

**Clinical trial results:****A Multicentre, Randomized, Double-blind, Parallel Group, Placebo Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Tralokinumab in Reducing Oral Corticosteroid Use in Adults and Adolescents with Oral Corticosteroid dependent Asthma (TROPOS)
Summary**

EudraCT number	2014-001391-54
Trial protocol	DE NL BE FR PL
Global end of trial date	07 September 2017

Results information

Result version number	v1 (current)
This version publication date	15 March 2018
First version publication date	15 March 2018

Trial information**Trial identification**

Sponsor protocol code	D2210C00013
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02281357
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	200 Orchard Ridge Drive, Gaithersburg, United States, MD 20878
Public contact	Global Clinical Lead, AstraZeneca, 1 3013980582, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, 1 3013980582, ClinicalTrialTransparency@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000782-PIP01-09
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	07 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 September 2017
Global end of trial reached?	Yes
Global end of trial date	07 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of tralokinumab compared to placebo in reducing the prescribed oral corticosteroid (OCS) maintenance dose in adult and adolescent patients in the primary population with asthma requiring chronic treatment with maintenance OCS in addition to inhaled corticosteroid (ICS) plus long-acting β 2-agonists (LABA).

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council on Harmonisation / Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy:

Patients were maintained on their currently prescribed ICS-LABA therapy and any additional maintenance asthma controller medications throughout the study period.

Evidence for comparator: -

Actual start date of recruitment	19 February 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 42
Country: Number of subjects enrolled	Ukraine: 24
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	United States: 19
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Belgium: 4
Worldwide total number of subjects	140
EEA total number of subjects	97

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)	113
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient enrolled: 19 February 2015; Last patient last visit: 07 September 2017. Study performed at 56 sites in 7 countries.

Pre-assignment

Screening details:

218 patients signed informed consent. 140 patients were randomised and all those randomised received study treatment. Prior to randomisation, patients completed a run-in period or run-in/OCS optimisation period (reached minimum effective dose of OCS and remained stable on that dose for 2 weeks). Primary population was the full analysis set (FAS).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Tralokinumab

Arm description:

Tralokinumab 300 milligrams (mg) administered by subcutaneous (SC) injection every two weeks (Q2W) over a 40-week treatment period.

Arm type	Experimental
Investigational medicinal product name	Tralokinumab
Investigational medicinal product code	CAT-354
Other name	Tralo
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

150 milligrams/millilitre (mg/mL) solution for injection in an accessorised pre-filled syringe, 1.0 mL fill volume. Each patient received 2 SC injections of 150 mg tralokinumab at each dosing interval to receive a total dose of 300 mg.

Arm title	Placebo
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Arm description:

Placebo was administered by SC injection over a 40-week treatment period.

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 solution for injection in an accessorised pre-filled syringe, 1.0 mL fill volume. Each patient received 2 SC injections of placebo at each dosing interval.

Number of subjects in period 1	Tralokinumab	Placebo
Started	70	70
Completed	63	66
Not completed	7	4
Consent withdrawn by subject	4	3
Adverse event, non-fatal	2	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Tralokinumab
Reporting group description: Tralokinumab 300 milligrams (mg) administered by subcutaneous (SC) injection every two weeks (Q2W) over a 40-week treatment period.	
Reporting group title	Placebo
Reporting group description: Placebo was administered by SC injection over a 40-week treatment period.	

Reporting group values	Tralokinumab	Placebo	Total
Number of subjects	70	70	140
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	1	0	1
Adults (18-64 years)	58	55	113
From 65-84 years	11	15	26
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	54.0	55.4	-
standard deviation	± 11.05	± 10.26	-
Sex: Female, Male Units: Subjects			
Female	48	39	87
Male	22	31	53
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	5	7
White	66	63	129
More than one race	0	0	0
Unknown or Not Reported	1	2	3

End points

End points reporting groups

Reporting group title	Tralokinumab
Reporting group description: Tralokinumab 300 milligrams (mg) administered by subcutaneous (SC) injection every two weeks (Q2W) over a 40-week treatment period.	
Reporting group title	Placebo
Reporting group description: Placebo was administered by SC injection over a 40-week treatment period.	

Primary: Percent change from baseline in the final daily, average, OCS dose at Week 40 while not losing asthma control.

End point title	Percent change from baseline in the final daily, average, OCS dose at Week 40 while not losing asthma control.
End point description: The 40-week treatment period consisted of 3 phases: an induction phase (Week 0 to Week 12) where patients remained on their optimised OCS dose; an OCS reduction phase (Week 12 to Week 32) where OCS dose reduction could have started at Week 12 with the possibility of dose titration every 4 weeks to reach the lowest possible OCS dose; and a maintenance phase (Week 32 to Week 40) where patients remained on the OCS dose reached at Week 32 to demonstrate asthma control was maintained after achieving the lowest OCS dose. The least squares (LS) mean percent change from baseline in average daily OCS dose is presented for the FAS, comprising all randomised patients who received at least one dose of study treatment. The average OCS dose was defined as $\{(Final\ daily\ average\ dose - baseline\ daily\ average\ dose)/baseline\ daily\ average\ dose\} * 100\%$.	
End point type	Primary
End point timeframe: Baseline (Week 0) and Week 40	

End point values	Tralokinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	70		
Units: Percent change from baseline				
least squares mean (standard error)	-37.62 (\pm 4.98)	-29.85 (\pm 4.98)		

Statistical analyses

Statistical analysis title	Percent change from baseline in OCS dose
Statistical analysis description: Tralokinumab vs placebo.	
Comparison groups	Tralokinumab v Placebo

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.271
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-7.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.7
upper limit	6.15

Secondary: The number of patients with final daily average OCS dose ≤ 5 mg at Week 40.

End point title	The number of patients with final daily average OCS dose ≤ 5 mg at Week 40.
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End point description:

The 40-week treatment period consisted of 3 phases: an induction phase (Week 0 to Week 12) where patients remained on their optimised OCS dose; an OCS reduction phase (Week 12 to Week 32) where OCS dose reduction could have started at Week 12 with the possibility of dose titration every 4 weeks to reach the lowest possible OCS dose; and a maintenance phase (Week 32 to Week 40) where patients remained on the OCS dose reached at Week 32 to demonstrate asthma control was maintained after achieving the lowest OCS dose. The number of patients with a final daily average OCS dose ≤ 5.0 mg is presented for the FAS, comprising all randomised patients who received at least one dose of study treatment. The average OCS dose was defined as $\{(\text{Final daily average dose} - \text{baseline daily average dose})/\text{baseline daily average dose}\} \times 100\%$.

End point type	Secondary
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End point timeframe:

At Week 40

End point values	Tralokinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	70		
Units: Participants	32	28		

Statistical analyses

Statistical analysis title	Number of patients with OCS dose ≤ 5 mg
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Statistical analysis description:

Tralokinumab vs placebo.

Comparison groups	Tralokinumab v Placebo
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Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.442
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	2.73

Secondary: The number of patients with $\geq 50\%$ reduction in final average daily OCS dose at Week 40.

End point title	The number of patients with $\geq 50\%$ reduction in final average daily OCS dose at Week 40.
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End point description:

The 40-week treatment period consisted of 3 phases: an induction phase (Week 0 to Week 12) where patients remained on their optimised OCS dose; an OCS reduction phase (Week 12 to Week 32) where OCS dose reduction could have started at Week 12 with the possibility of dose titration every 4 weeks to reach the lowest possible OCS dose; and a maintenance phase (Week 32 to Week 40) where patients remained on the OCS dose reached at Week 32 to demonstrate asthma control was maintained after achieving the lowest OCS dose. The number of patients with $\geq 50\%$ reduction in average daily OCS dose is presented for the FAS, comprising all randomised patients who received at least one dose of study treatment. The average OCS dose was defined as $\{(\text{Final daily average dose} - \text{baseline daily average dose}) / \text{baseline daily average dose} \} * 100\%$. If this resulted in a value of -50% or less (more negative), that patient was classified as having at least a 50% reduction in final daily average OCS dose.

End point type	Secondary
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End point timeframe:

At Week 40

End point values	Tralokinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	70		
Units: Participants	31	26		

Statistical analyses

Statistical analysis title	Number of patients with $\geq 50\%$ reduction in OCS dose
Statistical analysis description:	
Tralokinumab vs placebo.	
Comparison groups	Tralokinumab v Placebo

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.356
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2.74

Secondary: Annual asthma exacerbation rate (AAER) up to Week 40.

End point title	Annual asthma exacerbation rate (AAER) up to Week 40.
End point description:	
<p>Asthma exacerbation was defined as a worsening of asthma that led to any of the following: • Use of systemic corticosteroids for at least 3 days; a single depo-injectable dose of corticosteroids was considered equivalent to a 3-day course of systemic corticosteroids. • An emergency room (ER) or urgent care (UC) visit (defined as evaluation and treatment for <24 hours in an ER or UC centre) due to asthma that required systemic corticosteroids (see above). • An inpatient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma. AAER = number of exacerbations*365.25 / (follow-up date - date of randomisation + 1) (where maximum follow-up for a patient was 40 weeks). AAER in tralokinumab group was compared with AAER in placebo group up to Week 40 using a negative binomial model. AAER is presented for the FAS, comprising all randomised patients who received at least one dose of study treatment.</p>	
End point type	Secondary
End point timeframe:	
Baseline (Week 0) up to Week 40	

End point values	Tralokinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	70		
Units: Events/year				
number (confidence interval 95%)	1.84 (1.43 to 2.36)	2.31 (1.83 to 2.92)		

Statistical analyses

Statistical analysis title	AAER
Statistical analysis description:	
Tralokinumab vs placebo.	
Comparison groups	Tralokinumab v Placebo

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.186
Method	Negative binomial
Parameter estimate	Rate Ratio
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.12

Adverse events

Adverse events information

Timeframe for reporting adverse events:

40 weeks.

Adverse event reporting additional description:

Data is reported for adverse events with an onset date \geq the first day of study treatment and \leq (the last day of study treatment + 2 weeks). Patient population was the safety analysis set which included all patients who received at least one dose of study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo was administered by SC injection over a 40-week treatment period.

Reporting group title	Tralo 300 mg Q2W
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Reporting group description:

Tralokinumab 300 mg administered by SC injection Q2W over a 40-week treatment period.

Serious adverse events	Placebo	Tralo 300 mg Q2W	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 70 (22.86%)	9 / 70 (12.86%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Pulmonary function test abnormal			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer female			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Uterine leiomyoma			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal prolapse			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	8 / 70 (11.43%)	5 / 70 (7.14%)	
occurrences causally related to treatment / all	0 / 12	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Rotator cuff syndrome			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 70 (1.43%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Tralo 300 mg Q2W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 70 (62.86%)	55 / 70 (78.57%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 70 (2.86%)	4 / 70 (5.71%)	
occurrences (all)	2	4	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 70 (15.71%)	14 / 70 (20.00%)	
occurrences (all)	15	33	

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 70 (7.14%)	3 / 70 (4.29%)	
occurrences (all)	6	3	
Injection site erythema			
subjects affected / exposed	0 / 70 (0.00%)	6 / 70 (8.57%)	
occurrences (all)	0	13	
Injection site pain			
subjects affected / exposed	2 / 70 (2.86%)	6 / 70 (8.57%)	
occurrences (all)	2	12	
Injection site pruritus			
subjects affected / exposed	0 / 70 (0.00%)	5 / 70 (7.14%)	
occurrences (all)	0	6	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	9 / 70 (12.86%)	3 / 70 (4.29%)	
occurrences (all)	10	4	
Cough			
subjects affected / exposed	1 / 70 (1.43%)	4 / 70 (5.71%)	
occurrences (all)	1	4	
Dyspnoea			
subjects affected / exposed	2 / 70 (2.86%)	4 / 70 (5.71%)	
occurrences (all)	2	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 70 (8.57%)	2 / 70 (2.86%)	
occurrences (all)	7	3	
Back pain			
subjects affected / exposed	2 / 70 (2.86%)	7 / 70 (10.00%)	
occurrences (all)	2	7	
Infections and infestations			
Bronchitis			
subjects affected / exposed	16 / 70 (22.86%)	11 / 70 (15.71%)	
occurrences (all)	20	12	
Sinusitis			

subjects affected / exposed	4 / 70 (5.71%)	5 / 70 (7.14%)	
occurrences (all)	4	7	
Oral candidiasis			
subjects affected / exposed	4 / 70 (5.71%)	2 / 70 (2.86%)	
occurrences (all)	4	2	
Urinary tract infection			
subjects affected / exposed	4 / 70 (5.71%)	2 / 70 (2.86%)	
occurrences (all)	4	2	
Viral upper respiratory tract infection			
subjects affected / exposed	10 / 70 (14.29%)	25 / 70 (35.71%)	
occurrences (all)	12	33	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2015	<ul style="list-style-type: none">- Text clarified to state that only adult patients (and not adolescent) were to be stratified by the baseline OCS dose.- The OCS dose reduction categories were revised to increase the granularity of the categories. The timing of the OCS dose reduction was also clarified.- The adjudication committee responsibilities were updated to include review of cardiovascular, cerebrovascular and malignancy adverse events occurring after randomisation since patients with severe asthma have been described to suffer from an increased risk of co- morbid illnesses.- Inclusion criteria were revised to clarify that every other day dosing of OCS was allowed and to provide clarification on the administration of theophylline relative to lung function measurements.- Procedures for discontinuation of a patient from study treatment were clarified to allow a patient with an asthma-related event requiring non-invasive ventilation to continue receiving treatment.- The run-in reversibility procedure was clarified.
07 August 2015	<ul style="list-style-type: none">- The OCS dose titration details were revised to clarify that for patients entering the OCS dose optimisation period, dose titration had to begin at Visit 2, and to clarify that the minimum maintenance OCS dose required applied to patients on a dose between 15 to 30 mg/day.
22 February 2016	<ul style="list-style-type: none">- Inclusion criteria were revised to allow patients with a pre-bronchodilator (BD) forced expiratory volume in 1 second (FEV1) <80% (<90% for patients 12 to 17 years of age) of their predicted normal value to be included into the study, and to remove the requirement of a post-BD reversibility in FEV1 being ≥200 mL.- Exclusion criteria were revised to clarify the time restrictions for receipt of any marketed or investigational biologic agents by study patients, and to clarify the time restrictions for receipt of live attenuated vaccines by study patients.
02 August 2017	<ul style="list-style-type: none">- The possible primary populations for this study were clarified, based on the biomarker fractional exhaled nitric oxide concentrations, in light of the results from the pivotal study D2210C00007.- The primary objective was modified to clarify that this objective applies to the primary population.- The secondary objectives regarding the proportion of patients with prescribed OCS maintenance dose ≤5 mg at Week 40 and reduction of at least 50% of prescribed OCS dose at Week 40 were modified to clarify that each objective applies to the primary population.- The reduction of exacerbation rate was elevated from an exploratory objective to a secondary objective.- Removal of the term "at steady-state" regarding the serum trough concentration exploratory outcome variable for clarification purposes.- The Biomarker objective was modified to allow the implementation of the biomarker strategy that is being decided from the pivotal study D2210C00007. Consequently, the sample size rationale was also modified.- The PK analysis set description was updated.- Testing strategy for primary and key secondary variables was revised.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported