Clinical trial results:
A 52-Week, Multicentre, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Tralokinumab in Adults and Adolescents with Asthma Inadequately Controlled on Inhaled Corticosteroid Plus Long-Acting 2-Agonist (STRATOS 1)

Summary

EudraCT number	2013-005614-35
Trial protocol	DE HU PL SK BG BE
Global end of trial date	18 July 2017

Results information

Result version number	v2 (current)
This version publication date	21 June 2018
First version publication date	27 January 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	D2210C00007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02161757
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)	EMEA-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	18 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2017
Global end of trial reached?	Yes
Global end of trial date	18 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of tralokinumab 300 milligrams (mg) administered every 2 weeks compared with placebo on the annualised asthma exacerbation rate (AAER) in adult and adolescent patients with asthma that is inadequately controlled with inhaled corticosteroid (ICS) plus long-acting β2-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 for 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	13 June 2014
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	United States: 281
Country: Number of subjects enrolled	Bulgaria: 170
Country: Number of subjects enrolled	Poland: 166
Country: Number of subjects enrolled	Argentina: 119
Country: Number of subjects enrolled	Peru: 101
Country: Number of subjects enrolled	Ukraine: 80
Country: Number of subjects enrolled	Vietnam: 80
Country: Number of subjects enrolled	Korea, Republic of: 75
Country: Number of subjects enrolled	Hungary: 59
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Colombia: 15
Country: Number of subjects enrolled	Slovakia: 12
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Spain: 3

Worldwide total number of subjects	1202
EEA total number of subjects	451

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)	43
Adults (18-64 years)	963
From 65 to 84 years	196
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient enrolled: 13 Jun 2014; Week 52 cut-off: 28 Feb 2017; Last Patient Last Visit Week 72: 18 Jul 2017. Study performed at 254 sites in 14 countries.
Patients were maintained on currently prescribed inhaled corticosteroid long-acting β2-agonist therapy + any additional maintenance asthma controller medications throughout the study period.

Pre-assignment

Screening details:

2248 patients signed informed consent, 1669 entered screening/run-in period, 1207 patients were randomised to receive treatment with tralokinumab 300 mg, or placebo, every 2 weeks (Q2W) or every 4 weeks (Q4W). Of the 1207 patients randomised, 1202 received investigational product (IP).

Period 1

Period 1 title	Randomised Through Start Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Assessor, Subject

Blinding implementation details:

Neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the patients will be aware of the study treatment received. Since tralokinumab and placebo are visually distinct, investigational product (IP) will be handled by an unblinded IP manager at the site and will be administered by an unblinded investigational site study team member who will not be involved in the management of study patients.

Arms

Are arms mutually exclusive?	Yes
Arm title	Tralo 300 mg Q2W

Arm description:

Tralokinumab 300 mg administered subcutaneously Q2W over a 52-week treatment period (up to 26 doses). Follow-up visits were conducted at Weeks 56 and 72.

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

Arm title	Tralo 300 mg Q4W

Arm description:

Tralokinumab 300 mg administered subcutaneously Q4W over a 52-week treatment period (up to 13 doses). Follow-up visits were conducted at Weeks 56 and 72.

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

Arm title	Placebo

Arm description:

Placebo was administered subcutaneously over a 52-week treatment period. The placebo treatment group is a pooled treatment group (placebo Q2W + placebo Q4W) where the 2 placebo cohorts were given weights proportional to the number of patients in each cohort. Follow-up visits were conducted at Weeks 56 and 72.

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 injections of placebo at each dosing interval.

Number of subjects in period 1	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo
Started	401	406	400
Completed	398	404	400
Not completed	3	2	0
Did not receive treatment	3	2	-

Period 2

Period 2 title	Treatment Through Study Completion
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

Neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the patients will be aware of the study treatment received. Since tralokinumab and placebo are visually distinct, investigational product (IP) will be handled by an unblinded IP manager at the site and will be administered by an unblinded investigational site study team member who will not be involved in the management of study patients.

Arms

Are arms mutually exclusive?	Yes

Arm title	Tralo 300 mg Q2W

Arm description:

Tralokinumab 300 mg administered subcutaneously Q2W over a 52-week treatment period (up to 26 doses).

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

Arm title	Tralo 300 mg Q4W

Arm description:

Tralokinumab 300 mg administered subcutaneously Q4W over a 52-week treatment period (up to 13 doses).

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

Arm title	Placebo

Arm description:

Placebo was administered subcutaneously over a 52-week treatment period. The placebo treatment group is a pooled treatment group (placebo Q2W + placebo Q4W) where the 2 placebo cohorts were given weights proportional to the number of patients in each cohort.

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 injections of placebo at each dosing interval.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 presents data for all patients randomised until the start of treatment and Period 2 presents data for all patients who received study treatment (tralokinumab or placebo). The analysis population for baseline characteristics was the full analysis set, defined as all patients who received at least one dose of IP. Period 2 is therefore the baseline period.

Number of subjects in period 2	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo
Started	398	404	400
Completed treatment for Week 52 cut-off	332 [2]	355 [3]	360 [4]
Completed	341	361	361
Not completed	57	43	39

Adverse event, serious fatal	2	1	1
Consent withdrawn by subject	27	19	20
Adverse event, non-fatal	1	1	-
Unspecified	20	19	12
Lost to follow-up	7	2	4
Protocol deviation	-	1	2

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The Milestone field reports the number of patients who completed treatment up to the Week 52 data cut-off, whereas the Completed field reports the number of patients who completed the study up to Week 72. The results are correctly stated for the Placebo arm that more patients completed the study overall compared to those completing treatment up to Week 52 since the latter also included patients who discontinued treatment but who completed study assessments.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The Milestone field reports the number of patients who completed treatment up to the Week 52 data cut-off, whereas the Completed field reports the number of patients who completed the study up to Week 72. The results are correctly stated for the Tralo 300 mg Q2W arm that more patients completed the study overall compared to those completing treatment up to Week 52 since the latter also included patients who discontinued treatment but who completed study assessments.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The Milestone field reports the number of patients who completed treatment up to the Week 52 data cut-off, whereas the Completed field reports the number of patients who completed the study up to Week 72. The results are correctly stated for the Tralo 300 mg Q4W arm that more patients completed the study overall compared to those completing treatment up to Week 52 since the latter also included patients who discontinued treatment but who completed study assessments.

Baseline characteristics

Reporting groups	
Reporting group title	Tralo 300 mg Q2W
Reporting group description:	
Tralokinumab 300 mg administered subcutaneously Q2W over a 52-week treatment period (up to 26 doses).	
Reporting group title	Tralo 300 mg Q4W
Reporting group description:	
Tralokinumab 300 mg administered subcutaneously Q4W over a 52-week treatment period (up to 13 doses).	
Reporting group title	Placebo
Reporting group description:	
Placebo was administered subcutaneously over a 52-week treatment period. The placebo treatment group is a pooled treatment group (placebo Q2W + placebo Q4W) where the 2 placebo cohorts were given weights proportional to the number of patients in each cohort.	

Reporting group values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo
Number of subjects	398	404	400
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)	14	15	14
Adults (18-64 years)	332	322	309
From 65-84 years	52	67	77
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	49.4	51.1	51.4
standard deviation	± 14.3	± 13.9	± 14.3
Sex: Female, Male Units: Subjects			
Female	252	281	265
Male	146	123	135
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	21	22	25
Asian	53	55	55
Native Hawaiian or Other Pacific Islander	1	0	0
Black or African American	21	16	14
White	285	297	288
More than one race	0	0	0
Unknown or Not Reported	17	14	18

Reporting group values	Total		
Number of subjects	1202		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	43		
Adults (18-64 years)	963		
From 65-84 years	196		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	798		
Male	404		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	68		
Asian	163		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	51		
White	870		
More than one race	0		
Unknown or Not Reported	49		

End points

End points reporting groups

Reporting group title	Tralo 300 mg Q2W
Reporting group description:	
Tralokinumab 300 mg administered subcutaneously Q2W over a 52-week treatment period (up to 26 doses). Follow-up visits were conducted at Weeks 56 and 72.	
Reporting group title	Tralo 300 mg Q4W
Reporting group description:	
Tralokinumab 300 mg administered subcutaneously Q4W over a 52-week treatment period (up to 13 doses). Follow-up visits were conducted at Weeks 56 and 72.	
Reporting group title	Placebo
Reporting group description:	
Placebo was administered subcutaneously over a 52-week treatment period. The placebo treatment group is a pooled treatment group (placebo Q2W + placebo Q4W) where the 2 placebo cohorts were given weights proportional to the number of patients in each cohort. Follow-up visits were conducted at Weeks 56 and 72.	
Reporting group title	Tralo 300 mg Q2W
Reporting group description:	
Tralokinumab 300 mg administered subcutaneously Q2W over a 52-week treatment period (up to 26 doses).	
Reporting group title	Tralo 300 mg Q4W
Reporting group description:	
Tralokinumab 300 mg administered subcutaneously Q4W over a 52-week treatment period (up to 13 doses).	
Reporting group title	Placebo
Reporting group description:	
Placebo was administered subcutaneously over a 52-week treatment period. The placebo treatment group is a pooled treatment group (placebo Q2W + placebo Q4W) where the 2 placebo cohorts were given weights proportional to the number of patients in each cohort.	

Primary: Annualised asthma exacerbation rate (AAER) up to Week 52

End point title	Annualised asthma exacerbation rate (AAER) up to Week 52
End point description:	
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 time for a patient was approximately 52 weeks). AAER in the tralokinumab group was compared to that seen in the placebo group up to Week 52 using a negative binomial model; rate ratios and rate reductions are both presented for comparative statistical analyses.	
End point type	Primary
End point timeframe:	
Baseline (Week 0) up to Week 52	

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	398	404	400	
Units: Events/year				
number (confidence interval 95%)	0.56 (0.46 to 0.67)	0.54 (0.45 to 0.65)	0.60 (0.50 to 0.72)	

Statistical analyses

Statistical analysis title	AAER: rate ratio

Statistical analysis description:

Tralo 300 mg Q2W vs placebo. The null hypothesis was that the exacerbation rate during the 52-week double-blind treatment period on tralokinumab was equal to the corresponding exacerbation rate on placebo.

Comparison groups	Tralo 300 mg Q2W v Placebo
Number of subjects included in analysis	798
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.5859
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.21

Notes:

[1] - Covariates in the model included treatment group, geographical region, age group, periostin group at baseline and number of exacerbations in the year before the study.

Statistical analysis title	AAER: rate ratio

Statistical analysis description:

Tralo 300 mg Q4W vs placebo. The null hypothesis was that the exacerbation rate during the 52-week double-blind treatment period on tralokinumab was equal to the corresponding exacerbation rate on placebo.

Comparison groups	Tralo 300 mg Q4W v Placebo
Number of subjects included in analysis	804
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.4406
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.17

Notes:

[2] - Covariates in the model included treatment group, geographical region, age group, periostin group at baseline and number of exacerbations in the year before the study.

Statistical analysis title	AAER: rate reduction

Statistical analysis description:

Tralo 300 mg Q2W vs placebo. The null hypothesis was that the exacerbation rate during the 52-week double-blind treatment period on tralokinumab was equal to the corresponding exacerbation rate on placebo.

Comparison groups	Tralo 300 mg Q2W v Placebo
Number of subjects included in analysis	798
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.5859
Method	Negative binominal
Parameter estimate	Rate reduction
Point estimate	7.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.76
upper limit	28.39

Notes:

[3] - Covariates in the model included treatment group, geographical region, age group, periostin group at baseline and number of exacerbations in the year before the study.

Statistical analysis title	AAER: rate reduction

Statistical analysis description:

Tralo 300 mg Q4W vs placebo. The null hypothesis was that the exacerbation rate during the 52-week double-blind treatment period on tralokinumab was equal to the corresponding exacerbation rate on placebo.

Comparison groups	Tralo 300 mg Q4W v Placebo
Number of subjects included in analysis	804
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.4406
Method	Negative binominal
Parameter estimate	Rate reduction
Point estimate	9.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.16
upper limit	30.5

Notes:

[4] - Covariates in the model included treatment group, geographical region, age group, periostin group at baseline and number of exacerbations in the year before the study.

Secondary: Percent change from baseline to Week 52 in pre-dose/pre-bronchodilator (BD) forced expiratory volume in 1 second (FEV1)

End point title	Percent change from baseline to Week 52 in pre-dose/pre-bronchodilator (BD) forced expiratory volume in 1 second (FEV1)

End point description:

Lung function was assessed by FEV1 which was measured by spirometry. Spirometry was performed by

the Investigator or authorised delegate according to American Thoracic Society/European Respiratory Society guidelines. The mean percent change from baseline in pre-BD FEV1 at Week 52 is presented. Only patients with data available at the timepoints of testing were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 52

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	357	373	363	
Units: Percent change from baseline				
arithmetic mean (standard deviation)	16.366 (± 27.349)	12.099 (± 26.253)	10.136 (± 24.206)	

Statistical analyses

Statistical analysis title	Percent change from baseline in pre-BD FEV1

Statistical analysis description:

Tralo 300 mg Q2W vs placebo. Restricted maximum likelihood (REML) based repeated measures analysis performed on patients with a baseline pre-dose/pre-BD FEV1 assessment.

Comparison groups	Tralo 300 mg Q2W v Placebo
Number of subjects included in analysis	720
Analysis specification	Pre-specified
Analysis type	superiority[5]
Parameter estimate	Least square (LS) Mean difference
Point estimate	6.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.34
upper limit	9.73

Notes:

[5] - Fixed categorical effects of treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction and number of asthma exacerbations in year before study as a fixed covariate.

Statistical analysis title	Percent change from baseline in pre-BD FEV1

Statistical analysis description:

Tralo 300 mg Q4W vs placebo. REML based repeated measures analysis performed on patients with a baseline pre-dose/pre-BD FEV1 assessment.

Comparison groups	Tralo 300 mg Q4W v Placebo
Number of subjects included in analysis	736
Analysis specification	Pre-specified
Analysis type	superiority[6]
Parameter estimate	LS Mean difference
Point estimate	2.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.58
upper limit	5.77

Notes:

[6] - Fixed categorical effects of treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction and number of asthma exacerbations in year before study as a fixed covariate.

Secondary: Change from baseline to Week 52 in total asthma symptom score (bi-weekly means)

End point title	Change from baseline to Week 52 in total asthma symptom score (bi-weekly means)

End point description:

Asthma symptoms during night-time and daytime were recorded by the patient each morning and evening in the Asthma Daily Diary. Symptoms were recorded using a 4-point response scale, which ranged from 0 to 3, where 0 indicated no asthma symptoms. Asthma symptom daytime score (recorded in the evening), night-time score (recorded in the morning), and total score were calculated separately. The daily asthma symptom total score was calculated by taking the sum of the night-time and daytime asthma symptom scores recorded each day, ranging from 0 to 6. A lower symptom score indicated a better outcome. The change from baseline in bi-weekly mean daily asthma symptom total score is presented. Only patients with data available at the timepoints of testing were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 52

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	313	313	312	
Units: Scores on a scale				
arithmetic mean (standard deviation)	-1.09 (± 1.22)	-1.00 (± 1.11)	-1.03 (± 1.13)	

Statistical analyses

Statistical analysis title	Change from baseline in total asthma symptom score

Statistical analysis description:

Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis.

Comparison groups	Tralo 300 mg Q2W v Placebo
Number of subjects included in analysis	625
Analysis specification	Pre-specified
Analysis type	superiority[7]
Parameter estimate	LS Mean difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.04

Notes:

[7] - Fixed categorical effects of baseline asthma symptom score, treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction and number of asthma exacerbations in year before study as a fixed covariate.

Statistical analysis title	Change from baseline in total asthma symptom score

Statistical analysis description:

Tralo 300 mg Q4W vs placebo. REML based repeated measures analysis.

Comparison groups	Tralo 300 mg Q4W v Placebo
Number of subjects included in analysis	625
Analysis specification	Pre-specified
Analysis type	superiority[8]
Parameter estimate	LS Mean difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.12

Notes:

[8] - Fixed categorical effects of baseline asthma symptom score, treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction and number of asthma exacerbations in year before study as a fixed covariate.

Secondary: Change from baseline to Week 52 in Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ(S)+12) total score

End point title	Change from baseline to Week 52 in Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ(S)+12) total score

End point description:

The AQLQ(S)+12 is a questionnaire that measures health-related quality of life for patients with asthma aged 12 and older. The questionnaire comprises 32 questions and has 4 separate domains (asthma symptoms, activity limitations, emotional function and environmental stimuli). Patients were asked to recall their experiences during the previous 2 weeks and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The total score was calculated as the mean response to all questions, ranging from 1 (severe impairment) to 7 (no impairment). Individual AQLQ(S)+12 total score changes of ≥0.5 were considered to be clinically meaningful. The mean change from baseline in AQLQ(S)+12 score at Week 52 is presented. Only patients with data available at the timepoints of testing were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 52

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	304	321	315	
Units: Scores on a scale				
arithmetic mean (standard deviation)	1.18 (± 1.17)	1.16 (± 1.14)	1.03 (± 1.24)	

Statistical analyses

Statistical analysis title	Change in mean score from baseline for AQLQ(S)+12

Statistical analysis description:

Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis.

Comparison groups	Tralo 300 mg Q2W v Placebo
Number of subjects included in analysis	619
Analysis specification	Pre-specified
Analysis type	superiority[9]
Parameter estimate	LS Mean difference
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.31

Notes:

[9] - Fixed categorical effects of baseline AQLQ(S)+12 score, treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction and number of asthma exacerbations in year before study as a fixed covariate.

Statistical analysis title	Change in mean score from baseline for AQLQ(S)+12

Statistical analysis description:

Tralo 300 mg Q4W vs placebo. REML based repeated measures analysis.

Comparison groups	Tralo 300 mg Q4W v Placebo
Number of subjects included in analysis	636
Analysis specification	Pre-specified
Analysis type	superiority[10]
Parameter estimate	LS Mean difference
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.28

Notes:

[10] - Fixed categorical effects of baseline AQLQ(S)+12 score, treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction and number of asthma exacerbations in year before study as a fixed covariate.

Secondary: Change from baseline to Week 52 in Asthma Control Questionnaire-6 (ACQ-6) score

End point title	Change from baseline to Week 52 in Asthma Control Questionnaire-6 (ACQ-6) score

End point description:

The ACQ-6 questionnaire is a shortened version of the ACQ (omitting FEV1 measurement) that assesses asthma symptoms (night-time awakenings, symptoms on waking, activity limitation, dyspnoea, wheezing) and rescue short-acting β2-agonists medication use during the past week. Questions were weighted equally and scored on a 7-point scale from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score was the mean of the responses, ranging from 0 (totally controlled) to 6 (severely uncontrolled). Mean scores of ≤0.75 indicate well-controlled asthma, scores between 0.75 and ≤1.5 indicate partly controlled asthma and a score >1.5 indicates not well-controlled asthma. Individual changes of at least 0.5 were considered to be clinically meaningful. The mean change from baseline in ACQ-6 score at Week 52 is presented. Only patients with data available at the timepoints of testing were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 52

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324	344	329	
Units: Scores on a scale				
arithmetic mean (standard deviation)	-1.19 (± 1.06)	-1.12 (± 1.03)	-1.02 (± 1.14)	

Statistical analyses

Statistical analysis title	Change in mean score from baseline for ACQ-6
Statistical analysis description:	
Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis.	
Comparison groups	Tralo 300 mg Q2W v Placebo
Number of subjects included in analysis	653
Analysis specification	Pre-specified
Analysis type	superiority[11]
Parameter estimate	LS Mean difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	-0.02

Notes:

[11] - Fixed categorical effects of baseline ACQ-6 score, treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction and number of asthma exacerbations in year before study as a fixed covariate.

Statistical analysis title	Change in mean score from baseline for ACQ-6
Statistical analysis description:	
Tralo 300 mg Q4W vs placebo. REML based repeated measures analysis.	
Comparison groups	Tralo 300 mg Q4W v Placebo
Number of subjects included in analysis	673
Analysis specification	Pre-specified
Analysis type	superiority[12]
Parameter estimate	LS Mean difference
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.01

Notes:

[12] - Fixed categorical effects of baseline ACQ-6 score, treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction and number of asthma exacerbations in year before study as a fixed covariate.

Secondary: AAER associated with an ER/UC visit, or a hospitalisation up to Week 52	
End point title	AAER associated with an ER/UC visit, or a hospitalisation up to Week 52

End point description:

The annual rate of exacerbations associated with an ER/UC visit or hospitalisation up to Week 52 are presented for non-adjudicated data (i.e. events assessed by the Investigator and recorded in the electronic case report form). AAER = Number of Exacerbations*365.25 / (Follow-up date – Date of randomisation + 1) (where maximum follow-up time for a patient was approximately 52 weeks).

End point type	Secondary

End point timeframe:

Baseline (Week 0) up to Week 52

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	398	404	400	
Units: Events/year				
number (confidence interval 95%)	0.04 (0.02 to 0.06)	0.06 (0.04 to 0.09)	0.07 (0.05 to 0.11)	

Statistical analyses

Statistical analysis title	AAER associated with ER/UC visit / hospitalisation

Statistical analysis description:

Tralo 300 mg Q2W vs placebo.

Comparison groups	Tralo 300 mg Q2W v Placebo
Number of subjects included in analysis	798
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.0369
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.96

Notes:

[13] - Covariates in the model included treatment group, geographical region, age group, periostin group at baseline and number of exacerbations resulting in hospitalisation or ER treatment (yes/no) in the year before the study.

Statistical analysis title	AAER associated with ER/UC visit / hospitalisation

Statistical analysis description:

Tralo 300 mg Q4W vs placebo.

Comparison groups	Tralo 300 mg Q4W v Placebo

Number of subjects included in analysis	804
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.3603
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.33

Notes:

[14] - Covariates in the model included treatment group, geographical region, age group, periostin group at baseline and number of exacerbations resulting in hospitalisation or ER treatment (yes/no) in the year before the study.

Secondary: Change from baseline in European Quality of Life - 5 Dimension 5 Levels (EQ-5D-5L) visual analogue scale (VAS) scores at Week 52

End point title	Change from baseline in European Quality of Life - 5 Dimension 5 Levels (EQ-5D-5L) visual analogue scale (VAS) scores at Week 52

End point description:

The EQ-5D-5L questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems and extreme problems) that reflect increasing levels of difficulty. The patient was asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also included a VAS, where the patient was asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state. The mean change from baseline in EQ-5D-5L VAS scores at Week 52 is presented. Only patients with data available at the timepoints of testing were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 52

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	306	319	324	
Units: Scores on a scale				
arithmetic mean (standard deviation)	10.68 (± 20.33)	9.00 (± 18.99)	10.06 (± 18.92)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in total asthma rescue medication use at Week 52 (bi-weekly means)

End point title	Change from baseline in total asthma rescue medication use at Week 52 (bi-weekly means)

End point description:

Salbutamol, albuterol or levalbuterol were used as rescue medication during the study in the event of a worsening of asthma symptoms. Rescue medication use was measured by the bi-weekly mean number of inhalations (puffs) per day, calculated as: total morning puffs + total evening puffs + 2*(total morning nebuliser use + total evening nebuliser use)/ total number of days with data in bi-weekly period. The change from baseline in bi-weekly mean total asthma rescue medication use at Week 52 is presented. Only patients with data available at the timepoints of testing were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 52

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	313	313	312	
Units: Puffs/day				
arithmetic mean (standard deviation)	-2.18 (± 3.46)	-2.15 (± 3.69)	-2.04 (± 3.84)	

Statistical analyses

Statistical analysis title	Mean change from baseline in rescue medication use

Statistical analysis description:

Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis.

Comparison groups	Tralo 300 mg Q2W v Placebo
Number of subjects included in analysis	625
Analysis specification	Pre-specified
Analysis type	superiority[15]
Parameter estimate	LS Mean difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.29

Notes:

[15] - Fixed categorical effects of baseline rescue medication use, treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction and number of asthma exacerbations in year before study as a fixed covariate.

Statistical analysis title	Mean change from baseline in rescue medication use

Statistical analysis description:

Tralo 300 mg Q4W vs placebo. REML based repeated measures analysis.

Comparison groups	Tralo 300 mg Q4W v Placebo

Number of subjects included in analysis	625
Analysis specification	Pre-specified
Analysis type	superiority[16]
Parameter estimate	LS Mean difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	0.24

Notes:

[16] - Fixed categorical effects of baseline rescue medication use, treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction and number of asthma exacerbations in year before study as a fixed covariate.

Secondary: Change from baseline in home peak expiratory flow (PEF) (morning and evening) at Week 52

End point title	Change from baseline in home peak expiratory flow (PEF) (morning and evening) at Week 52

End point description:

Home PEF testing was performed by the patient using an electronic, hand-held spirometer (peak flow meter) and was performed in the morning upon awakening (prior to taking their morning asthma controller) and in the evening at bedtime (prior to taking their evening asthma controller). The mean change from baseline in home PEF values at Week 52 are presented separately for morning and evening. Only patients with data available at the timepoints of testing were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 52

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	321	326	329	
Units: L/min				
arithmetic mean (standard deviation)				
Morning PEF (n=320,326,329)	12.95 (± 85.66)	7.55 (± 74.97)	5.23 (± 74.10)	
Evening PEF (n=321,319,326)	8.89 (± 83.02)	0.68 (± 73.19)	-0.28 (± 76.05)	

Statistical analyses

Statistical analysis title	Mean change from baseline in morning PEF

Statistical analysis description:

Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis.

Comparison groups	Tralo 300 mg Q2W v Placebo

Number of subjects included in analysis	650
Analysis specification	Pre-specified
Analysis type	superiority[17]
Parameter estimate	LS Mean difference
Point estimate	6.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.53
upper limit	16.03

Notes:

[17] - Fixed categorical effects of baseline PEF (morning), treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction and number of asthma exacerbations in year before study as a fixed covariate.

Statistical analysis title	Mean change from baseline in morning PEF

Statistical analysis description:

Tralo 300 mg Q4W vs placebo. REML based repeated measures analysis.

Comparison groups	Tralo 300 mg Q4W v Placebo
Number of subjects included in analysis	655
Analysis specification	Pre-specified
Analysis type	superiority[18]
Parameter estimate	LS Mean difference
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.99
upper limit	11.53

Notes:

[18] - Fixed categorical effects of baseline PEF (morning), treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction and number of asthma exacerbations in year before study as a fixed covariate.

Statistical analysis title	Mean change from baseline in evening PEF

Statistical analysis description:

Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis.

Comparison groups	Tralo 300 mg Q2W v Placebo
Number of subjects included in analysis	650
Analysis specification	Pre-specified
Analysis type	superiority[19]
Parameter estimate	LS Mean difference
Point estimate	7.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	16.87

Notes:

[19] - Fixed categorical effects of baseline PEF (evening), treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction and number of asthma exacerbations in year before study as a fixed covariate.

Statistical analysis title	Mean change from baseline in evening PEF

Statistical analysis description:	
Traco 300 mg Q4W vs placebo. REML based repeated measures analysis.	
Comparison groups	Tralo 300 mg Q4W v Placebo
Number of subjects included in analysis	655
Analysis specification	Pre-specified
Analysis type	superiority[20]
Parameter estimate	LS Mean difference
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.13
upper limit	10.35

Notes:

[20] - Fixed categorical effects of baseline PEF (evening), treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction and number of asthma exacerbations in year before study as a fixed covariate.

Secondary: Change from baseline in night-time awakenings due to asthma requiring rescue medication use at Week 52 (bi-weekly means [percentage])

End point title	Change from baseline in night-time awakenings due to asthma requiring rescue medication use at Week 52 (bi-weekly means [percentage])

End point description:

The patient captured night-time awakenings (yes/no) and the use of rescue medication during these awakenings (yes/no) each morning in the Asthma Daily Diary. Night-time awakenings (percentage) was defined as the number of nights with awakenings due to asthma and requiring rescue medication divided by number of nights with data. The change from baseline in bi-weekly means (percentage) night-time awakenings due to asthma requiring rescue medication use at Week 52 is presented. Only patients with data available at the timepoints of testing were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 52

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	346	357	357	
Units: Percentage of nights with awakenings				
arithmetic mean (standard deviation)	-37.63 (± 37.27)	-35.17 (± 37.49)	-36.00 (± 36.69)	

Statistical analyses

Statistical analysis title	Mean change from baseline in % of awakenings

Statistical analysis description:

Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis.

Comparison groups	Tralo 300 mg Q2W v Placebo

Number of subjects included in analysis	703
Analysis specification	Pre-specified
Analysis type	superiority[21]
Parameter estimate	LS Mean difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.29
upper limit	1.69

Notes:

[21] - Fixed categorical effects of baseline number (%) of awakenings, treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction and number of asthma exacerbations in year before study as a fixed covariate.

Statistical analysis title	Mean change from baseline in % of awakenings

Statistical analysis description:

Tralo 300 mg Q4W vs placebo. REML based repeated measures analysis.

Comparison groups	Tralo 300 mg Q4W v Placebo
Number of subjects included in analysis	714
Analysis specification	Pre-specified
Analysis type	superiority[22]
Parameter estimate	LS Mean difference
Point estimate	-2.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.84
upper limit	1.12

Notes:

[22] - Fixed categorical effects of baseline number (%) of awakenings, treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction and number of asthma exacerbations in year before study as a fixed covariate.

Secondary: Number of patients with ≥1 asthma exacerbation up to Week 52

End point title	Number of patients with ≥1 asthma exacerbation up to Week 52

End point description:

The number of patients with ≥1 asthma exacerbation up to Week 52 is presented.

End point type	Secondary

End point timeframe:

Baseline (Week 0) up to Week 52

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	398	404	400	
Units: Participants	128	124	133	

Statistical analyses

Statistical analysis title	Proportion of patients ≥ 1 asthma exacerbations
Statistical analysis description: Tralo 300 mg Q2W vs placebo.	
Comparison groups	Tralo 300 mg Q2W v Placebo
Number of subjects included in analysis	798
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.732
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.28

Notes:

[23] - The estimate of each odds ratio was obtained from two separate models, from a Cochran-Mantel-Haenszel test controlling for geographical region, age group and periostin group at baseline.

Statistical analysis title	Proportion of patients ≥ 1 asthma exacerbations
Statistical analysis description: Tralo 300 mg Q4W vs placebo.	
Comparison groups	Tralo 300 mg Q4W v Placebo
Number of subjects included in analysis	804
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.421
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.19

Notes:

[24] - The estimate of each odds ratio was obtained from two separate models, from a Cochran-Mantel-Haenszel test controlling for geographical region, age group and periostin group at baseline.

Secondary: Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questions (WPAI+CIQ): Productivity Loss at Week 52

End point title	Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questions (WPAI+CIQ): Productivity Loss at Week 52

End point description:

The WPAI+CIQ consists of questions about how asthma and asthma-related issues impact a patient's ability to work, attend classes and perform regular daily activities. The questionnaire contains 10 questions relating to the patient's experience over the previous 7 days. The WPAI+CIQ outcomes for productivity loss are presented separately for those currently employed and for those currently in school and are expressed as mean productivity loss (percentage) at Week 52, with higher numbers indicating less productivity. Work Productivity Loss = {Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))x(Q5/10)]}*100 (Absenteeism = Q2/(Q2+Q4)*100; Presenteeism = (Q5/10)*100). Class Productivity Loss = {Q7/(Q7+Q8) + [(1-Q7/(Q7+Q8))x(Q9/10)]}*100 (Absenteeism = Q7/ (Q7+Q8)*100; Presenteeism = (Q9/10)*100). Note: QX refers to response to question number X on WPAI+CIQ questionnaire. Only patients with data available at the timepoints of testing were included in the analysis.

End point type	Secondary

End point timeframe:

At Week 52

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	130	137	
Units: Percent productivity loss				
arithmetic mean (standard deviation)				
Currently employed (n=112,116,118)	27.71 (± 24.06)	28.48 (± 25.11)	31.25 (± 25.34)	
Currently in school (n=11,14,19)	33.13 (± 28.03)	31.79 (± 34.28)	32.31 (± 28.46)	

Statistical analyses

No statistical analyses for this end point

Secondary: WPAI+CIQ: Activity Impairment at Week 52

End point title	WPAI+CIQ: Activity Impairment at Week 52

End point description:

The WPAI+CIQ consists of questions about how asthma and asthma-related issues impact a patient's ability to work, attend classes and perform regular daily activities. The questionnaire contains 10 questions relating to the patient's experience over the previous 7 days. The WPAI+CIQ outcomes for activity impairment are presented separately for those currently employed and for those currently in school and are expressed as mean impairment percentages at Week 52, with higher numbers indicating greater impairment. Activity impairment = (Q10/10)*100. Note: QX refers to response to question number X on WPAI+CIQ questionnaire. Only patients with data available at the timepoints of testing were included in the analysis.

End point type	Secondary

End point timeframe:

At Week 52

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	135	146	
Units: Percent Impairment				
arithmetic mean (standard deviation)				
Currently employed (n=120,119,127)	23.25 (± 21.31)	23.53 (± 22.57)	27.01 (± 23.21)	
Currently in school (n=14,16,19)	29.29 (± 20.56)	27.50 (± 29.55)	28.95 (± 23.07)	

Statistical analyses

No statistical analyses for this end point

Secondary: Asthma-related healthcare encounters by type up to Week 52

End point title	Asthma-related healthcare encounters by type up to Week 52

End point description:

Broad-based healthcare utilisation asthma-related event information was collected by the Investigator/authorised delegate at each visit. At Visit 1, healthcare resource utilisation information was collected with a 1-year recall period; subsequent visits collected information with a recall period of 'since the last scheduled visit'. Total number of times the healthcare encounter occurred was calculated across all patients for each of the following categories: • Ambulance transport, • Emergency room visits, • Unscheduled outpatient visits (visit to specialist and/or visit to primary healthcare physician and/or other healthcare visit), • Home visits (home visit, physician and/or other healthcare professional), • Telephone calls (telephone calls to physician and/or nurse), and • Advanced pulmonary function test.

End point type	Secondary

End point timeframe:

Baseline (Week 0) up to Week 52

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	398	404	400	
Units: Encounters				
Ambulance transport	5	15	16	
Emergency room visits	59	87	64	
Unscheduled outpatient visits	1750	1786	1705	
Home visits	21	5	6	
Telephone calls	515	463	198	
Advanced pulmonary function test	84	70	67	

Statistical analyses

No statistical analyses for this end point

Secondary: Asthma-related healthcare encounters by type up to Week 52:

Hospitalisations

End point title	Asthma-related healthcare encounters by type up to Week 52: Hospitalisations

End point description:

Broad-based healthcare utilisation asthma-related event information was collected by the Investigator/authorised delegate at each visit. At Visit 1, healthcare resource utilisation information was collected with a 1-year recall period; subsequent visits collected information with a recall period of 'since the last scheduled visit'. Total number of days spent in hospital was calculated across all patients for the following healthcare encounter category: • Hospitalisations (hospitalisations, intensive care and/or general care).

End point type	Secondary

End point timeframe:

Baseline (Week 0) up to Week 52

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	398	404	400	
Units: Days	270	345	482	

Statistical analyses

No statistical analyses for this end point

Secondary: Asthma-related healthcare encounters by type up to Week 52: Spirometry

End point title	Asthma-related healthcare encounters by type up to Week 52: Spirometry

End point description:

Broad-based healthcare utilisation asthma-related event information was collected by the Investigator/authorised delegate at each visit. At Visit 1, healthcare resource utilisation information was collected with a 1-year recall period; subsequent visits collected information with a recall period of 'since the last scheduled visit'. Total number of assessments was calculated across all patients for the following healthcare encounter category: • Spirometry.

End point type	Secondary

End point timeframe:

Baseline (Week 0) up to Week 52

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	398	404	400	
Units: Assessments	489	520	502	

Statistical analyses

No statistical analyses for this end point

Secondary: Serum trough concentration (Ctrough) of tralokinumab during the study period up to Week 72

End point title	Serum trough concentration (Ctrough) of tralokinumab during the study period up to Week 72[25]

End point description:

To evaluate the pharmacokinetics (PK), pre-dose blood samples were collected at each visit and tralokinumab concentrations in serum were determined. Mean Ctrough concentrations are presented at each indicated visit up to Week 72. All patients in the full analysis set who received tralokinumab and who had PK blood samples were included in the PK analysis set. Only patients with data available at the timepoints of testing were included in the analysis.

End point type	Secondary

End point timeframe:

Blood samples were collected pre-dose at Baseline (Week 0), and at Week 4, Week 8, Week 26, Week 52 and Week 72 (follow-up)

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The baseline period arms were 'Tralo 300 mg Q2W', 'Tralo 300 mg Q4W' and 'Placebo'. Since this particular end point presents pharmacokinetic data of tralokinumab, it was not applicable to select the Placebo arm for the analysis.

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	394[26]	401[27]		
Units: micrograms/millilitre				
geometric mean (geometric coefficient of variation)				
Baseline (n=394,401)	99999999 (± 99999999)	99999999 (± 99999999)		
Week 4 (n=353,353)	34.690 (± 199.269)	13.151 (± 188.026)		
Week 8 (n=358,366)	55.262 (± 159.824)	19.243 (± 112.830)		
Week 26 (n=358,370)	52.766 (± 257.341)	30.305 (± 255.039)		
Week 52 (n=354,373)	37.074 (± 675.764)	14.290 (± 437.472)		
Week 72 (follow-up) (n=339,356)	0.419 (± 238.749)	0.172 (± 171.973)		

Notes:

[26] - 99999999 denotes that the value was not calculable.

[27] - 99999999 denotes that the value was not calculable.

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence rate of positive anti-drug antibodies (ADAs) including the characterisation of their neutralising potential

End point title	Incidence rate of positive anti-drug antibodies (ADAs) including the characterisation of their neutralising potential

End point description:

ADA assessments performed using a tiered approach (screening, confirmatory and titering assays). Confirmed ADA positive samples were also tested for neutralising antibodies (nAb). ADA prevalence defined as proportion of study population with drug-reactive antibodies at any point in time. ADA incidence (treatment-emergent ADA) defined as sum of treatment-induced (post-baseline ADA positive only) and treatment-boosted ADA. Persistently positive defined as positive at ≥2 post-baseline assessments (with ≥16 weeks between first and last positive) or positive at last post-baseline assessment. Transiently positive defined as having ≥1 post-baseline ADA positive assessment and not fulfilling conditions of persistently positive. Treatment-boosted ADA defined as baseline positive ADA titer boosted to a 4-fold or higher level following drug administration. In some category titles 'positive' is denoted by 'pos'. Only patients with data available at timepoints of testing included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Week 26, Week 56 (follow-up) and Week 72 (follow-up)

End point values	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	373	382	374	
Units: Participants				
ADA prevalence|	7	7	9	
ADA incidence	3	2	3	
ADA positive at baseline	4	5	7	
ADA positive post-baseline	3	3	8	
ADA pos post-baseline & pos at baseline	0	1	6	
ADA pos post-baseline & not detected at baseline	3	2	2	
ADA not detected post-baseline & pos at baseline	4	4	1	
Persistent Positive	2	2	7	
Transient Positive	1	1	1	
Treatment-boosted ADA	0	0	1	
nAB positive at any visit	5	5	4	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious and non-serious adverse event (AE) data reported for the treatment period, from baseline (Week 0) to end of treatment (Week 52). Deaths (all causes) is reported for the overall study period (including the extended follow-up period), up to Week 72.

Adverse event reporting additional description:

Treatment-emergent AEs were defined with an onset date ≥ the first day of IP and ≤ (the last day of IP + dosing frequency). 'Dosing frequency' was 2 or 4 weeks depending on whether patients were randomised to Q2W or Q4W dosing regimens. Patient population was safety analysis set which included all patients who received at least one dose of any IP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Tralo 300 mg Q2W

Reporting group description:

Tralokinumab 300 mg administered subcutaneously Q2W over a 52-week treatment period (up to 26 doses). Follow-up visits were conducted at Weeks 56 and 72.

Reporting group title	Tralo 300 mg Q4W

Reporting group description:

Tralokinumab 300 mg administered subcutaneously Q4W over a 52-week treatment period (up to 13 doses). Follow-up visits were conducted at Weeks 56 and 72.

Reporting group title	Placebo

Reporting group description:

Placebo was administered subcutaneously over a 52-week treatment period. The placebo treatment group is a pooled treatment group (placebo Q2W + placebo Q4W) where the 2 placebo cohorts were given weights proportional to the number of patients in each cohort. Follow-up visits were conducted at Weeks 56 and 72.

Serious adverse events	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 398 (10.05%)	39 / 404 (9.65%)	48 / 400 (12.00%)
number of deaths (all causes)	2	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 398 (0.25%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix carcinoma			

subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine cancer			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Eosinophilic granulomatosis with polyangiitis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metrorrhagia			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	12 / 398 (3.02%)	19 / 404 (4.70%)	25 / 400 (6.25%)
occurrences causally related to treatment / all	0 / 15	0 / 23	0 / 39
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atelectasis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal oedema			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			

complications			
Facial bones fracture			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	2 / 398 (0.50%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 398 (0.25%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			

subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-traumatic pain			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	2 / 400 (0.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			

subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular disorder			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Radiculopathy			

subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	2 / 398 (0.50%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular encephalopathy			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebrobasilar insufficiency			

subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 398 (0.00%)	2 / 404 (0.50%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erosive duodenitis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Swollen tongue			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	2 / 398 (0.50%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 398 (0.00%)	2 / 404 (0.50%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankylosing spondylitis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			

subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovitis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigger finger			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Chronic sinusitis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 398 (0.75%)	3 / 404 (0.74%)	4 / 400 (1.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 398 (0.00%)	1 / 404 (0.25%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 398 (0.25%)	0 / 404 (0.00%)	0 / 400 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	0 / 398 (0.00%)	0 / 404 (0.00%)	1 / 400 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Tralo 300 mg Q2W	Tralo 300 mg Q4W	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	134 / 398 (33.67%)	145 / 404 (35.89%)	107 / 400 (26.75%)
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 398 (5.78%)	31 / 404 (7.67%)	17 / 400 (4.25%)
occurrences (all)	35	42	28
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	24 / 398 (6.03%)	12 / 404 (2.97%)	0 / 400 (0.00%)
occurrences (all)	58	29	0
Respiratory, thoracic and mediastinal			

disorders			
Asthma			
subjects affected / exposed	35 / 398 (8.79%)	33 / 404 (8.17%)	28 / 400 (7.00%)
occurrences (all)	55	43	45
Infections and infestations			
Bronchitis			
subjects affected / exposed	20 / 398 (5.03%)	23 / 404 (5.69%)	18 / 400 (4.50%)
occurrences (all)	29	27	24
Upper respiratory tract infection			
subjects affected / exposed	26 / 398 (6.53%)	48 / 404 (11.88%)	36 / 400 (9.00%)
occurrences (all)	40	61	73
Viral upper respiratory tract infection			
subjects affected / exposed	44 / 398 (11.06%)	48 / 404 (11.88%)	37 / 400 (9.25%)
occurrences (all)	62	67	55

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2014	- Change in Forced Vital Capacity and Forced Expiratory Flow 25-75% were added as exploratory variables. - Death events were included in the adjudication process. - Additional samples were added for PK analysis to allow more extensive characterisation of the PK-pharmacodynamic relationship for tralokinumab. - Inclusion criteria were amended for the following reasons: to increase lower weight limit for adolescents to 40 kg; to clarify calculation of total daily ICS dose; to clarify what constitutes acceptable documentation to support patient eligibility; to make the protocol consistent with standard of care across included regions; to clarify the washout period for BD prior to the pre-BD FEV1 test and the reversibility test. - To allow use of selective β-adrenergic antagonists. - Exclusion criteria were amended to include 5-lipoxygenase inhibitors (eg, Zileuton) and roflumilast as restricted medications and to disallow bronchial thermoplasty before study entry or during the study. - Asthma medication restrictions were amended to allow background asthma therapy according to local standard of care; to clarify the use of once daily asthma medications and to clarify the restrictions on BDs. - Safety analysis set definition was revised. - Testing strategy for primary and key secondary objectives was revised.
23 February 2015	- Clinical - Global Impression of Change assessment was added to obtain an early indicator of subjects' response to treatment. - Evaluation of cardiovascular, cerebrovascular and malignancy adverse events occurring after randomisation were added to the adjudication committee responsibilities as a result of sponsor decision to proactively implement independent adjudication of these across all Phase 3 studies conducted with human antibodies in patients with severe asthma.
08 October 2015	- Dosing requirements and restrictions were clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported