



## Clinical trial results:

### A Phase 3, 24-Week Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study of Reslizumab Subcutaneous Dosing (110 mg Every 4 weeks) in Patients with Oral Corticosteroid Dependent Asthma and Elevated Blood Eosinophils

#### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2015-001580-39          |
| Trial protocol           | CZ HU BE ES IT NL PL DE |
| Global end of trial date | 04 December 2017        |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 05 August 2018 |
| First version publication date | 05 August 2018 |

#### Trial information

##### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | C38072-AS-30027 |
|-----------------------|-----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02501629 |
| 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 Products R&D, Inc., 01 888-483-8279, info.era-clinical@teva.de |
| Scientific contact           | Director, Clinical Research, Teva Global Branded Products R&D, Inc., 01 888-483-8279, info.era-clinical@teva.de |

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                       | 11 April 2018    |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 04 December 2017 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study was to establish the safety and efficacy of the subcutaneous (sc) formulation of reslizumab in patients with oral corticosteroid (OCS) dependent asthma and elevated blood eosinophils.

The primary objective of this study is to determine the ability of reslizumab (110 mg) administered subcutaneously (sc) once every 4 weeks to produce a corticosteroid-sparing effect (as demonstrated by percent reduction in daily OCS use) in patients with OCS-dependent asthma and elevated blood eosinophils, without loss of asthma control.

Protection of trial subjects:

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

Written and/or oral information about the study was provided to all patients in a language understandable by the patients. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from each patient before any study procedures or assessments were done. It was explained to the patients that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Each patient's willingness to participate in the study was documented in writing in a consent form that was signed by the patient with the date of that signature indicated. Each investigator kept the original consent forms, and copies were given to the patients.

Background therapy: -

Evidence for comparator: -

|                                                           |                   |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment                          | 21 September 2015 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Netherlands: 5 |
| Country: Number of subjects enrolled | Poland: 11     |
| Country: Number of subjects enrolled | Spain: 4       |

|                                      |                                           |
|--------------------------------------|-------------------------------------------|
| Country: Number of subjects enrolled | Belgium: 3                                |
| Country: Number of subjects enrolled | Czech Republic: 5                         |
| Country: Number of subjects enrolled | France: 2                                 |
| Country: Number of subjects enrolled | Germany: 14                               |
| Country: Number of subjects enrolled | Hungary: 2                                |
| Country: Number of subjects enrolled | Italy: 2                                  |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 5 |
| Country: Number of subjects enrolled | Mexico: 24                                |
| Country: Number of subjects enrolled | Russian Federation: 10                    |
| Country: Number of subjects enrolled | Ukraine: 47                               |
| Country: Number of subjects enrolled | United States: 19                         |
| Country: Number of subjects enrolled | Argentina: 11                             |
| Country: Number of subjects enrolled | Australia: 2                              |
| Country: Number of subjects enrolled | Israel: 11                                |
| Worldwide total number of subjects   | 177                                       |
| EEA total number of subjects         | 48                                        |

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)                 | 1   |
| Adults (18-64 years)                      | 137 |
| From 65 to 84 years                       | 39  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 273 patients with OCS-dependent severe eosinophilic asthma were screened, and 180 of these patients (at 78 centers) were considered eligible for enrollment. Three of the eligible patients were not randomized due to failure to meet randomization criteria.

### Period 1

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

Blinding implementation details:

Patients were randomly assigned to treatment through an IRT. Using this system ensured a balance across treatment groups; no effort was made to maintain a balance among treatment groups within a study center.

Eosinophils and monocytes were redacted from the post baseline differential cell count reports.

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Matching placebo was administered by subcutaneous injection (sc) 1.0 mL every 4 weeks for a total of six doses.

|                                        |                                              |
|----------------------------------------|----------------------------------------------|
| Arm type                               | Placebo                                      |
| Investigational medicinal product name | Placebo                                      |
| Investigational medicinal product code |                                              |
| Other name                             |                                              |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Placebo was administered by qualified study personnel as subcutaneous injections in the upper arm(s) once every 4 weeks for a total of 6 doses. Drug was supplied in pre-filled syringes.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Reslizumab 110 mg |
|------------------|-------------------|

Arm description:

Reslizumab was administered by subcutaneous injection (sc) in a dosage of 110 mg (1.0 mL) every 4 weeks for a total of six doses.

|                                        |                                              |
|----------------------------------------|----------------------------------------------|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Reslizumab                                   |
| Investigational medicinal product code |                                              |
| Other name                             | CEP38072, Cinqair, Cinqaero                  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Reslizumab 110 mg was administered by qualified study personnel as subcutaneous injections in the upper arm(s) once every 4 weeks for a total of 6 doses. Drug was supplied in pre-filled syringes.

| <b>Number of subjects in period 1</b> | Placebo | Reslizumab 110 mg |
|---------------------------------------|---------|-------------------|
| Started                               | 89      | 88                |
| Safety Population                     | 89      | 88                |
| Intent to Treat (ITT) population      | 89      | 88                |
| Completed                             | 84      | 81                |
| Not completed                         | 5       | 7                 |
| Adverse event, serious fatal          | -       | 1                 |
| Consent withdrawn by subject          | 3       | 5                 |
| At request of sponsor                 | 2       | -                 |
| Lost to follow-up                     | -       | 1                 |

## Baseline characteristics

### Reporting groups

|                                                                                                                                   |                   |
|-----------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Reporting group title                                                                                                             | Placebo           |
| Reporting group description:                                                                                                      |                   |
| Matching placebo was administered by subcutaneous injection (sc) 1.0 mL every 4 weeks for a total of six doses.                   |                   |
| Reporting group title                                                                                                             | Reslizumab 110 mg |
| Reporting group description:                                                                                                      |                   |
| Reslizumab was administered by subcutaneous injection (sc) in a dosage of 110 mg (1.0 mL) every 4 weeks for a total of six doses. |                   |

| Reporting group values                    | Placebo  | Reslizumab 110 mg | Total |
|-------------------------------------------|----------|-------------------|-------|
| Number of subjects                        | 89       | 88                | 177   |
| Age categorical                           |          |                   |       |
| Units: Subjects                           |          |                   |       |
| 12-<18 years                              | 1        | 0                 | 1     |
| 18 to <65 years                           | 74       | 63                | 137   |
| >=65 years                                | 14       | 25                | 39    |
| Age continuous                            |          |                   |       |
| Units: years                              |          |                   |       |
| arithmetic mean                           | 53.1     | 55.5              |       |
| standard deviation                        | ± 11.99  | ± 12.72           | -     |
| Gender categorical                        |          |                   |       |
| Units: Subjects                           |          |                   |       |
| Female                                    | 57       | 60                | 117   |
| Male                                      | 32       | 28                | 60    |
| Race                                      |          |                   |       |
| Units: Subjects                           |          |                   |       |
| White                                     | 80       | 72                | 152   |
| Black or African American                 | 1        | 3                 | 4     |
| Asian                                     | 3        | 2                 | 5     |
| American Indian or Alaska Native          | 1        | 3                 | 4     |
| Native Hawaiian or Other Pacific Islander | 0        | 0                 | 0     |
| Other                                     | 4        | 8                 | 12    |
| Ethnicity                                 |          |                   |       |
| Units: Subjects                           |          |                   |       |
| Not Hispanic or Latino                    | 72       | 65                | 137   |
| Hispanic or Latino                        | 16       | 22                | 38    |
| Unknown                                   | 1        | 1                 | 2     |
| Geographic Region Group                   |          |                   |       |
| Units: Subjects                           |          |                   |       |
| U.S. / Canada                             | 10       | 9                 | 19    |
| Europe                                    | 58       | 47                | 105   |
| Other                                     | 21       | 32                | 53    |
| Weight                                    |          |                   |       |
| Units: kg                                 |          |                   |       |
| arithmetic mean                           | 82.69    | 79.58             |       |
| standard deviation                        | ± 18.949 | ± 21.390          | -     |

|                          |          |          |   |
|--------------------------|----------|----------|---|
| Body Mass Index (BMI)    |          |          |   |
| Units: kg/m <sup>2</sup> |          |          |   |
| arithmetic mean          | 29.859   | 29.389   |   |
| standard deviation       | ± 6.3499 | ± 8.0105 | - |

## End points

### End points reporting groups

|                                                                                                                                   |                   |
|-----------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Reporting group title                                                                                                             | Placebo           |
| Reporting group description:                                                                                                      |                   |
| Matching placebo was administered by subcutaneous injection (sc) 1.0 mL every 4 weeks for a total of six doses.                   |                   |
| Reporting group title                                                                                                             | Reslizumab 110 mg |
| Reporting group description:                                                                                                      |                   |
| Reslizumab was administered by subcutaneous injection (sc) in a dosage of 110 mg (1.0 mL) every 4 weeks for a total of six doses. |                   |

### Primary: Categorized Percent Reduction In Daily Oral Corticosteroid (OCS) Dose During Weeks 20-24 As Compared to the Optimized Dose At Baseline

|                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                | Categorized Percent Reduction In Daily Oral Corticosteroid (OCS) Dose During Weeks 20-24 As Compared to the Optimized Dose At Baseline |
| End point description:                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                        |
| The primary endpoint was the 5-level categorized percent reduction in OCS dose during weeks 20 to 24 compared with the optimized dose at baseline. The primary analysis incorporated data from all randomized patients. Analysis of the primary and secondary variables related to categorical OCS dose reduction incorporated missing data as non-responders. |                                                                                                                                        |
| No decrease indicates there was no decrease in OCS, loss of baseline asthma control during weeks 20 to 24, or discontinuation from study drug.                                                                                                                                                                                                                 |                                                                                                                                        |
| End point type                                                                                                                                                                                                                                                                                                                                                 | Primary                                                                                                                                |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                        |
| Baseline (Day 1), Weeks 20-24                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                        |

| End point values            | Placebo           | Reslizumab 110 mg |  |  |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type          | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed | 89 <sup>[1]</sup> | 88 <sup>[2]</sup> |  |  |
| Units: participants         |                   |                   |  |  |
| 90% - 100%                  | 20                | 18                |  |  |
| 75% - <90%                  | 4                 | 8                 |  |  |
| 50% - <75%                  | 8                 | 13                |  |  |
| >0% - <50%                  | 9                 | 7                 |  |  |
| No decrease                 | 48                | 42                |  |  |

Notes:

[1] - ITT

[2] - ITT

### Statistical analyses

|                                                                                                                                                                                                                           |                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Statistical analysis title                                                                                                                                                                                                | OCS Dose Reduction |
| Statistical analysis description:                                                                                                                                                                                         |                    |
| The proportional odds ratio (reslizumab/placebo) was estimated from this model, representing the ratio of the odds of a patient outcome being in a higher OCS dose reduction category for reslizumab compared to placebo. |                    |



|                                         |                             |
|-----------------------------------------|-----------------------------|
| Comparison groups                       | Placebo v Reslizumab 110 mg |
| Number of subjects included in analysis | 177                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| P-value                                 | = 0.468 <sup>[3]</sup>      |
| Method                                  | proportional odds model     |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 1.23                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.702                       |
| upper limit                             | 2.157                       |

Notes:

[3] - Significance at 0.05.

Factors for treatment group and randomization strata (age and OCS dose); baseline OCS dose and duration of OCS use prior to study were covariates.

### Secondary: Percentage of Participants Achieving a $\geq 50\%$ Reduction in OCS dose at Weeks 20-24 Compared to Baseline While Maintaining Asthma Control

|                 |                                                                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants Achieving a $\geq 50\%$ Reduction in OCS dose at Weeks 20-24 Compared to Baseline While Maintaining Asthma Control |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Percentage of patients whose OCS dose at weeks 20-24 was reduced  $\geq 50\%$  compared to baseline while maintaining asthma control.

Patients listed as "no" did not achieve the 50% reduction in baseline OCS dose goal, or did achieve that goal but lost asthma control during weeks 20 to 24, or discontinued from study drug.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Weeks 20-24

| End point values                  | Placebo           | Reslizumab 110 mg |  |  |
|-----------------------------------|-------------------|-------------------|--|--|
| Subject group type                | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed       | 89 <sup>[4]</sup> | 88 <sup>[5]</sup> |  |  |
| Units: percentage of participants |                   |                   |  |  |
| number (not applicable)           |                   |                   |  |  |
| Yes                               | 36                | 44                |  |  |
| No                                | 64                | 56                |  |  |

Notes:

[4] - ITT

[5] - ITT

### Statistical analyses

|                            |                                               |
|----------------------------|-----------------------------------------------|
| Statistical analysis title | OCS Dose Reduction: $\geq 50\%$ from Baseline |
|----------------------------|-----------------------------------------------|

Statistical analysis description:

As the analysis of the primary efficacy endpoint did not meet criteria for statistical significance ( $p \leq 0.05$ ), the secondary efficacy endpoints were not interpreted inferentially according to the pre-defined hierarchy. P-values are nominal, meaning they were obtained from the analysis without adjustments to protect family-wise errors and should be interpreted with caution. Nominal p-values do not indicate treatment differences.

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Comparison groups                       | Placebo v Reslizumab 110 mg |
| Number of subjects included in analysis | 177                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| P-value                                 | = 0.596 <sup>[6]</sup>      |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 1.45                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.786                       |
| upper limit                             | 2.683                       |

Notes:

[6] - Significance of 0.05. Logistic regression model adjusted for treatment, stratification factors (age group and OCS dose group), duration of OCS use, and baseline value.

### Secondary: Percentage of Participants Achieving an OCS dose of ≤5 mg at Weeks 20-24 While Maintaining Asthma Control

|                 |                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants Achieving an OCS dose of ≤5 mg at Weeks 20-24 While Maintaining Asthma Control |
|-----------------|-----------------------------------------------------------------------------------------------------------|

End point description:

Percentage of participants whose OCS dose at weeks 20-24 was ≤5 mg and they maintained asthma control.

Patients listed as "no" had a week 20-24 OCS dose > 5 mg, or whose OCS dose was ≤5 mg at weeks 20-24 but did not maintain asthma control, or they discontinued from study drug.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 20 - 24

| End point values                  | Placebo           | Reslizumab 110 mg |  |  |
|-----------------------------------|-------------------|-------------------|--|--|
| Subject group type                | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed       | 89 <sup>[7]</sup> | 88 <sup>[8]</sup> |  |  |
| Units: percentage of participants |                   |                   |  |  |
| number (not applicable)           |                   |                   |  |  |
| YES                               | 38                | 42                |  |  |
| NO                                | 62                | 58                |  |  |

Notes:

[7] - ITT

[8] - ITT

### Statistical analyses

|                            |                |
|----------------------------|----------------|
| Statistical analysis title | OCS Dose ≤5 mg |
|----------------------------|----------------|

Statistical analysis description:

As the analysis of the primary efficacy endpoint did not meet criteria for statistical significance ( $p \leq 0.05$ ), the secondary efficacy endpoints were not interpreted inferentially according to the pre-defined hierarchy. P-values are nominal, meaning they were obtained from the analysis without adjustments to protect family-wise errors and should be interpreted with caution. Nominal p-values do not indicate treatment differences.

|                   |                             |
|-------------------|-----------------------------|
| Comparison groups | Placebo v Reslizumab 110 mg |
|-------------------|-----------------------------|

|                                         |                        |
|-----------------------------------------|------------------------|
| Number of subjects included in analysis | 177                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.596 <sup>[9]</sup> |
| Method                                  | Regression, Logistic   |
| Parameter estimate                      | Odds ratio (OR)        |
| Point estimate                          | 1.19                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 0.631                  |
| upper limit                             | 2.229                  |

Notes:

[9] - Significance of 0.05. Logistic regression model adjusted for treatment, stratification factors (age group and OCS dose group), duration of OCS use, and baseline value.

### Secondary: Percentage of Participants Achieving an OCS dose of 0 mg at Weeks 20-24 While Maintaining Asthma Control

|                        |                                                                                                                                                                                                                                                                                                     |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Percentage of Participants Achieving an OCS dose of 0 mg at Weeks 20-24 While Maintaining Asthma Control                                                                                                                                                                                            |
| End point description: | Percentage of participants who discontinue use of OCS during weeks 20-24 while maintaining asthma control.<br>Patients listed as "no" continued to use OCS during weeks 20-24, or who discontinued use of OCS during weeks 20-24 but lost control of their asthma, or discontinued from study drug. |
| End point type         | Secondary                                                                                                                                                                                                                                                                                           |
| End point timeframe:   | Weeks 24-26                                                                                                                                                                                                                                                                                         |

| End point values                  | Placebo            | Reslizumab 110 mg  |  |  |
|-----------------------------------|--------------------|--------------------|--|--|
| Subject group type                | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed       | 89 <sup>[10]</sup> | 88 <sup>[11]</sup> |  |  |
| Units: percentage of participants |                    |                    |  |  |
| number (not applicable)           |                    |                    |  |  |
| YES                               | 22                 | 20                 |  |  |
| NO                                | 78                 | 80                 |  |  |

Notes:

[10] - ITT

[11] - ITT

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Achieving a $\geq 5$ mg Reduction in OCS dose at Weeks 20-24 Compared to Baseline While Maintaining Asthma Control

|                 |                                                                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants Achieving a $\geq 5$ mg Reduction in OCS dose at Weeks 20-24 Compared to Baseline While Maintaining Asthma Control |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Percentage of participants whose OCS dose at weeks 20-24 was reduced by at least 5mg from baseline and maintained asthma control. Patients listed as "no" had a week 20-24 OCS dose that did not meet the threshold of a 5mg reduction, or whose OCS dose met the threshold but did not maintain asthma control, or discontinued from study drug.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 20-24

| End point values                  | Placebo            | Reslizumab<br>110 mg |  |  |
|-----------------------------------|--------------------|----------------------|--|--|
| Subject group type                | Reporting group    | Reporting group      |  |  |
| Number of subjects analysed       | 89 <sup>[12]</sup> | 88 <sup>[13]</sup>   |  |  |
| Units: percentage of participants |                    |                      |  |  |
| number (not applicable)           |                    |                      |  |  |
| YES                               | 35                 | 41                   |  |  |
| NO                                | 65                 | 59                   |  |  |

Notes:

[12] - ITT

[13] - ITT

## Statistical analyses

|                            |                                |
|----------------------------|--------------------------------|
| Statistical analysis title | >=5 mg Reduction From Baseline |
|----------------------------|--------------------------------|

Statistical analysis description:

As the analysis of the primary efficacy endpoint did not meet criteria for statistical significance ( $p \leq 0.05$ ), the secondary efficacy endpoints were not interpreted inferentially according to the pre-defined hierarchy. P-values are nominal, meaning they were obtained from the analysis without adjustments to protect family-wise errors and should be interpreted with caution. Nominal p-values do not indicate treatment differences.

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Comparison groups                       | Placebo v Reslizumab 110 mg |
| Number of subjects included in analysis | 177                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| P-value                                 | = 0.341 <sup>[14]</sup>     |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 1.36                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.722                       |
| upper limit                             | 2.562                       |

Notes:

[14] - Significance at 0.05.

Logistic regression model adjusted for treatment, stratification factors (age group and OCS dose group), duration of OCS use, and baseline value.

## Secondary: Annualized Rate of Clinical Asthma Exacerbations (CAEs)

|                 |                                                         |
|-----------------|---------------------------------------------------------|
| End point title | Annualized Rate of Clinical Asthma Exacerbations (CAEs) |
|-----------------|---------------------------------------------------------|

End point description:

The annual exacerbation rate is based on clinical asthma exacerbations reported by the investigator in the eCRF.

|                       |           |
|-----------------------|-----------|
| End point type        | Secondary |
| End point timeframe:  |           |
| Day 1 through Week 24 |           |

| End point values                 | Placebo               | Reslizumab 110 mg     |  |  |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type               | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed      | 89 <sup>[15]</sup>    | 88 <sup>[16]</sup>    |  |  |
| Units: CAEs / year               |                       |                       |  |  |
| number (confidence interval 95%) | 1.86 (1.283 to 2.682) | 1.51 (1.052 to 2.177) |  |  |

Notes:

[15] - ITT

[16] - ITT

### Statistical analyses

| Statistical analysis title              | Adjusted CAE Rate                  |
|-----------------------------------------|------------------------------------|
| Comparison groups                       | Placebo v Reslizumab 110 mg        |
| Number of subjects included in analysis | 177                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | superiority                        |
| P-value                                 | = 0.407 <sup>[17]</sup>            |
| Method                                  | Negative binomial regression model |
| Parameter estimate                      | CAE rate ratio                     |
| Point estimate                          | 0.82                               |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | 0.504                              |
| upper limit                             | 1.321                              |

Notes:

[17] - significance at 0.05.

Negative binomial regression model adjusted for stratification factors (OCS dose group), age, number of prior exacerbations, and an offset variable.

### Secondary: Participants with Treatment-Emergent Anti-Drug Antibody (ADA) Responses

|                 |                                                                         |
|-----------------|-------------------------------------------------------------------------|
| End point title | Participants with Treatment-Emergent Anti-Drug Antibody (ADA) Responses |
|-----------------|-------------------------------------------------------------------------|

End point description:

Treatment-emergent responses were defined as a positive sample post-baseline (negative baseline) OR a titer increase of  $\geq 4$ -fold relative to a positive baseline sample.

Two types of antibody assay were performed, an immunogenicity status assay (ADA) and neutralizing assay (NAb).

The ADA assay produces a positive or negative result. For samples with a positive result, a neutralizing assay was performed, which also produces a positive or negative result.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

before the administration of study drug at baseline (Day 1), weeks 4, 8, 12, 24 or early withdrawal.

| End point values            | Placebo            | Reslizumab<br>110 mg |  |  |
|-----------------------------|--------------------|----------------------|--|--|
| Subject group type          | Reporting group    | Reporting group      |  |  |
| Number of subjects analysed | 89 <sup>[18]</sup> | 88 <sup>[19]</sup>   |  |  |
| Units: participants         |                    |                      |  |  |
| Positive ADA samples        | 0                  | 11                   |  |  |
| Positive Nab samples        | 0                  | 0                    |  |  |

Notes:

[18] - ITT

[19] - ITT

## Statistical analyses

No statistical analyses for this end point

## 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. 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.

Treatment-related adverse events or adverse events related to OCS use included events with missing relationship to study drug or OCS use, respectively.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 up to Week 24 (end of treatment visit); Data were included between Day 1 and Week 24 for completed patients, and Day 1 and 4 weeks after the last dose of study drug for patients who discontinued treatment early.

| End point values                        | Placebo            | Reslizumab<br>110 mg |  |  |
|-----------------------------------------|--------------------|----------------------|--|--|
| Subject group type                      | Reporting group    | Reporting group      |  |  |
| Number of subjects analysed             | 89 <sup>[20]</sup> | 88 <sup>[21]</sup>   |  |  |
| Units: participants                     |                    |                      |  |  |
| Any treatment-emergent AE               | 47                 | 57                   |  |  |
| Treatment-related AE                    | 3                  | 7                    |  |  |
| Serious AE (SAE)                        | 4                  | 10                   |  |  |
| Treatment-related SAE                   | 0                  | 0                    |  |  |
| SAE resulting in death                  | 0                  | 1                    |  |  |
| AE leading to treatment discontinuation | 1                  | 0                    |  |  |
| AE related to OCS withdrawal            | 2                  | 3                    |  |  |
| AE related to OCS use                   | 2                  | 5                    |  |  |

Notes:

[20] - Safety analysis set

[21] - Safety analysis set

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change from Baseline in Daily Oral Corticosteroid (OCS) Dose During Weeks 20-24 Using a Mixed Model for Repeated Measures

|                 |                                                                                                                                   |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percent Change from Baseline in Daily Oral Corticosteroid (OCS) Dose During Weeks 20-24 Using a Mixed Model for Repeated Measures |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------|

End point description:

The baseline OCS dose is the prescribed optimized OCS dose following the OCS optimization period. Endpoint data are presented using an on-treatment approach. In this context, 'endpoint' was defined as the last observation obtained at a scheduled or qualified early termination visit during the treatment period. Weeks 20-24 data is included between the Week 20 dose and Week 24 for completed patients; last dose of study drug to 4 weeks after the last dose of study drug for patients who discontinued treatment early. Measurements collected outside of these defined timeframes are excluded from the analyses.

The mixed model repeated measures (MMRM) included fixed effects for treatment, visit, treatment by visit interaction, age group, and OCS dose group, duration of OCS use and baseline value as covariates, and patient as a random effect. Unstructured covariance was assumed for the repeated measures.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Weeks 20-24

| End point values                    | Placebo            | Reslizumab 110 mg  |  |  |
|-------------------------------------|--------------------|--------------------|--|--|
| Subject group type                  | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed         | 83 <sup>[22]</sup> | 84 <sup>[23]</sup> |  |  |
| Units: percent change from baseline |                    |                    |  |  |
| least squares mean (standard error) | -40.34 (± 17.318)  | -58.08 (± 17.633)  |  |  |

Notes:

[22] - ITT analysis population with available data using the on-treatment approach.

[23] - ITT analysis population with available data using the on-treatment approach.

## Statistical analyses

|                            |              |
|----------------------------|--------------|
| Statistical analysis title | % Change OCS |
|----------------------------|--------------|

Statistical analysis description:

Mixed model repeated measures (MMRM) with fixed effects for treatment, visit, treatment by visit interaction, age group, and OCS dose group, duration of OCS use and baseline value as covariates, and patient as a random effect. Unstructured covariance was assumed for the repeated measures.

|                   |                             |
|-------------------|-----------------------------|
| Comparison groups | Reslizumab 110 mg v Placebo |
|-------------------|-----------------------------|

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| Number of subjects included in analysis | 167                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.101                           |
| Method                                  | mixed model for repeated measures |
| Parameter estimate                      | Mean difference (final values)    |
| Point estimate                          | -17.75                            |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -38.986                           |
| upper limit                             | 3.494                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 10.759                            |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 to Week 24

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Matching placebo was administered by subcutaneous injection (sc) 1.0 mL every 4 weeks for a total of six doses.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Reslizumab 110 mg |
|-----------------------|-------------------|

Reporting group description:

Reslizumab was administered by subcutaneous injection (sc) in a dosage of 110 mg (1.0 mL) every 4 weeks for a total of six doses.

| Serious adverse events                            | Placebo        | Reslizumab 110 mg |  |
|---------------------------------------------------|----------------|-------------------|--|
| Total subjects affected by serious adverse events |                |                   |  |
| subjects affected / exposed                       | 4 / 89 (4.49%) | 10 / 88 (11.36%)  |  |
| number of deaths (all causes)                     | 0              | 1                 |  |
| number of deaths resulting from adverse events    |                |                   |  |
| Injury, poisoning and procedural complications    |                |                   |  |
| Rib fracture                                      |                |                   |  |
| subjects affected / exposed                       | 1 / 89 (1.12%) | 0 / 88 (0.00%)    |  |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0             |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0             |  |
| Head injury                                       |                |                   |  |
| subjects affected / exposed                       | 1 / 89 (1.12%) | 0 / 88 (0.00%)    |  |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0             |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0             |  |
| Foot fracture                                     |                |                   |  |
| subjects affected / exposed                       | 1 / 89 (1.12%) | 0 / 88 (0.00%)    |  |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0             |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0             |  |
| Fibula fracture                                   |                |                   |  |

|                                                      |                |                |  |
|------------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                          | 1 / 89 (1.12%) | 0 / 88 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Facial bones fracture                                |                |                |  |
| subjects affected / exposed                          | 1 / 89 (1.12%) | 0 / 88 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Contusion                                            |                |                |  |
| subjects affected / exposed                          | 1 / 89 (1.12%) | 0 / 88 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                             |                |                |  |
| Syncope                                              |                |                |  |
| subjects affected / exposed                          | 0 / 89 (0.00%) | 1 / 88 (1.14%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General disorders and administration site conditions |                |                |  |
| Sudden death                                         |                |                |  |
| subjects affected / exposed                          | 0 / 89 (0.00%) | 1 / 88 (1.14%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 1          |  |
| Immune system disorders                              |                |                |  |
| Drug hypersensitivity                                |                |                |  |
| subjects affected / exposed                          | 0 / 89 (0.00%) | 1 / 88 (1.14%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                           |                |                |  |
| Inguinal hernia                                      |                |                |  |
| subjects affected / exposed                          | 0 / 89 (0.00%) | 1 / 88 (1.14%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders      |                |                |  |
| Asthma                                               |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 2 / 89 (2.25%) | 3 / 88 (3.41%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Infections and infestations</b>              |                |                |  |
| Pneumonia bacterial                             |                |                |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 88 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Influenza                                       |                |                |  |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 1 / 88 (1.14%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cellulitis                                      |                |                |  |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 1 / 88 (1.14%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia                                       |                |                |  |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 1 / 88 (1.14%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                            | Placebo          | Reslizumab 110 mg |  |
|--------------------------------------------------------------|------------------|-------------------|--|
| <b>Total subjects affected by non-serious adverse events</b> |                  |                   |  |
| subjects affected / exposed                                  | 20 / 89 (22.47%) | 20 / 88 (22.73%)  |  |
| <b>Vascular disorders</b>                                    |                  |                   |  |
| Hypertension                                                 |                  |                   |  |
| subjects affected / exposed                                  | 5 / 89 (5.62%)   | 1 / 88 (1.14%)    |  |
| occurrences (all)                                            | 5                | 1                 |  |
| <b>Respiratory, thoracic and mediastinal disorders</b>       |                  |                   |  |
| Asthma                                                       |                  |                   |  |
| subjects affected / exposed                                  | 4 / 89 (4.49%)   | 5 / 88 (5.68%)    |  |
| occurrences (all)                                            | 6                | 6                 |  |
| <b>Infections and infestations</b>                           |                  |                   |  |

|                                                                                             |                     |                        |  |
|---------------------------------------------------------------------------------------------|---------------------|------------------------|--|
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 5 / 89 (5.62%)<br>5 | 11 / 88 (12.50%)<br>13 |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                              | 4 / 89 (4.49%)<br>4 | 6 / 88 (6.82%)<br>6    |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)       | 5 / 89 (5.62%)<br>5 | 1 / 88 (1.14%)<br>1    |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 27 January 2016 | <p>Amendment 1 to the protocol was issued after 2 patients had been enrolled in the study under the original protocol.</p> <ul style="list-style-type: none"><li>• The wording for adverse drug reactions, malignancy risk, pregnancy, immunogenicity, and risks of reslizumab was updated based on the most recent data.</li><li>• The population to be studied was updated to clarify the exclusion of pediatric patients in the Netherlands.</li><li>• Other pre-specified efficacy endpoints were updated to accommodate inhaled rescue medications other than SABA.</li><li>• The number of nighttime awakenings due to asthma was updated to make this endpoint more general.</li><li>• Other pre-specified efficacy measures and time points were revised to clarify that the asthma control diary will measure asthma symptoms, reliever bronchodilator inhalation use, and nighttime awakenings due to asthma on a daily basis.</li><li>• The table of study procedures and assessments was updated for clarity.</li><li>• Time of study drug administration was updated because the exact hour is not critical; the study drug is an anti inflammatory drug with a long half-life.</li><li>• Procedures/assessments to be performed during and after administration of study drug were updated to capture events that occurred during or after study drug administration.</li><li>• Inclusion criteria were updated to encompass the medium (and higher) daily dose range for a given ICS formulation.</li><li>• Section 4.5.1 (Discontinuation of Study Treatment) and Section 4.5.2 (Complete Withdrawal from Study) were inserted to clarify discontinuation of study treatment and complete withdrawal from the study.</li><li>• Section 7.1.7.3.1 (Anaphylaxis/Hypersensitivity Reactions CRF) and Section 7.1.7.3.2 (Creatine Phosphokinase/Muscular Adverse Events CRF) were added to address the reporting of anaphylaxis/hypersensitivity and muscular adverse events, respectively.</li><li>• An additional blood sample collection to measure serum reslizumab concentrations was added for patients who experienced a serious adverse event... others.....</li></ul> |

|              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 18 July 2016 | <p>Amendment 2 to the protocol was issued after 44 patients had been enrolled in the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled in the study.</p> <ul style="list-style-type: none"> <li>• The text for OCS medication in run-in period and eligibility criteria with respect to asthma control was revised.</li> <li>• Information regarding the natural rubber component of the prefilled syringe was added for transparency.</li> <li>• Stopping rules and discontinuation criteria were revised with regard to pregnancy, specifying that the administration of study drug should be discontinued, but the patient does not need to be withdrawn from the study for being pregnant.</li> <li>• Additional language was added to describe reasons for patient withdrawal.</li> <li>• Time points for CPK assessments were added at weeks 4, 8, 16, and 20 to address requests from the Health Authorities.</li> <li>• The inclusion criteria were revised to encompass the medium (and higher) daily dose range for a given ICS formulation (as per GINA 2015).</li> <li>• The schedule of assessments was updated.</li> <li>• Total blood volume was increased to account for additional CPK draws.</li> <li>• Text was added for the reporting of the disease under study as an adverse event.</li> <li>• Serious adverse event definition was updated for alignment between protocol language, adverse event reporting instructions, and processes.</li> <li>• A list of opportunistic infections was included in the protocol to aid in the accurate reporting of potential opportunistic infection adverse events.</li> <li>• Text for CPK/muscular adverse events CSR was updated per request of Health Authority and for overall clarity.</li> <li>• Immunogenicity analysis was updated to accommodate baseline ADA testing in previous placebo patients.</li> <li>• Appendix I (Opportunistic Infections) was added per request of Health Authority</li> </ul> |
|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported