



## Clinical trial results:

### MEA115575: A Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study of Mepolizumab Adjunctive Therapy to Reduce Steroid Use in Subjects with Severe Refractory Asthma

#### Summary

EudraCT number	2012-001497-29
Trial protocol	GB DE NL CZ
Global end of trial date	12 December 2013

#### Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	04 June 2015

#### Trial information

##### Trial identification

Sponsor protocol code	MEA115575
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000069-PIP02-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 December 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To compare the effects of mepolizumab adjunctive therapy with placebo on reducing the use of maintenance oral corticosteroids (OCS) in systemic corticosteroid dependent subjects with severe refractory asthma with elevated eosinophils.

Protection of trial subjects:

Numbing cream or spray was permitted at the site of injection and rescue medications (salbuterol/albuterol) are available to the participant throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 October 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 25
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Czech Republic: 13
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	135
EEA total number of subjects	98

Notes:

### Subjects enrolled per age group

In utero	0
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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)	2
Adults (18-64 years)	119
From 65 to 84 years	14
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study consisted 4 phases: oral corticosteroids (OCS) Optimization (Run-in); Induction; OCS Reduction and Maintenance. Participants (par.) who completed the 4 phases and met the eligibility criteria were offered the opportunity to participate in an open label extension (OLE) study. Par. not entering the OLE study completed the Follow-up Visit.

### Pre-assignment

Screening details:

A total of 185 Par were enrolled; 3 Par were Screen failures; 47 Par were Run-in failures; 135 Par were randomized and received  $\geq 1$  dose of study drug.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

Participants received placebo subcutaneously (SC) every 4 weeks (for a total of 6 doses), with the last dose at Week 20. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.

Arm type	Placebo
Investigational medicinal product name	Placebo (normal saline)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Every 4 weeks

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

Participants received mepolizumab 100 mg SC every 4 weeks (for a total of 6 doses), with the last dose at Week 20. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.

Arm type	Experimental
Investigational medicinal product name	Mepolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

100 mg every 4 weeks

<b>Number of subjects in period 1</b>	Placebo	Mepolizumab
Started	66	69
Completed	62	66
Not completed	4	3
Consent withdrawn by subject	1	-
Adverse event, non-fatal	3	3

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneously (SC) every 4 weeks (for a total of 6 doses), with the last dose at Week 20. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.	
Reporting group title	Mepolizumab
Reporting group description:	
Participants received mepolizumab 100 mg SC every 4 weeks (for a total of 6 doses), with the last dose at Week 20. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.	

Reporting group values	Placebo	Mepolizumab	Total
Number of subjects	66	69	135
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	49.9	49.8	
standard deviation	± 10.3	± 14.1	-
Gender categorical			
Units: Subjects			
Female	30	44	74
Male	36	25	61
Race			
Units: Subjects			
American Indian or Alaskan Native	1	0	1
Asian - Central/South Asian Heritage	1	0	1
Asian - East Asian Heritage	0	1	1
Asian - South East Asian Heritage	1	0	1
Native Hawaiian or Other Pacific Islander	1	0	1
White - Arabic/North African Heritage	1	2	3
White - White/Caucasian/European Heritage	60	65	125
Mixed Race	1	1	2

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants received placebo subcutaneously (SC) every 4 weeks (for a total of 6 doses), with the last dose at Week 20. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.	
Reporting group title	Mepolizumab
Reporting group description: Participants received mepolizumab 100 mg SC every 4 weeks (for a total of 6 doses), with the last dose at Week 20. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.	

### Primary: Number of participants with the indicated percent reduction from Baseline in oral corticosteroid (OCS) dose during Weeks 20 to 24 while maintaining asthma control

End point title	Number of participants with the indicated percent reduction from Baseline in oral corticosteroid (OCS) dose during Weeks 20 to 24 while maintaining asthma control
End point description: Baseline (BL) dose was the prescribed optimized prednisone/prednisolone dose following the OCS Optimization Phase. Maintenance (MN) dose was the mean of all daily prednisone/prednisolone doses during the MN Phase (weeks 20 to 24). The percent reduction of OCS dose during weeks 20 to 24 compared to BL dose was calculated as: $100 \times (\text{BL dose} - \text{MN dose}) / \text{BL dose}$ . Asthma control between weeks 20 and 24 was defined as no clinically significant exacerbation (worsening of asthma that required use of systemic corticosteroids or hospitalization and/or emergency department visits) during this period. The percent reduction of OCS was categorized as: 90 to 100%; 75 to <90%; 50 to <75%; >0 to <50%; no decrease in prednisone dose, or lack of asthma control, or withdrawal (WD) from treatment. Analysis was performed using a proportional odds model with terms for treatment group, region, duration of OCS use at BL (<5 years vs. ≥5 years) and BL OCS dose.	
End point type	Primary
End point timeframe: Baseline; Weeks 20 to 24	

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66 <sup>[1]</sup>	69 <sup>[2]</sup>		
Units: Participants				
90 to 100%	7	16		
75 to <90%	5	12		
50 to <75%	10	9		
>0 to <50%	7	7		
No decrease /lack of asthma control/early WD	37	25		

Notes:

[1] - Intent-to-Treat (ITT) Population: all randomized par. who received at ≥ 1 dose of study medication.

## Statistical analyses

<b>Statistical analysis title</b>	Analysis 1
Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Proportional odds model
Parameter estimate	Odds ratio (OR)
Point estimate	2.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.25
upper limit	4.56

## Secondary: Number of participants who achieved a reduction of $\geq 50\%$ in their daily oral corticosteroid (OCS) dose compared with Baseline dose, during weeks 20 to 24 while maintaining asthma control

End point title	Number of participants who achieved a reduction of $\geq 50\%$ in their daily oral corticosteroid (OCS) dose compared with Baseline dose, during weeks 20 to 24 while maintaining asthma control
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### End point description:

Baseline (BL) dose was the prescribed optimized prednisone/prednisolone dose following the OCS Optimization Phase. Maintenance (MN) dose was the mean of all daily prednisone/prednisolone doses during the MN Phase (weeks 20 to 24). The percent reduction of OCS dose during weeks 20 to 24 compared to BL dose was calculated as:  $100 \times (\text{BL dose} - \text{MN dose}) / \text{BL dose}$ . Asthma control between weeks 20 and 24 was defined as no clinically significant exacerbation (worsening of asthma that required use of systemic corticosteroids or hospitalization and/or emergency department visits) during this period. Analysis was performed using a binary logistic regression model with terms for treatment group, region, duration of OCS use at BL ( $< 5$  years vs.  $\geq 5$  years) and BL OCS dose.

End point type	Secondary
End point timeframe:	
Baseline; Weeks 20 to 24	



End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66 <sup>[3]</sup>	69 <sup>[4]</sup>		
Units: Participants				
50 to 100%	22	37		
<50% or no decrease/lack of asthma control/WD	44	32		

Notes:

[3] - ITT Population

[4] - ITT Population

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants who achieved a reduction of their daily OCS dose to ≤5.0 mg during weeks 20 to 24 while maintaining asthma control

End point title	Number of participants who achieved a reduction of their daily OCS dose to ≤5.0 mg during weeks 20 to 24 while maintaining asthma control
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End point description:

Maintenance (MN) dose was the mean of all daily prednisone/prednisolone doses during the MN Phase (weeks 20 to 24). Asthma control between weeks 20 and 24 was defined as no clinically significant exacerbation (worsening of asthma that required use of systemic corticosteroids or hospitalization and/or emergency department visits) during this period. Number of participants who achieved a reduction of their daily OCS dose to ≤5.0 mg was based on the value of the MN dose. Analysis was performed using a binary logistic regression model with terms for treatment group, region, duration of OCS use at BL (<5 years vs. ≥5 years) and BL OCS dose.

End point type	Secondary
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End point timeframe:

Weeks 20 to 24

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66 <sup>[5]</sup>	69 <sup>[6]</sup>		
Units: Participants				
≤5 mg/day	21	37		
>5 mg/day or lack of asthma control or WD	45	32		

Notes:

[5] - ITT Population

[6] - ITT Population

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants who achieved a total reduction of OCS dose during weeks 20 to 24 while maintaining asthma control

End point title	Number of participants who achieved a total reduction of OCS dose during weeks 20 to 24 while maintaining asthma control
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**End point description:**

MN dose was the mean of all daily prednisone/prednisolone doses during the MN Phase (weeks 20 to 24). Asthma control between weeks 20 and 24 was defined as no clinically significant exacerbation (worsening of asthma that required use of systemic corticosteroids or hospitalization and/or emergency department visits) during this period. The number of participants who achieved a total reduction of OCS dose was based on the value of the MN dose. Total reduction implied no OCS use during the entire MN phase. Analysis was performed using a binary logistic regression model with terms for treatment group, region, duration of OCS use at BL (<5 years vs. ≥5 years) and BL OCS dose.

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End point type	Secondary
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End point timeframe:

Weeks 20 to 24

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End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66 <sup>[7]</sup>	69 <sup>[8]</sup>		
Units: Participants				
0 mg/day	5	10		
OCS taken or lack of asthma control or WD	61	59		

Notes:

[7] - ITT Population

[8] - ITT Population

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Median percentage reduction from Baseline in daily OCS dose during weeks 20 to 24 while maintaining asthma control**

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End point title	Median percentage reduction from Baseline in daily OCS dose during weeks 20 to 24 while maintaining asthma control
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End point description:

BL dose was the prescribed optimized prednisone/prednisolone dose following the OCS Optimization Phase. MN dose was the mean of all daily prednisone/prednisolone doses during the MN Phase (weeks 20 to 24). The percent reduction of OCS dose during weeks 20 to 24 compared to BL dose was calculated as:  $100 \times (\text{BL dose} - \text{MN dose}) / \text{BL dose}$ . Asthma control between weeks 20 and 24 was defined as no clinically significant exacerbation (worsening of asthma that required use of systemic corticosteroids or hospitalization and/or emergency department visits) during this period. For participants who withdrew from the study prior to the Maintenance Phase, and for participants with a lack of asthma control during the Maintenance Phase, a value equal to the minimum percent reduction in OCS use across all subjects was imputed for the analysis.

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End point type	Secondary
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End point timeframe:

Baseline; Weeks 20 to 24

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<b>End point values</b>	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66 <sup>[9]</sup>	69 <sup>[10]</sup>		
Units: Percentage reduction in OCS dose				
median (confidence interval 95%)	0 (-20 to 33.3)	50 (20 to 75)		

Notes:

[9] - ITT Population

[10] - ITT Population

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious AEs were defined as events occurring from the first dose of investigational product until 28 days after the last dose of investigational product.

Adverse event reporting additional description:

SAEs and Non-serious AEs were collected in members of Intent-to-Treat (ITT) Population, comprised of all participants who were randomized and who received at least one dose of study medication. The number of occurrences for non-serious AEs was not collected; therefore, 0 has been entered.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Participants received placebo subcutaneously (SC) every 4 weeks (for a total of 6 doses), with the last dose at Week 20. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medication salbutamol/albuterol) /equipment were available throughout the study.

Reporting group title	Mepolizumab
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Reporting group description:

Participants received mepolizumab 100 mg SC every 4 weeks (for a total of 6 doses), with the last dose at Week 20. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.

Serious adverse events	Placebo	Mepolizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 66 (18.18%)	1 / 69 (1.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basosquamous carcinoma			
subjects affected / exposed	1 / 66 (1.52%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 66 (1.52%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Post gastric surgery syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 66 (1.52%) 0 / 1 0 / 0	0 / 69 (0.00%) 0 / 0 0 / 0	
Reproductive system and breast disorders Prostatitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 66 (1.52%) 0 / 1 0 / 0	0 / 69 (0.00%) 0 / 0 0 / 0	
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	7 / 66 (10.61%) 0 / 8 0 / 0	0 / 69 (0.00%) 0 / 0 0 / 0	
Musculoskeletal and connective tissue disorders Fistula subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 66 (0.00%) 0 / 0 0 / 0	1 / 69 (1.45%) 0 / 1 0 / 0	
Infections and infestations Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 66 (4.55%) 0 / 3 0 / 0	0 / 69 (0.00%) 0 / 0 0 / 0	
Chronic sinusitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 66 (0.00%) 0 / 0 0 / 0	1 / 69 (1.45%) 0 / 1 0 / 0	
Urinary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 66 (1.52%) 0 / 1 0 / 0	0 / 69 (0.00%) 0 / 0 0 / 0	
Metabolism and nutrition disorders			

Hypokalaemia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 69 (1.45%)	
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: 3 %

<b>Non-serious adverse events</b>	Placebo	Mepolizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 66 (80.30%)	47 / 69 (68.12%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	2 / 66 (3.03%)	0 / 69 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 66 (6.06%)	7 / 69 (10.14%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	4 / 66 (6.06%)	3 / 69 (4.35%)	
occurrences (all)	0	0	
Injection site reaction			
subjects affected / exposed	2 / 66 (3.03%)	4 / 69 (5.80%)	
occurrences (all)	0	0	
Oedema peripheral			
subjects affected / exposed	2 / 66 (3.03%)	4 / 69 (5.80%)	
occurrences (all)	0	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	3 / 66 (4.55%)	1 / 69 (1.45%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	5 / 66 (7.58%)	4 / 69 (5.80%)	
occurrences (all)	0	0	
Psychiatric disorders			

Insomnia subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 0	3 / 69 (4.35%) 0	
Injury, poisoning and procedural complications Injection related reaction subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 0	2 / 69 (2.90%) 0	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 0	0 / 69 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)  Dizziness subjects affected / exposed occurrences (all)  Sinus headache subjects affected / exposed occurrences (all)	14 / 66 (21.21%) 0  3 / 66 (4.55%) 0  2 / 66 (3.03%) 0	14 / 69 (20.29%) 0  2 / 69 (2.90%) 0  1 / 69 (1.45%) 0	
Eye disorders Eye pruritus subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 0	0 / 69 (0.00%) 0	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)  Toothache subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 0  3 / 66 (4.55%) 0  2 / 66 (3.03%) 0	4 / 69 (5.80%) 0  1 / 69 (1.45%) 0  0 / 69 (0.00%) 0	
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	2 / 66 (3.03%)	2 / 69 (2.90%)	
occurrences (all)	0	0	
Urticaria			
subjects affected / exposed	2 / 66 (3.03%)	1 / 69 (1.45%)	
occurrences (all)	0	0	
Rash			
subjects affected / exposed	2 / 66 (3.03%)	0 / 69 (0.00%)	
occurrences (all)	0	0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	4 / 66 (6.06%)	3 / 69 (4.35%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 66 (6.06%)	5 / 69 (7.25%)	
occurrences (all)	0	0	
Pain in extremity			
subjects affected / exposed	1 / 66 (1.52%)	4 / 69 (5.80%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	2 / 66 (3.03%)	2 / 69 (2.90%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	0 / 66 (0.00%)	4 / 69 (5.80%)	
occurrences (all)	0	0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 66 (3.03%)	0 / 69 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 66 (15.15%)	10 / 69 (14.49%)	
occurrences (all)	0	0	
Bronchitis			
subjects affected / exposed	6 / 66 (9.09%)	7 / 69 (10.14%)	
occurrences (all)	0	0	



Sinusitis			
subjects affected / exposed	6 / 66 (9.09%)	7 / 69 (10.14%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 66 (7.58%)	3 / 69 (4.35%)	
occurrences (all)	0	0	
Rhinitis			
subjects affected / exposed	1 / 66 (1.52%)	5 / 69 (7.25%)	
occurrences (all)	0	0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 66 (3.03%)	3 / 69 (4.35%)	
occurrences (all)	0	0	
Influenza			
subjects affected / exposed	1 / 66 (1.52%)	3 / 69 (4.35%)	
occurrences (all)	0	0	
Urinary tract infection			
subjects affected / exposed	2 / 66 (3.03%)	2 / 69 (2.90%)	
occurrences (all)	0	0	
Cystitis			
subjects affected / exposed	2 / 66 (3.03%)	1 / 69 (1.45%)	
occurrences (all)	0	0	
Otitis media			
subjects affected / exposed	2 / 66 (3.03%)	1 / 69 (1.45%)	
occurrences (all)	0	0	
Oral candidiasis			
subjects affected / exposed	2 / 66 (3.03%)	0 / 69 (0.00%)	
occurrences (all)	0	0	
Tooth infection			
subjects affected / exposed	2 / 66 (3.03%)	0 / 69 (0.00%)	
occurrences (all)	0	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2012	<ul style="list-style-type: none"><li>- Clarified inclusion criteria 6</li><li>- Modified randomisation criteria 4</li><li>- Clarified primary endpoint</li><li>- Reduced number of secondary endpoints</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported