# 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<br>QC'd |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | C38072/3081 |

### 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 |

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 |

Arm description:

3.0 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.

| **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<br>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<br>Units: kg<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Height<br>Units: cm<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Body Mass Index<br>Units: kg/m^2<br>arithmetic mean<br>standard deviation | -<br>- | | |
| 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<br>arithmetic mean<br>standard deviation | -<br>- | | |
| 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<br>arithmetic mean<br>standard deviation | -<br>- | | |
| 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<br>arithmetic mean<br>standard deviation | -<br>- | | |
| % 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<br>arithmetic mean<br>standard deviation | -<br>- | | |
| 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<br>arithmetic mean<br>standard deviation | -<br>- | | |
| 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<br>arithmetic mean<br>standard deviation | -<br>- | | |
| 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<br>arithmetic mean<br>standard deviation | -<br>- | | |
| 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<br>arithmetic mean<br>standard deviation | -<br>- | | |
| 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<br>arithmetic mean<br>standard deviation | -<br>- | | |

## 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 |
|---|---|

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 |
|---|---|

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:

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 Resizumab 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 Resizumab 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 Resizumab 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 Resizumab 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 | = 0.802 [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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |

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 Resizumab 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 | 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 Resizumab 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 | 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 |

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 |

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 Resizumab 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 | 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 |
|---|---|

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 |

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 Resizumab 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 | 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 Resizumab 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 | 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 |

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 |

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 Resizumab 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 [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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

End point description:

Data represents participants with potentially clinically significant (PCS) abnormal serum chemistry, hematology (except for eosinophil values), and urinalysis values.
Significance criteria:
Blood urea nitrogen: >=10.71 mmol/L
Creatinine: >=177 µmol/L
Uric acid: M>=625, F>=506 µmol/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: <=3.0 10^9/L
Hemoglobin: M<=115, F<=95 g/dL
Hematocrit: M<0.37, F<0.32 %
Platelets: >=700 10^9/L
Absolute neutrophil count: <=1.0 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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 15.0 |

### 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.

| 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.<br>The following major procedural changes (not all-inclusive) were made to the protocol:<br>Body weight was to be measured only at screening and baseline.<br>The requirement to document the use of the anti-IgE monoclonal antibody omalizumab (XOLAIR®) taken 12 months before study drug administration was added.<br>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.<br>The following major procedural changes (not all-inclusive) were made to the protocol:<br>- The inclusion criterion describing required asthma therapy was clarified.<br>- 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.<br>- 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.<br>- An independent Data and Safety Monitoring Board (DSMB) was added to further ensure the safety of the patients.<br>- 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.<br>The following major procedural changes (not all-inclusive) were made to the protocol:<br>- Country-specific changes and clarifications were made to study inclusion and exclusion criteria.<br>- 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.<br>- The anti-IgE monoclonal antibody omalizumab (XOLAIR®) was added as a prohibited medication within 6 months prior to screening.<br>- 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.<br>The following major procedural changes (not all-inclusive) were made to the protocol:<br>- 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.<br>The following major procedural changes (not all-inclusive) were made to the protocol:<br>- 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.<br>- Three new subsections (Immunogenicity, Pharmacokinetics, and Pharmacodynamics) were added to the Primary and Secondary Measures and Endpoints section for clarification.<br>- The exploratory objectives of biomarkers, sputum eosinophil levels, and change in presence or absence of nasal polyps were clarified. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported