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
Arm title	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.

Arm title	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-filledsyringes.

Number of subjects in period 1	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^2			
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[1]	88[2]		
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 [3]
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 >=50% Reduction in OCS dose at Weeks 20-24 Compared to Baseline While Maintaining Asthma Control

End point title	Percentage of Participants Achieving a >=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 >=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[4]	88[5]		
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: >=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 [6]
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 Contro

End point title	Percentage of Participants Achieving an OCS dose of <=5 mg at Weeks 20-24 While Maintaining Asthma Contro

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[7]	88[8]		
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≤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 [9]
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.
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[10]	88[11]		
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 >=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 >=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 110 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89[12]	88[13]		
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 [14]
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[15]	88[16]		
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 [17]
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 >=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 110 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89[18]	88[19]		
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 110 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89[20]	88[21]		
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[22]	84[23]		
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	
Infections and infestations			
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 %

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2016	Amendment 1 to the protocol was issued after 2 patients had been enrolled in the study under the original protocol. • The wording for adverse drug reactions, malignancy risk, pregnancy, immunogenicity, and risks of reslizumab was updated based on the most recent data. • The population to be studied was updated to clarify the exclusion of pediatric patients in the Netherlands. • Other pre-specified efficacy endpoints were updated to accommodate inhaled rescue medications other than SABA. • The number of nighttime awakenings due to asthma was updated to make this endpoint more general. • 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. • The table of study procedures and assessments was updated for clarity. • 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. • 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. • Inclusion criteria were updated to encompass the medium (and higher) daily dose range for a given ICS formulation. • 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. • 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. • An additional blood sample collection to measure serum reslizumab concentrations was added for patients who experienced a serious adverse event... others.....

18 July 2016	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. • The text for OCS medication in run-in period and eligibility criteria with respect to asthma control was revised. • Information regarding the natural rubber component of the prefilled syringe was added for transparency. • 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. • Additional language was added to describe reasons for patient withdrawal. • Time points for CPK assessments were added at weeks 4, 8, 16, and 20 to address requests from the Health Authorities. • The inclusion criteria were revised to encompass the medium (and higher) daily dose range for a given ICS formulation (as per GINA 2015). • The schedule of assessments was updated. • Total blood volume was increased to account for additional CPK draws. • Text was added for the reporting of the disease under study as an adverse event. • Serious adverse event definition was updated for alignment between protocol language, adverse event reporting instructions, and processes. • A list of opportunistic infections was included in the protocol to aid in the accurate reporting of potential opportunistic infection adverse events. • Text for CPK/muscular adverse events CSR was updated per request of Health Authority and for overall clarity. • Immunogenicity analysis was updated to accommodate baseline ADA testing in previous placebo patients. • Appendix I (Opportunistic Infections) was added per request of Health Authority

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported