



## Clinical trial results:

### **A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-Controlled, 12-Week, Phase 2 Study to Evaluate the Effect of Tralokinumab on Airway Inflammation in Adults with Asthma Inadequately Controlled on Inhaled Corticosteroid (MESOS)**

#### **Summary**

EudraCT number	2015-000857-19
Trial protocol	GB DK
Global end of trial date	21 June 2017

#### **Results information**

Result version number	v1 (current)
This version publication date	23 May 2018
First version publication date	23 May 2018

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	D2210C00014
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02449473
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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	21 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2017
Global end of trial reached?	Yes
Global end of trial date	21 June 2017
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

To evaluate the effect of tralokinumab on eosinophilic airway infiltration in adult patients with asthma inadequately controlled with inhaled corticosteroid (ICS).

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 ( $\geq 250$  micrograms fluticasone dry powder formulation equivalents total daily dose) + any additional maintenance asthma controller medication throughout the study.

Evidence for comparator: -

Actual start date of recruitment	29 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	United Kingdom: 45
Country: Number of subjects enrolled	Denmark: 23
Country: Number of subjects enrolled	Canada: 11
Worldwide total number of subjects	79
EEA total number of subjects	68

Notes:

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**Subjects enrolled per age group**

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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)	0

Adults (18-64 years)	66
From 65 to 84 years	13
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

First patient enrolled: 29 Sep 2015; Last patient last visit: 21 Jun 2017. Study performed at 14 sites in 3 countries.

### Pre-assignment

Screening details:

224 patients signed informed consent, 172 entered screening/run-in period, 79 patients were randomised to receive investigational product (IP) and all those randomised received treatment.

### Period 1

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

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
<b>Arm title</b>	Tralo 300 mg Q2W

Arm description:

Tralokinumab 300 milligrams (mg) administered subcutaneously every 2 weeks (Q2W) over a 12-week treatment period (up to 6 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 subcutaneous injections of 150 mg tralokinumab at each dosing interval to receive a total dose of 300 mg.

<b>Arm title</b>	Placebo
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Arm description:

Placebo administered subcutaneously Q2W over a 12-week treatment period (up to 6 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 subcutaneous injections of placebo at each dosing interval.

<b>Number of subjects in period 1</b>	Tralo 300 mg Q2W	Placebo
Started	39	40
Completed	39	40

## Baseline characteristics

### Reporting groups

Reporting group title	Tralo 300 mg Q2W
Reporting group description: Tralokinumab 300 milligrams (mg) administered subcutaneously every 2 weeks (Q2W) over a 12-week treatment period (up to 6 doses).	
Reporting group title	Placebo
Reporting group description: Placebo administered subcutaneously Q2W over a 12-week treatment period (up to 6 doses).	

Reporting group values	Tralo 300 mg Q2W	Placebo	Total
Number of subjects	39	40	79
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)	0	0	0
Adults (18-64 years)	34	32	66
From 65-84 years	5	8	13
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	47.1	50.1	
standard deviation	± 14.2	± 14.2	-
Sex: Female, Male Units: Subjects			
Female	23	20	43
Male	16	20	36
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	0	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	1	3
White	34	39	73
More than one race	0	0	0
Unknown or Not Reported	0	0	0

## End points

### End points reporting groups

Reporting group title	Tralo 300 mg Q2W
Reporting group description: Tralokinumab 300 milligrams (mg) administered subcutaneously every 2 weeks (Q2W) over a 12-week treatment period (up to 6 doses).	
Reporting group title	Placebo
Reporting group description: Placebo administered subcutaneously Q2W over a 12-week treatment period (up to 6 doses).	

### Primary: Change from baseline to Week 12, expressed as a ratio, in number of airway submucosal eosinophils

End point title	Change from baseline to Week 12, expressed as a ratio, in number of airway submucosal eosinophils
End point description: The number of airway submucosal eosinophils per millimetre squared (mm <sup>2</sup> ) was determined by microscopic evaluation of bronchoscopic biopsies. The ratio of post-randomisation value at Week 12 to baseline value was computed as (Week 12 value / baseline value). The change from baseline to Week 12 (ratio) in the number of airway submucosal eosinophils is presented as geometric mean (back-transformed to be original scale), with standard deviation (SD) values presented on the log scale. Results are presented for the FAS comprising all randomised patients who received any IP.	
End point type	Primary
End point timeframe: Baseline (Week 0) and Week 12	

End point values	Tralo 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	39		
Units: Ratio				
geometric mean (standard deviation)	1.29 (± 2.06)	1.07 (± 1.87)		

### Statistical analyses

Statistical analysis title	Change from baseline; airway submucosal eosinophil
Statistical analysis description: Comparison of change from baseline, expressed as a ratio, in airway submucosal eosinophils; Tralo 300 mg Q2W vs placebo. The null hypothesis was that the change in airway submucosal eosinophils at Week 12 on tralokinumab was equal to the corresponding change on placebo.	
Comparison groups	Tralo 300 mg Q2W v Placebo

Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	= 0.3862
Method	ANCOVA
Parameter estimate	Least square (LS) geometric mean ratio
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	3.27

Notes:

[1] - The model included treatment group as fixed effect and baseline log-transformed airway submucosal eosinophils as a continuous covariate. No interaction terms were included in the model. The analysis was performed using log-transformed data. All group comparisons from analysis of covariance (ANCOVA) model were based on Type III sums of squares.

### Secondary: Change from baseline to Week 12, expressed as a ratio, in number of blood eosinophils

End point title	Change from baseline to Week 12, expressed as a ratio, in number of blood eosinophils
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End point description:

The blood eosinophil count was obtained from the total and differential white blood cell counts. The ratio of post-randomisation value at Week 12 to baseline value was computed as (Week 12 value / baseline value). The change from baseline to Week 12 (ratio) in the number of blood eosinophils is presented as geometric mean (back-transformed to be original scale), with SD values presented on the log scale. Results are presented for the FAS comprising all randomised patients who received any IP.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) and Week 12

End point values	Tralo 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	37		
Units: Ratio				
geometric mean (standard deviation)	1.10 (± 0.38)	0.91 (± 0.46)		

### Statistical analyses

Statistical analysis title	Change from baseline; blood eosinophils
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Statistical analysis description:

Comparison of change from baseline, expressed as a ratio, in blood eosinophil count; Tralo 300 mg Q2W vs placebo.

Comparison groups	Tralo 300 mg Q2W v Placebo
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Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority <sup>[2]</sup>
P-value	= 0.0546
Method	Repeated measures analysis
Parameter estimate	LS geometric mean ratio
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.48

Notes:

[2] - The repeated measures analysis included treatment group, baseline log-transformed eosinophils and visit as fixed effects. Treatment-by-visit interaction was also included. The analysis was performed using log-transformed data. A restricted maximum likelihood (REML) approach was used. An unstructured variance-covariance matrix was used to model the within-subject errors.

### Secondary: Change from baseline to Week 12, expressed as a ratio, in number of differential sputum eosinophils

End point title	Change from baseline to Week 12, expressed as a ratio, in number of differential sputum eosinophils
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End point description:

Sputum induction was performed to obtain satisfactory samples of sputum originating from the airways. The ratio of post-randomisation value at Week 12 to baseline value was computed as (Week 12 value / baseline value). The change from baseline to Week 12 (ratio) in the number of eosinophils in induced sputum is presented as geometric mean (back-transformed to be original scale), with SD values presented on the log scale. Results are presented for the FAS comprising all randomised patients who received any IP.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) and Week 12

End point values	Tralo 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: Ratio				
geometric mean (standard deviation)	0.20 (± 3.16)	0.47 (± 3.63)		

### Statistical analyses

Statistical analysis title	Change from baseline; induced sputum eosinophils
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Statistical analysis description:

Comparison of change from baseline, expressed as a ratio, in differential sputum eosinophils; Tralo 300 mg Q2W vs placebo.

Comparison groups	Tralo 300 mg Q2W v Placebo
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Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority <sup>[3]</sup>
P-value	= 0.6334
Method	Repeated measures analysis
Parameter estimate	LS geometric mean ratio
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	6

Notes:

[3] - The repeated measures analysis included treatment group, baseline log-transformed differential sputum eosinophils and visit as fixed effects. Treatment-by-visit interaction was also included. The analysis was performed using log-transformed data. A REML approach was used. An unstructured variance-covariance matrix was used to model the within-subject errors.

### Secondary: Change from baseline to Week 12, expressed as a ratio, in blood free eosinophil cationic protein (ECP) concentrations

End point title	Change from baseline to Week 12, expressed as a ratio, in blood free eosinophil cationic protein (ECP) concentrations
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End point description:

ECP concentrations were determined to assess evidence of activation of eosinophils in blood. The ratio of post-randomisation value at Week 12 to baseline value was computed as (Week 12 value / baseline value). The change from baseline to Week 12 (ratio) in blood free ECP concentrations is presented as geometric mean (back-transformed to be original scale), with SD values presented on the log scale. Results are presented for the FAS comprising all randomised patients who received any IP.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) and Week 12

End point values	Tralo 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	28		
Units: Ratio				
geometric mean (standard deviation)	1.07 (± 0.40)	0.92 (± 0.47)		

### Statistical analyses

<b>Statistical analysis title</b>	Change from baseline; blood free ECP
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Statistical analysis description:

Comparison of change from baseline, expressed as a ratio, in blood free ECP concentration; Tralo 300 mg Q2W vs placebo.

Comparison groups	Tralo 300 mg Q2W v Placebo
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Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority <sup>[4]</sup>
P-value	= 0.3769
Method	Repeated measures analysis
Parameter estimate	LS geometric mean ratio
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.4

Notes:

[4] - The repeated measures analysis included treatment group, baseline log-transformed blood free ECP and visit as fixed effects. Treatment-by-visit interaction was also included. The analysis was performed using log-transformed data. A REML approach was used. An unstructured variance-covariance matrix was used to model the within-subject errors.

### Secondary: Change from baseline to Week 12, expressed as a ratio, in sputum free ECP concentrations

End point title	Change from baseline to Week 12, expressed as a ratio, in sputum free ECP concentrations
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End point description:

ECP concentrations were determined to assess evidence of activation of eosinophils in sputum. The ratio of post-randomisation value at Week 12 to baseline value was computed as (Week 12 value / baseline value). The change from baseline to Week 12 (ratio) in sputum free ECP concentrations is presented as geometric mean (back-transformed to be original scale), with SD values presented on the log scale. Results are presented for the FAS comprising all randomised patients who received any IP.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) and Week 12

End point values	Tralo 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: Ratio				
geometric mean (standard deviation)	0.66 (± 1.21)	1.83 (± 1.41)		

### Statistical analyses

Statistical analysis title	Change from baseline; sputum free ECP
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Statistical analysis description:

Comparison of change from baseline, expressed as a ratio, in sputum free ECP concentration; Tralo 300 mg Q2W vs placebo.

Comparison groups	Tralo 300 mg Q2W v Placebo
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Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority <sup>[5]</sup>
P-value	= 0.1126
Method	Repeated measures analysis
Parameter estimate	LS geometric mean ratio
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.2

Notes:

[5] - The repeated measures analysis included treatment group, baseline log-transformed sputum free ECP and visit as fixed effects. Treatment-by-visit interaction was also included. The analysis was performed using log-transformed data. A REML approach was used. An unstructured variance-covariance matrix was used to model the within-subject errors.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

12 weeks

Adverse event reporting additional description:

Data is reported for adverse events during the treatment period (onset date  $\geq$  the first day of IP and  $\leq$  the last day of IP + 2 weeks). Patient population was the safety analysis set which included all patients who received any IP, classified according to the treatment they actually received.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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### Reporting groups

Reporting group title	Tralo 300 mg Q2W
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Reporting group description:

Tralokinumab 300 mg administered subcutaneously Q2W over a 12-week treatment period (up to 6 doses).

Reporting group title	Placebo
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Reporting group description:

Placebo administered subcutaneously Q2W over a 12-week treatment period (up to 6 doses).

Serious adverse events	Tralo 300 mg Q2W	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tralo 300 mg Q2W	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 39 (76.92%)	27 / 40 (67.50%)	
Investigations			

Weight increased subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	1 / 40 (2.50%) 1	
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	3 / 40 (7.50%) 3	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	9 / 40 (22.50%) 18	
General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all)  Injection site pain subjects affected / exposed occurrences (all)  Injection site pruritus subjects affected / exposed occurrences (all)  Injection site swelling subjects affected / exposed occurrences (all)  Non-cardiac chest pain subjects affected / exposed occurrences (all)  Fatigue subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3  2 / 39 (5.13%) 3  2 / 39 (5.13%) 3  2 / 39 (5.13%) 3  2 / 39 (5.13%) 2  1 / 39 (2.56%) 1	0 / 40 (0.00%) 0  0 / 40 (0.00%) 0  0 / 40 (0.00%) 0  0 / 40 (0.00%) 0  0 / 40 (0.00%) 0  3 / 40 (7.50%) 3	
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)  Nausea	3 / 39 (7.69%) 3	2 / 40 (5.00%) 3	

subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	1 / 40 (2.50%) 2	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	6 / 39 (15.38%)	2 / 40 (5.00%)	
occurrences (all)	7	2	
Cough			
subjects affected / exposed	3 / 39 (7.69%)	2 / 40 (5.00%)	
occurrences (all)	4	3	
Rhinorrhoea			
subjects affected / exposed	3 / 39 (7.69%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Dyspnoea			
subjects affected / exposed	2 / 39 (5.13%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Epistaxis			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	8 / 39 (20.51%)	17 / 40 (42.50%)	
occurrences (all)	10	20	
Influenza			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	2	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2015	- Text was revised to state that all patients would be followed up for a period of 14 weeks and that women of child bearing potential only would have an on-site follow-up visit at Week 26 to ascertain their pregnancy status. This revision was implemented following a request by the Medicines and Healthcare products Regulatory Agency.
15 January 2016	- For completion of the eosinophil evaluation, secondary objectives were updated to include assessment of sputum eosinophil levels. Submucosal eosinophil staining was removed as an outcome variable since this was included in the primary outcome variable. - To clarify that functional respiratory imaging analysis was optional and may be performed later pending other results from the study as well as the outcome of the pivotal studies, exploratory objectives relating to airway volume and resistance for entire airway tree were updated. - Revisions were applied to other exploratory objectives for the following reasons: to build flexibility to perform additional exploratory analysis; to clarify that both pre-bronchodilator (BD); and post-BD spirometry could be included; to allow the acceptance of both 'PC20' (provocative concentration required to achieve a 20% reduction in forced expiratory volume in 1 second [FEV1]) and 'PD20' (provocative dose required to achieve a 20% reduction in FEV1) in the airway hyper-responsiveness exploratory objective outcome variable; to make the RNA exploratory objective more specific; to remove sputum eosinophils from the exploratory variables since this was included as a secondary outcome measure; to provide flexibility for spirometry assessments; to clarify that whole body plethysmography was to be performed post-BD. - Discontinuation criteria were revised to allow subjects with an asthma-related event requiring non-invasive ventilation to continue with IP.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The results for differential sputum eosinophils and sputum free ECP levels should be viewed cautiously due to the small sample size and wide variability in results for sputum analyses.

Notes: