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 2)

Summary

EudraCT number	2013-005615-27
Trial protocol	GB IT CZ PL
Global end of trial date	21 September 2017

Results information

Result version number	v1 (current)
This version publication date	07 April 2018
First version publication date	07 April 2018

Trial information

Trial identification

Sponsor protocol code	D2210C00008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02194699
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	21 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 September 2017
Global end of trial reached?	Yes
Global end of trial date	21 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 300 milligrams (mg) administered every 2 weeks (Q2W) compared with placebo on the annualised asthma exacerbation rate (AAER) in 2 populations. The primary population was the biomarker positive population, defined as all patients with baseline fractional exhaled nitric oxide (FeNO) ≥37 parts per billion (ppb). The secondary population included all 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	30 October 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: 179
Country: Number of subjects enrolled	Ukraine: 153
Country: Number of subjects enrolled	Russian Federation: 130
Country: Number of subjects enrolled	Philippines: 123
Country: Number of subjects enrolled	Chile: 81
Country: Number of subjects enrolled	Mexico: 45
Country: Number of subjects enrolled	Czech Republic: 40
Country: Number of subjects enrolled	Japan: 29
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	South Africa: 12
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Taiwan: 2
Worldwide total number of subjects	837
EEA total number of subjects	66

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)	55
Adults (18-64 years)	665
From 65 to 84 years	117
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient enrolled: 30 Oct 2014; Last Patient Last Visit: 21 Sep 2017. Study performed at 242 sites in 13 countries.

Pre-assignment

Screening details:

1696 patients signed informed consent, 1163 entered screening/run-in period, 856 patients were randomised to receive investigational product (IP) and 847 received treatment (note 847 excludes 2 duplicate patients administered tralokinumab).

Period 1

Period 1 title	Randomised
Is this the baseline period?	No
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, 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 milligrams/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	Placebo

Arm description:

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

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

Dosage and administration details:

Placebo 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	Placebo
Started	428	428
Completed	420	417
Not completed	8	11
Did not receive treatment	1	5
Without potential for 52 weeks of IP	5	5
Duplicate patient	2	1

Period 2

Period 2 title	With potential to receive 52 weeks of IP
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, 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	Placebo

Arm description:

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

Arm type	Placebo

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

Dosage and administration details:

Placebo 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 with the potential to receive 52 weeks of treatment and who received any 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 study treatment. Period 2 is therefore the baseline period.

Number of subjects in period 2	Tralo 300 mg Q2W	Placebo
Started	420	417
Completed	370	365
Not completed	50	52
Adverse event, serious fatal	1	3
Consent withdrawn by subject	14	20
Adverse event, non-fatal	4	3
Unspecified	24	16
Lost to follow-up	5	8
Protocol deviation	2	2

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	Placebo
Reporting group description:	
Placebo administered subcutaneously Q2W over a 52-week treatment period (up to 26 doses).	

Reporting group values	Tralo 300 mg Q2W	Placebo	Total
Number of subjects	420	417	837
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)	29	26	55
Adults (18-64 years)	332	333	665
From 65-84 years	59	58	117
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	47.3	48.0	
standard deviation	± 15.6	± 15.5	-
Sex: Female, Male			
Units: Subjects			
Female	276	290	566
Male	144	127	271
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	3	3	6
Asian	83	88	171
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	27	24	51
White	283	281	564
More than one race	0	0	0
Unknown or Not Reported	24	21	45

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).	
Reporting group title	Placebo
Reporting group description:	
Placebo administered subcutaneously Q2W over a 52-week treatment period (up to 26 doses).	
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	Placebo
Reporting group description:	
Placebo administered subcutaneously Q2W over a 52-week treatment period (up to 26 doses).	
Subject analysis set title	Biomarker positive - Tralo 300 mg Q2W
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Tralokinumab 300 mg administered subcutaneously Q2W over a 52-week treatment period (up to 26 doses). Patients in the biomarker positive population (primary population) had baseline FeNO ≥37 ppb.	
Subject analysis set title	Biomarker positive - Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Placebo administered subcutaneously Q2W over a 52-week treatment period (up to 26 doses). Patients in the biomarker positive population (primary population) had baseline FeNO ≥37 ppb.	
Subject analysis set title	Biomarker negative - Tralo 300 mg Q2W
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Tralokinumab 300 mg administered subcutaneously Q2W over a 52-week treatment period (up to 26 doses). Patients in the biomarker negative population (complement population) had baseline FeNO <37 ppb.	
Subject analysis set title	Biomarker negative - Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Placebo administered subcutaneously Q2W over a 52-week treatment period (up to 26 doses). Patients in the biomarker negative population (complement population) had baseline FeNO <37 ppb.	
Subject analysis set title	Total - Tralo 300 mg Q2W
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Tralokinumab 300 mg administered subcutaneously Q2W over a 52-week treatment period (up to 26 doses). 'Total' treatment arm represents all patients receiving tralokinumab and providing pharmacokinetic (PK) blood samples.	

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	Placebo	Biomarker positive - Tralo 300 mg Q2W	Biomarker positive - Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	420	417	108	121
Units: Events/year				
number (confidence interval 95%)	0.84 (0.71 to 1.00)	0.82 (0.69 to 0.97)	0.80 (0.57 to 1.11)	0.95 (0.68 to 1.31)

End point values	Biomarker negative - Tralo 300 mg Q2W	Biomarker negative - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	308	290		
Units: Events/year				
number (confidence interval 95%)	0.87 (0.71 to 1.06)	0.77 (0.63 to 0.95)		

Statistical analyses

Statistical analysis title	AAER (rate ratio): Biomarker positive

Statistical analysis description:

Comparison of AAER (rate ratio): Biomarker positive population; Tralo 300 mg Q2W vs placebo. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term was included in the analysis model.

Comparison groups	Biomarker positive - Tralo 300 mg Q2W v Biomarker positive - Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.4656
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.34

Notes:

[1] - 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. 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): Biomarker negative

Statistical analysis description:

Comparison of AAER (rate ratio): Biomarker negative population; Tralo 300 mg Q2W vs placebo. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term was included in the analysis model.

Comparison groups	Biomarker negative - Tralo 300 mg Q2W v Biomarker negative - Placebo
Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.4126
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.5

Notes:

[2] - 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. 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): Biomarker positive

Statistical analysis description:

Comparison of AAER (rate reduction): Biomarker positive population; Tralo 300 mg Q2W vs placebo. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term was included in the analysis model.

Comparison groups	Biomarker positive - Tralo 300 mg Q2W v Biomarker positive - Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.4656
Method	Negative binominal
Parameter estimate	Rate reduction
Point estimate	15.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.71
upper limit	47.01

Notes:

[3] - 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. 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): FAS

Statistical analysis description:

Comparison of AAER (rate ratio): FAS population; Tralo 300 mg Q2W vs placebo.

Comparison groups	Tralo 300 mg Q2W v Placebo
Number of subjects included in analysis	837
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.8027
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.31

Notes:

[4] - 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. 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): FAS

Statistical analysis description:

Comparison of AAER (rate reduction): FAS population; Tralo 300 mg Q2W vs placebo.

Comparison groups	Tralo 300 mg Q2W v Placebo
Number of subjects included in analysis	837
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.8027
Method	Negative binominal
Parameter estimate	Rate reduction
Point estimate	-3.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.46
upper limit	19.08

Notes:

[5] - 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. 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	Placebo	Biomarker positive - Tralo 300 mg Q2W	Biomarker positive - Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	384	358	99	103
Units: Percent change from baseline				
arithmetic mean (standard deviation)	14.546 (± 26.065)	10.528 (± 25.475)	18.769 (± 29.628)	16.632 (± 31.906)

End point values	Biomarker negative - Tralo 300 mg Q2W	Biomarker negative - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	282	250		
Units: Percent change from baseline				
arithmetic mean (standard deviation)	13.103 (± 24.641)	8.395 (± 21.962)		

Statistical analyses

Statistical analysis title	Pre-BD FEV1: Biomarker positive

Statistical analysis description:

Comparison of % change from baseline in pre-dose/pre-BD FEV1 at Week 52: Biomarker positive population; Tralo 300 mg Q2W vs placebo. Restricted maximum likelihood (REML) based repeated measures analysis on patients with a baseline pre-dose/pre-BD FEV1 assessment. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term was included in the analysis model.

Comparison groups	Biomarker positive - Tralo 300 mg Q2W v Biomarker positive - Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.6033
Method	Repeated measures analysis
Parameter estimate	Least square (LS) Mean difference
Point estimate	1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.16
upper limit	8.88

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.

Statistical analysis title	Pre-BD FEV1: Biomarker negative

Statistical analysis description:

Comparison of % change from baseline in pre-dose/pre-BD FEV1 at Week 52: Biomarker negative population; Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis on patients with a baseline pre-dose/pre-BD FEV1 assessment. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term was included in the analysis model.

Comparison groups	Biomarker negative - Tralo 300 mg Q2W v Biomarker negative - Placebo
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.1276
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	3.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	7.7

Notes:

[7] - 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	Pre-BD FEV1: FAS

Statistical analysis description:

Comparison of % change from baseline in pre-dose/pre-BD FEV1 at Week 52: FAS population; Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis 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	742
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.1164
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	2.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	6.62

Notes:

[8] - 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	Placebo	Biomarker positive - Tralo 300 mg Q2W	Biomarker positive - Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	297	309	79	81
Units: Scores on a scale				
arithmetic mean (standard deviation)	-1.04 (± 1.04)	-1.02 (± 1.24)	-1.18 (± 0.98)	-1.06 (± 1.25)

End point values	Biomarker negative - Tralo 300 mg Q2W	Biomarker negative - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	215	223		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-0.98 (± 1.04)	-1.02 (± 1.24)		

Statistical analyses

Statistical analysis title	Total asthma symptom score: Biomarker positive

Statistical analysis description:

Comparison of mean change from baseline in total asthma symptom score at Week 52: Biomarker positive population; Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term was included in the analysis model.

Comparison groups	Biomarker positive - Tralo 300 mg Q2W v Biomarker positive - Placebo

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.1456
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.07

Notes:

[9] - 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	Total asthma symptom score: Biomarker negative

Statistical analysis description:

Comparison of mean change from baseline in total asthma symptom score at Week 52: Biomarker negative population; Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term was included in the analysis model.

Comparison groups	Biomarker negative - Tralo 300 mg Q2W v Biomarker negative - Placebo
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.6548
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.2

Notes:

[10] - 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	Total asthma symptom score: FAS

Statistical analysis description:

Comparison of mean change from baseline in total asthma symptom score at Week 52: FAS population; 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	606
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.5763
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.1

Notes:

[11] - 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	Placebo	Biomarker positive - Tralo 300 mg Q2W	Biomarker positive - Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	321	318	77	84
Units: Scores on a scale				
arithmetic mean (standard deviation)	1.18 (± 1.07)	1.21 (± 1.24)	1.35 (± 1.06)	1.20 (± 1.22)

End point values	Biomarker negative - Tralo 300 mg Q2W	Biomarker negative - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	242	230		
Units: Scores on a scale				
arithmetic mean (standard deviation)	1.13 (± 1.07)	1.23 (± 1.25)		

Statistical analyses

Statistical analysis title	AQLQ(S)+12 total score: Biomarker positive

Statistical analysis description:

Comparison of change in mean score from baseline for AQLQ(S)+12 at Week 52: Biomarker positive population; Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term was included in the analysis model.

Comparison groups	Biomarker positive - Tralo 300 mg Q2W v Biomarker positive - Placebo
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.0874
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.57

Notes:

[12] - 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	AQLQ(S)+12 total score: Biomarker negative

Statistical analysis description:

Comparison of change in mean score from baseline for AQLQ(S)+12 at Week 52: Biomarker negative population; Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term was included in the analysis model.

Comparison groups	Biomarker negative - Tralo 300 mg Q2W v Biomarker negative - Placebo
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.9083
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.17

Notes:

[13] - 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	AQLQ(S)+12 total score: FAS

Statistical analysis description:

Comparison of change in mean score from baseline for AQLQ(S)+12 at Week 52: FAS population; 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	639
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.4506
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.22

Notes:

[14] - 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	Placebo	Biomarker positive - Tralo 300 mg Q2W	Biomarker positive - Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	341	334	85	86
Units: Scores on a scale				
arithmetic mean (standard deviation)	-1.12 (± 1.02)	-1.11 (± 1.13)	-1.26 (± 1.01)	-1.14 (± 1.12)

End point values	Biomarker negative - Tralo 300 mg Q2W	Biomarker negative - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	254	243		
Units: Scores on a scale				

arithmetic mean (standard deviation)	-1.07 (± 1.02)	-1.11 (± 1.13)		

Statistical analyses

Statistical analysis title	ACQ-6 score: Biomarker positive

Statistical analysis description:

Comparison of change in mean score from baseline for ACQ-6 at Week 52: Biomarker positive population; Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term was included in the analysis model.

Comparison groups	Biomarker positive - Tralo 300 mg Q2W v Biomarker positive - Placebo
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.04
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	-0.01

Notes:

[15] - 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	ACQ-6 score: Biomarker negative

Statistical analysis description:

Comparison of change in mean score from baseline for ACQ-6 at Week 52: Biomarker negative population; Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term was included in the analysis model.

Comparison groups	Biomarker negative - Tralo 300 mg Q2W v Biomarker negative - Placebo
Number of subjects included in analysis	497
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.9735
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.16

Notes:

[16] - 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	ACQ-6 score: FAS

Statistical analysis description:

Comparison of change in mean score from baseline for ACQ-6 at Week 52: FAS population; 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	675
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.2432
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.05

Notes:

[17] - 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	Placebo	Biomarker positive - Tralo 300 mg Q2W	Biomarker positive - Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	420	417	108	121
Units: Events/year				
number (confidence interval 95%)	0.08 (0.06 to 0.12)	0.12 (0.09 to 0.18)	0.06 (0.03 to 0.14)	0.16 (0.09 to 0.29)

End point values	Biomarker negative - Tralo 300 mg	Biomarker negative - Placebo		

	Q2W			
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	308	290		
Units: Events/year				
number (confidence interval 95%)	0.09 (0.06 to 0.14)	0.11 (0.07 to 0.17)		

Statistical analyses

Statistical analysis title	AAER w ER/UC/hospitalisation: Biomarker positive

Statistical analysis description:

Comparison of AAER associated with an ER/UC visit or hospitalisation: Biomarker positive population; Tralo 300 mg Q2W vs placebo. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term was included in the analysis model.

Comparison groups	Biomarker positive - Tralo 300 mg Q2W v Biomarker positive - Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.0576
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	1.03

Notes:

[18] - 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 w ER/UC/hospitalisation: Biomarker negative

Statistical analysis description:

Comparison of AAER associated with an ER/UC visit or hospitalisation: Biomarker negative population; Tralo 300 mg Q2W vs placebo. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term was included in the analysis model.

Comparison groups	Biomarker negative - Tralo 300 mg Q2W v Biomarker negative - Placebo
Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.5249
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.48

Notes:

[19] - 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 w ER/UC/hospitalisation: FAS

Statistical analysis description:

Comparison of AAER associated with an ER/UC visit or hospitalisation: FAS population; Tralo 300 mg Q2W vs placebo.

Comparison groups	Tralo 300 mg Q2W v Placebo
Number of subjects included in analysis	837
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.1155
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.1

Notes:

[20] - 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	Placebo	Biomarker positive - Tralo 300 mg Q2W	Biomarker positive - Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	317	313	81	85
Units: Scores on a scale				
arithmetic mean (standard deviation)	12.46 (± 16.67)	11.66 (± 17.41)	14.58 (± 15.21)	11.58 (± 17.26)

End point values	Biomarker negative - Tralo 300 mg Q2W	Biomarker negative - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	233	224		
Units: Scores on a scale				
arithmetic mean (standard deviation)	11.67 (± 17.18)	12.01 (± 17.43)		

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	Placebo	Biomarker positive - Tralo 300 mg Q2W	Biomarker positive - Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	297	309	79	81
Units: Puffs/day				
arithmetic mean (standard deviation)	-2.25 (± 3.03)	-1.97 (± 4.34)	-2.86 (± 3.26)	-1.73 (± 4.59)

End point values	Biomarker negative - Tralo 300 mg Q2W	Biomarker negative - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	215	223		
Units: Puffs/day				
arithmetic mean (standard deviation)	-2.01 (± 2.93)	-2.08 (± 4.28)		

Statistical analyses

Statistical analysis title	Rescue medication use: Biomarker positive

Statistical analysis description:

Comparison of mean change from baseline in rescue medication use at Week 52: Biomarker positive population; Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term was included in the analysis model.

Comparison groups	Biomarker positive - Tralo 300 mg Q2W v Biomarker positive - Placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.036
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.85
upper limit	-0.06

Notes:

[21] - 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	Rescue medication use: Biomarker negative

Statistical analysis description:

Comparison of mean change from baseline in rescue medication use at Week 52: Biomarker negative population; Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term was included in the analysis model.

Comparison groups	Biomarker negative - Tralo 300 mg Q2W v Biomarker negative - Placebo
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.5864
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.7

Notes:

[22] - 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	Rescue medication use: FAS

Statistical analysis description:

Comparison of mean change from baseline in rescue medication use at Week 52: FAS population; 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	606
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.4689
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	0.29

Notes:

[23] - 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 for each individual category.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 52

End point values	Tralo 300 mg Q2W	Placebo	Biomarker positive - Tralo 300 mg Q2W	Biomarker positive - Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	322	313	86	86
Units: L/min				
arithmetic mean (standard deviation)				
Morning PEF (n=318, 308, 84, 81, 231, 222)	10.66 (± 73.88)	9.43 (± 76.01)	22.35 (± 74.00)	18.80 (± 86.24)
Evening PEF (n=322, 313, 86, 86, 233, 222)	5.72 (± 77.01)	2.91 (± 74.94)	18.15 (± 69.20)	8.88 (± 79.72)

End point values	Biomarker negative - Tralo 300 mg Q2W	Biomarker negative - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	233	222		
Units: L/min				
arithmetic mean (standard deviation)				
Morning PEF (n=318, 308, 84, 81, 231, 222)	6.72 (± 73.82)	6.10 (± 72.28)		
Evening PEF (n=322, 313, 86, 86, 233, 222)	1.72 (± 79.58)	0.17 (± 73.66)		

Statistical analyses

Statistical analysis title	Morning PEF: Biomarker positive

Statistical analysis description:

Comparison of mean change from baseline in morning PEF at Week 52: Biomarker positive population; Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term was included in the analysis model.

Comparison groups	Biomarker positive - Tralo 300 mg Q2W v Biomarker positive - Placebo
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.5094
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	6.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.13
upper limit	24.43

Notes:

[24] - 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	Morning PEF: Biomarker negative

Statistical analysis description:

Comparison of mean change from baseline in morning PEF at Week 52: Biomarker negative population; Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term was included in the analysis model.

Comparison groups	Biomarker negative - Tralo 300 mg Q2W v Biomarker negative - Placebo

Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.5984
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	3.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.22
upper limit	14.26

Notes:

[25] - 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	Evening PEF: Biomarker positive

Statistical analysis description:

Comparison of mean change from baseline in evening PEF at Week 52: Biomarker positive population; Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term was included in the analysis model.

Comparison groups	Biomarker positive - Tralo 300 mg Q2W v Biomarker positive - Placebo
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.3971
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	7.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.32
upper limit	26

Notes:

[26] - 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	Evening PEF: Biomarker negative

Statistical analysis description:

Comparison of mean change from baseline in evening PEF at Week 52: Biomarker negative population; Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term was included in the analysis model.

Comparison groups	Biomarker negative - Tralo 300 mg Q2W v Biomarker negative - Placebo

Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.531
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	3.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.65
upper limit	14.83

Notes:

[27] - 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	Morning PEF: FAS

Statistical analysis description:

Comparison of mean change from baseline in morning PEF at Week 52: FAS population; 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	635
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.4764
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	3.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.06
upper limit	12.97

Notes:

[28] - 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	Evening PEF: FAS

Statistical analysis description:

Comparison of mean change from baseline in evening PEF at Week 52: FAS population; 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	635
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.4221
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	3.88

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	13.37

Notes:

[29] - 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	Placebo	Biomarker positive - Tralo 300 mg Q2W	Biomarker positive - Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	368	348	94	96
Units: Night-time awakenings (percentage)				
arithmetic mean (standard deviation)	-35.60 (± 35.40)	-35.05 (± 36.63)	-37.86 (± 38.36)	-34.06 (± 34.96)

End point values	Biomarker negative - Tralo 300 mg Q2W	Biomarker negative - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	270	247		
Units: Night-time awakenings (percentage)				
arithmetic mean (standard deviation)	-34.65 (± 34.34)	-35.67 (± 37.37)		

Statistical analyses

Statistical analysis title	Night-time awakenings: Biomarker positive

Statistical analysis description:

Comparison of mean change from baseline in number (%) of awakenings at Week 52: Biomarker positive population; Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term was included in the analysis model.

Comparison groups	Biomarker positive - Tralo 300 mg Q2W v Biomarker positive - Placebo
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.1099
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-5.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.21
upper limit	1.14

Notes:

[30] - 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	Night-time awakenings: Biomarker negative

Statistical analysis description:

Comparison of mean change from baseline in number (%) of awakenings at Week 52: Biomarker positive population; Tralo 300 mg Q2W vs placebo. REML based repeated measures analysis. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term was included in the analysis model.

Comparison groups	Biomarker negative - Placebo v Biomarker negative - Tralo 300 mg Q2W
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.8112
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.33
upper limit	4.25

Notes:

[31] - 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	Night-time awakenings: FAS

Statistical analysis description:

Comparison of mean change from baseline in number (%) of awakenings at Week 52: FAS population; 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	716
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	= 0.4645
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	2.01

Notes:

[32] - 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	Placebo	Biomarker positive - Tralo 300 mg Q2W	Biomarker positive - Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	420	417	108	121
Units: Participants	163	171	38	50

End point values	Biomarker negative - Tralo 300 mg Q2W	Biomarker negative - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	308	290		
Units: Participants	125	117		

Statistical analyses

Statistical analysis title	≥ 1 asthma exacerbation: Biomarker positive

Statistical analysis description:

Comparison of number of patients with ≥ 1 asthma exacerbations up to Week 52: Biomarker positive population; Tralo 300 mg Q2W vs placebo.

Comparison groups	Biomarker positive - Tralo 300 mg Q2W v Biomarker positive - Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.344
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.33

Notes:

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

Statistical analysis title	≥ 1 asthma exacerbation: Biomarker negative

Statistical analysis description:

Comparison of number of patients with ≥ 1 asthma exacerbations up to Week 52: Biomarker negative population; Tralo 300 mg Q2W vs placebo.

Comparison groups	Biomarker negative - Tralo 300 mg Q2W v Biomarker negative - Placebo
Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.7768
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.46

Notes:

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

Statistical analysis title	≥ 1 asthma exacerbation: FAS

Statistical analysis description:

Comparison of number of patients with ≥ 1 asthma exacerbations up to Week 52: FAS population; Tralo 300 mg Q2W vs placebo.

Comparison groups	Tralo 300 mg Q2W v Placebo

Number of subjects included in analysis	837
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.5276
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.21

Notes:

[35] - The estimate of each odds ratio was obtained 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 for each individual category.

End point type	Secondary

End point timeframe:

At Week 52

End point values	Tralo 300 mg Q2W	Placebo	Biomarker positive - Tralo 300 mg Q2W	Biomarker positive - Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	154	151	46	46
Units: Percent productivity loss				
arithmetic mean (standard deviation)				
Currently employed (n=137, 125, 43, 34, 92, 90)	23.43 (± 23.66)	30.17 (± 27.08)	22.51 (± 24.47)	28.15 (± 27.39)
Currently in school (n=17, 26, 3, 12, 13, 14)	28.03 (± 31.01)	28.09 (± 29.80)	28.89 (± 34.21)	37.92 (± 28.72)

End point values	Biomarker negative - Tralo 300 mg	Biomarker negative - Placebo		

	Q2W			
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	105	104		
Units: Percent productivity loss				
arithmetic mean (standard deviation)				
Currently employed (n=137, 125, 43, 34, 92, 90)	23.36 (± 23.39)	31.05 (± 27.20)		
Currently in school (n=17, 26, 3, 12, 13, 14)	25.99 (± 32.17)	19.67 (± 29.06)		

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 for each individual category.

End point type	Secondary

End point timeframe:

At Week 52

End point values	Tralo 300 mg Q2W	Placebo	Biomarker positive - Tralo 300 mg Q2W	Biomarker positive - Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	169	160	50	49
Units: Percent impairment				
arithmetic mean (standard deviation)				
Currently employed (n=147, 131, 45, 36, 100, 94)	20.68 (± 19.82)	26.11 (± 24.89)	20.89 (± 18.81)	25.28 (± 28.63)
Currently in school (n=22, 29, 5, 13, 16, 16)	24.55 (± 27.38)	27.93 (± 28.71)	20.00 (± 18.71)	33.85 (± 26.63)

End point values	Biomarker negative - Tralo 300 mg Q2W	Biomarker negative - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	110		
Units: Percent impairment				

arithmetic mean (standard deviation)				
Currently employed (n=147, 131, 45, 36, 100, 94)	20.50 (± 20.42)	26.49 (± 23.59)		
Currently in school (n=22, 29, 5, 13, 16, 16)	26.88 (± 30.49)	23.13 (± 30.27)		

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	Placebo	Biomarker positive - Tralo 300 mg Q2W	Biomarker positive - Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	420	417	108	121
Units: Number of times				
Ambulance transport	35	41	14	21
Emergency room visits	87	99	20	28
Unscheduled outpatient visits	1798	1834	513	579
Home visits	59	44	10	18
Telephone calls	163	196	51	76
Advanced pulmonary function test	51	46	16	20

End point values	Biomarker negative - Tralo 300 mg Q2W	Biomarker negative - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	308	290		
Units: Number of times				
Ambulance transport	21	20		
Emergency room visits	65	70		
Unscheduled outpatient visits	1274	1216		

Home visits	49	26		
Telephone calls	112	117		
Advanced pulmonary function test	35	26		

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	Placebo	Biomarker positive - Tralo 300 mg Q2W	Biomarker positive - Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	420	417	108	121
Units: Days	417	590	82	175

End point values	Biomarker negative - Tralo 300 mg Q2W	Biomarker negative - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	308	290		
Units: Days	334	414		

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	Placebo	Biomarker positive - Tralo 300 mg Q2W	Biomarker positive - Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	420	417	108	121
Units: Number of assessments	434	426	148	151

End point values	Biomarker negative - Tralo 300 mg Q2W	Biomarker negative - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	308	290		
Units: Number of assessments	284	270		

Statistical analyses

No statistical analyses for this end point

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

End point title	Serum trough concentration (Ctrough) of tralokinumab during the treatment period up to Week 72

End point description:

To evaluate the 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 FAS who received tralokinumab and who had PK blood samples were included in the PK analysis set. Results are reported for patients in the biomarker positive, biomarker negative and 'total' PK groups. PK analyses were not performed on samples taken from patients in the placebo Q2W group. 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 2, Week 8, Week 26, Week 56 (follow-up) and Week 72 (follow-up)

End point values	Biomarker positive - Tralo 300 mg Q2W	Biomarker negative - Tralo 300 mg Q2W	Total - Tralo 300 mg Q2W	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	108[36]	302[37]	410[38]	
Units: micrograms/millilitre				
geometric mean (geometric coefficient of variation)				
Baseline (n=108, 302, 410)	99999999 (± 99999999)	99999999 (± 99999999)	99999999 (± 99999999)	
Week 2 (n=103, 293, 396)	24.049 (± 172.475)	20.916 (± 280.452)	21.690 (± 248.876)	
Week 8 (n=105, 280, 385)	55.887 (± 206.478)	52.324 (± 226.298)	53.272 (± 220.301)	
Week 26 (n=99, 274, 373)	58.375 (± 145.256)	47.707 (± 319.456)	50.332 (± 264.686)	
Week 56 (follow-up) (n=96, 275, 371)	12.363 (± 591.282)	12.513 (± 707.267)	12.474 (± 671.922)	
Week 72 (follow-up) (n=92, 264, 356)	0.325 (± 251.436)	0.384 (± 242.035)	0.368 (± 244.398)	

Notes:

[36] - 99999999 denotes that the value was not calculable since below level of detection.

[37] - 99999999 denotes that the value was not calculable since below level of detection.

[38] - 99999999 denotes that the value was not calculable since below level of detection.

Statistical analyses

No statistical analyses for this end point

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

End point title	Incidence rate of positive anti-drug antibodies (ADAs) including the characterization of their neutralizing 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	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	405	394		
Units: Participants				
ADA prevalence	7	8		
ADA incidence	5	3		
ADA positive at baseline	2	5		
ADA positive post-baseline	5	6		
ADA pos post-baseline & pos at baseline	0	3		
ADA pos post-baseline & not detected at baseline	5	3		
ADA not detected post-baseline & pos at baseline	2	2		
Persistent Positive	3	6		
Transient Positive	2	0		
Treatment-boosted ADA	0	0		
nAB positive at any visit	5	2		

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 + 2 weeks). Patient population was the safety analysis set which included all patients who received at least one dose of 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).

Reporting group title	Placebo

Reporting group description:

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

Serious adverse events	Tralo 300 mg Q2W	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 425 (8.24%)	39 / 422 (9.24%)	
number of deaths (all causes)	1	4	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal cancer			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Eosinophilic granulomatosis with polyangiitis			

subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adnexa uteri pain			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	17 / 425 (4.00%)	23 / 422 (5.45%)	
occurrences causally related to treatment / all	0 / 17	0 / 30	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis chronic			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			

subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			

subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Vascular headache			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			

subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Vitiligo			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Patellofemoral pain syndrome			

subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis A			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis viral			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 425 (0.94%)	3 / 422 (0.71%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			

subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (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	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	0 / 425 (0.00%)	1 / 422 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 425 (0.24%)	0 / 422 (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	Tralo 300 mg Q2W	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	159 / 425 (37.41%)	152 / 422 (36.02%)	
Nervous system disorders			
Headache			
subjects affected / exposed	40 / 425 (9.41%)	32 / 422 (7.58%)	
occurrences (all)	76	49	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	23 / 425 (5.41%)	3 / 422 (0.71%)	
occurrences (all)	93	5	
Respiratory, thoracic and mediastinal			

disorders			
Asthma			
subjects affected / exposed	35 / 425 (8.24%)	47 / 422 (11.14%)	
occurrences (all)	51	79	
Infections and infestations			
Bronchitis			
subjects affected / exposed	34 / 425 (8.00%)	31 / 422 (7.35%)	
occurrences (all)	59	50	
Upper respiratory tract infection			
subjects affected / exposed	29 / 425 (6.82%)	31 / 422 (7.35%)	
occurrences (all)	49	39	
Viral upper respiratory tract infection			
subjects affected / exposed	50 / 425 (11.76%)	52 / 422 (12.32%)	
occurrences (all)	71	80	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 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. - Inclusion criteria were amended for the following reasons: 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 add clarifications to the study plan and timing of procedures table. - To clarify the timing and procedures for an IP discontinuation (IPD) visit for those patients discontinuing IP prematurely. - To clarify that urinalysis will be completed at all unscheduled visits. - To include the haematology/haemostasis assessment schedule for the IPD visit. - To include the urinalysis schedule for the IPD visit and unscheduled visit, and to clarify the local dipstick test procedure. - Evaluation of cardiovascular and malignancy AEs 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. - To amend the asthma medications restrictions, including clarification for prophylactic use of short-acting β2-agonists, clarification of use of once daily asthma medications, to clarify the restrictions on bronchodilators prior to run-in visit and during the treatment period, and required rescheduling of the FEV1 visit if the indicated washout times are not adhered to. - To clarify the immunotherapy restrictions. - Testing strategy for primary and key secondary objectives was revised.
19 May 2015	- Global Impression of Change assessment was added to obtain an early indicator of patients' 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. A specialist in neurology was added to the adjudication committee. - An immunoglobulin E measurement was added during the treatment period to obtain an early indication of patients' response to treatment. - The AE follow-up reporting period definition was amended to include the whole period up to 72 weeks for all patients.
08 October 2015	- The minimum interval of 7 days required between 2 dosing visits was clarified.
09 June 2017	- Based on the results of the pivotal Phase 3 study (D2210C00007), the primary and secondary populations, the biomarker strategy and the hierarchical testing strategy population were all clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported