0.089
Variability estimate	Standard error of the mean
Dispersion value	0.0193

Notes:

[33] - The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the a priori significance level of 0.05.

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

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

At each clinic visit, to measure SABA use, patients were asked to recall their usage of SABA therapy within the last 3 days of the scheduled visit. If usage was confirmed, the number of puffs used was recorded.

End point type	Secondary
End point timeframe:	
Day 1 (baseline, pre-dose), Weeks 4, 8, 12, 16	

End point values	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102 ^[34]	101 ^[35]	102 ^[36]	
Units: SABA puffs per day				
least squares mean (standard error)	-0.3 (± 0.28)	-1 (± 0.28)	-0.9 (± 0.27)	

Notes:

[34] - Full analysis set, including patients who contributed at least once to the analysis.

[35] - Full analysis set, including patients who contributed at least once to the analysis.

[36] - Full analysis set, including patients who contributed at least once to the analysis.

Statistical analyses

Statistical analysis title	Placebo to Reslizumab 3.0 mg/kg
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Statistical analysis description:

As with the primary outcome, this respiratory test outcome was analyzed using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.

Comparison groups	Placebo v Reslizumab - 3.0 mg/kg
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0151 ^[37]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.624
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.126
upper limit	-0.121
Variability estimate	Standard error of the mean
Dispersion value	0.2551

Notes:

[37] - The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the a priori significance level of 0.05.

Statistical analysis title	Placebo to Reslizumab 0.3 mg/kg
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Statistical analysis description:

As with the primary outcome, this respiratory test outcome was analyzed using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.

Comparison groups	Placebo v Reslizumab - 0.3 mg/kg
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Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0119 ^[38]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.648
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.152
upper limit	-0.144
Variability estimate	Standard error of the mean
Dispersion value	0.2559

Notes:

[38] - The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the a priori significance level of 0.05.

Secondary: Change From Baseline in Blood Eosinophil Count over 16 Weeks

End point title	Change From Baseline in Blood Eosinophil Count over 16 Weeks
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End point description:

Blood eosinophil counts were measured using a standard CBC with differential blood test at each scheduled visit, and from all patients experiencing a serious adverse event, an adverse event leading to withdrawal, or an exacerbation of asthma symptoms.

End point type	Secondary
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End point timeframe:

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

End point values	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103 ^[39]	101 ^[40]	102 ^[41]	
Units: 10 ⁹ /L				
least squares mean (standard error)	-0.035 (± 0.0271)	-0.358 (± 0.0277)	-0.529 (± 0.027)	

Notes:

[39] - Full analysis set, including patients who contributed at least once to the analysis.

[40] - Full analysis set, including patients who contributed at least once to the analysis.

[41] - Full analysis set, including patients who contributed at least once to the analysis.

Statistical analyses

Statistical analysis title	Placebo to Reslizumab 3.0 mg/kg
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Statistical analysis description:

As with the primary outcome, this respiratory test outcome was analyzed using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.

Comparison groups	Placebo v Reslizumab - 3.0 mg/kg
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Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 ^[42]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.494
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.542
upper limit	-0.447
Variability estimate	Standard error of the mean
Dispersion value	0.0242

Notes:

[42] - The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the a priori significance level of 0.05.

Statistical analysis title	Copy of Placebo to Resizumab 0.3 mg/kg
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Statistical analysis description:

As with the primary outcome, this respiratory test outcome was analyzed using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements.

Comparison groups	Placebo v Reslizumab - 3.0 mg/kg v Reslizumab - 0.3 mg/kg
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 ^[43]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.323
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	-0.275
Variability estimate	Standard error of the mean
Dispersion value	0.0243

Notes:

[43] - The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the a priori significance level of 0.05.

Secondary: Participants with Adverse Events

End point title	Participants with Adverse Events
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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	Secondary
End point timeframe:	
Day 1 (post-dose) to Week 29. The last postbaseline value for approximately 10 patients in each treatment group is the 90-day follow-up visit post end-of-treatment (approx. Week 29).	

End point values	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105 ^[44]	103 ^[45]	103 ^[46]	
Units: participants				
At least 1 AE	66	59	61	
Severe AE	4	2	7	
Treatment-related AE	8	6	12	
Withdrawn from study due to AE	10	1	6	
Withdrawn from study due to treatment-related AE	0	0	1	
Death	0	0	0	
Serious AE without the outcome of death	1	0	4	
Treatment-related serious AEs	0	0	0	

Notes:

[44] - Safety analysis set

[45] - Safety analysis set

[46] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

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

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

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

Significance criteria:

Blood urea nitrogen: ≥ 10.71 mmol/L

Creatinine: ≥ 177 μ mol/L

Uric acid: M ≥ 625 , F ≥ 506 μ mol/L

GGT = gamma-glutamyl transpeptidase: $\geq 3 \times$ upper limit of normal. Normal range is 5-49 U/L.

Total bilirubin: ≥ 34.2 μ mol/L

White blood cells: $\leq 3.0 \times 10^9$ /L

Hemoglobin: M ≤ 115 , F ≤ 95 g/dL

Hematocrit: M < 0.37 , F < 0.32 %

Platelets: $\geq 700 \times 10^9$ /L

Absolute neutrophil count: $\leq 1.0 \times 10^9$ /L

Urinalysis: blood, glucose, ketones and total protein: ≥ 2 unit increase from baseline

Actual number of participants evaluated varies between 100-104 for each test and treatment arm.

End point type	Secondary
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End point timeframe:

Day 2 to Week 29. The last postbaseline hematology value for approximately 10 patients in each treatment group is the 90-day follow-up visit post end-of-treatment (approx. Week 29).

End point values	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105 ^[47]	103 ^[48]	103 ^[49]	
Units: participants				
At least 1 PCS abnormal serum chemistry value	1	5	2	
Blood urea nitrogen	0	0	1	
Creatinine	1	0	0	
Uric acid	0	0	2	
GGT	0	4	0	
Total bilirubin	0	1	0	
At least 1 PCS abnormal hematology value	4	7	3	
White blood cells	0	0	1	
Hemoglobin	0	2	0	
Hematocrit	2	6	2	
Platelets	0	0	1	
Absolute neutrophil count	2	1	0	
At least 1 PCS abnormal urinalysis value	21	21	18	
Blood in urine	10	11	6	
Glucose in urine	3	4	5	
Ketones in urine	0	1	3	
Total protein in urine	11	11	11	

Notes:

[47] - Safety analysis set

[48] - Safety analysis set

[49] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

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

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

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

Significance criteria

Sitting pulse - high: >100 and increase of ≥ 30 beats/minute

Sitting pulse - low: <50 and decrease of ≥30 beats/minute

Sitting diastolic blood pressure: >100 and increase of ≥12 mmHg

Respiration rate: >24 and increase of ≥10 breaths/minute

Body temperature: <96.5° Fahrenheit or <35.8° Celsius

End point type	Secondary
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End point timeframe:

Day 2 to Week 29. The last postbaseline value for approximately 10 patients in each treatment group is the 90-day follow-up visit post end-of-treatment (approx. Week 29).

End point values	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104 ^[50]	102 ^[51]	103 ^[52]	
Units: participants				
At least 1 PCS abnormal vital sign	12	16	16	
Sitting pulse - high	0	1	2	
Sitting pulse - low	0	1	1	
Sitting diastolic blood pressure	0	0	1	
Respiration rate	0	2	0	
Body temperature	12	13	13	

Notes:

[50] - Safety analysis set of patients with both a baseline and postbaseline vital sign value.

[51] - Safety analysis set of patients with both a baseline and postbaseline vital sign value.

[52] - Safety analysis set of patients with both a baseline and postbaseline vital sign value.

Statistical analyses

No statistical analyses for this end point

Secondary: Shifts from Baseline to Endpoint in Electrocardiogram Findings

End point title	Shifts from Baseline to Endpoint in Electrocardiogram Findings
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End point description:

Participant counts in each category of shift from baseline to endpoint of ECG finding. Findings summarized as normal or abnormal.

End point type	Secondary
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End point timeframe:

Weeks -4 to -2 (Screening Visit), Week 16

End point values	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102 ^[53]	99 ^[54]	101 ^[55]	
Units: participants				
Normal to Normal	64	70	63	
Normal to Abnormal	14	10	15	
Abnormal to Normal	11	9	13	
Abnormal to Abnormal	13	10	10	

Notes:

[53] - Safety analysis set of participants with both baseline and endpoint values.

[54] - Safety analysis set of participants with both baseline and endpoint values.

[55] - Safety analysis set of participants with both baseline and endpoint values.

Statistical analyses

No statistical analyses for this end point

Secondary: Participant With a Positive Anti-Reslizumab Antibody Status at Baseline, Week 8, Week 16, Endpoint, and Overall

End point title	Participant With a Positive Anti-Reslizumab Antibody Status at Baseline, Week 8, Week 16, Endpoint, and Overall
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End point description:

Counts of participants with a positive anti-drug antibody (ADA) response during treatment is offered for the two experimental treatment arms. Blood samples were collected for determination of ADAs before study drug infusion at baseline, visit 4 (week 8), and at visit 6 (week 16: EOT or early withdrawal) from patients in all 3 treatment groups (ie, placebo, 0.3 mg/kg reslizumab, and 3.0 mg/kg reslizumab); however, only the blood samples drawn from patients treated with either 0.3 mg/kg reslizumab or 3.0 mg/kg reslizumab were analyzed. Serum samples from patients who were treated with reslizumab were analyzed for ADA by Teva (Teva Biopharmaceuticals USA, Rockville, MD) using a validated homogeneous solution-based bridging enzyme-linked immunosorbent assay (ELISA).

End point type	Secondary
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End point timeframe:

Day 1 (pre-dose), week 8, 16 and endpoint

End point values	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[56]	103 ^[57]	103 ^[58]	
Units: participants				
Overall (n=102, 103)		12	11	
Baseline (n=99, 98)		8	8	
Week 8 (n=90, 94)		8	10	
Week 16 (n=91, 89)		7	5	
Endpoint (n=101, 102)		10	6	

Notes:

[56] - Anti-Reslizumab antibody status was not analyzed for patients in the Placebo treatment arm.

[57] - Pharmacokinetic analysis set

[58] - Pharmacokinetic analysis set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Week 29. The last postbaseline value for approximately 10 patients in each treatment group is the 90-day follow-up visit post end-of-treatment (approx. Week 29). Events reported during the follow-up were treated as treatment-emergent.

Adverse event reporting additional description:

Total subjects affected with non-serious AEs by treatment arm is consistent with the 5% threshold.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo administered intravenously (iv) once every 4 weeks, for a total of 4 doses.

Reporting group title	Reslizumab - 0.3 mg/kg
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Reporting group description:

0.3 mg/kg, administered intravenously (iv) once every 4 weeks, for a total of 4 doses

Reporting group title	Reslizumab - 3.0 mg/kg
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Reporting group description:

3.0 mg/kg, administered intravenously (iv) once every 4 weeks, for a total of 4 doses.

Serious adverse events	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	4 / 103 (3.88%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	3 / 103 (2.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 105 (0.00%)	0 / 103 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Reslizumab - 0.3 mg/kg	Reslizumab - 3.0 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 105 (26.67%)	20 / 103 (19.42%)	28 / 103 (27.18%)
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 105 (5.71%)	8 / 103 (7.77%)	11 / 103 (10.68%)
occurrences (all)	7	9	11
Asthma			
subjects affected / exposed	20 / 105 (19.05%)	6 / 103 (5.83%)	14 / 103 (13.59%)
occurrences (all)	24	10	14
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 105 (3.81%)	6 / 103 (5.83%)	6 / 103 (5.83%)
occurrences (all)	5	9	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2010	Amendment 1 (dated 22 December 2010) to the protocol was issued before any patients were enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: - Body weight was to be measured only at screening and baseline. - The requirement to document the use of the anti-IgE monoclonal antibody omalizumab (XOLAIR®) taken 12 months before study drug administration was added. - Several clarifications and corrections were made to the study design.
14 April 2011	Amendment 2 (dated 14 April 2011) to the protocol was issued after 15 of the 300 planned patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: - The inclusion criterion describing required asthma therapy was clarified. - An exclusion criterion was changed to exclude patients who had other pulmonary conditions with symptoms of asthma and blood eosinophilia such as Churg-Strauss syndrome. - Exclusion criteria were added to exclude patients who had or who were suspected of having a parasitic infestation/infection and to exclude patients who had received a live attenuated vaccine within 12-weeks before screening. - An independent Data and Safety Monitoring Board (DSMB) was added to further ensure the safety of the patients. - For patients who did not enroll in the open-label extension study, a 90-day follow-up evaluation was added to assess adverse events, blood eosinophils, and vital signs.
19 April 2011	Amendment 3 (dated 19 April 2011) to the protocol was issued after 17 of the 300 planned patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: - Country-specific changes and clarifications were made to study inclusion and exclusion criteria. - For patients experiencing a serious adverse event, an adverse event leading to withdrawal, or an exacerbation of asthma symptoms, the collection of a blood sample was added for pharmacokinetic evaluation, eosinophil determination, and ADA assessment. - The anti-IgE monoclonal antibody omalizumab (XOLAIR®) was added as a prohibited medication within 6 months prior to screening. - A full physical examination was added to the end-of-treatment visit.
29 February 2012	Amendment 4 (dated 29 February 2012) to the protocol was issued after 195 of the 300 planned patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: - The number of patients planned to be enrolled in the study was increased from approximately 180 to approximately 300 patients, to achieve 90% power for the primary efficacy variable instead of 85% power. The increase in sample size also resulted in a lowered effect size from 0.6 to 0.47. The lowered effect size reflected an anticipated greater variability in the FEV1 change as the result of broader geographic enrollment than initially planned.

19 April 2013	Amendment 5 (dated 19 April 2013) to the protocol was issued after 315 patients were enrolled into the study, ie, patient enrollment was complete. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: - Text related to the timings of blood sample collection for biomarkers (ECP, EDN, and EP) and ADA was clarified and minor terminology updates related to pharmacokinetic sampling were made. - Three new subsections (Immunogenicity, Pharmacokinetics, and Pharmacodynamics) were added to the Primary and Secondary Measures and Endpoints section for clarification. - The exploratory objectives of biomarkers, sputum eosinophil levels, and change in presence or absence of nasal polyps were clarified.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported