



Clinical trial results:

A Single-Centre, Open-Label, Randomised, 2-Way Cross-Over Study to Determine the Effects on the Short-Term Lower Leg Growth Rate Between Qvar® 100 Mcg BD Delivered via a Metered Dose Inhaler (MDI) (TEVA UK Ltd) With a Reference Beclometasone Formulation via a Reference MDI in Children with Mild to Moderate Asthma

Summary

EudraCT number	2007-007455-14
Trial protocol	DK
Global end of trial date	27 December 2008

Results information

Result version number	v1 (current)
This version publication date	05 January 2019
First version publication date	05 January 2019

Trial information

Trial identification

Sponsor protocol code	QV-001/2007-Pae
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Teva UK Ltd
Sponsor organisation address	Building V, Harlow Campus, London Road, Harlow, United Kingdom, CM17 9LP
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 001 2155913000, info.eraclinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 001 2155913000, info.eraclinical@teva.de

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 December 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 December 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate non-inferiority of Qvar 100 micrograms (mcg) twice daily (BD) relative to a reference formulation, Beclazone 200 mcg BD, in terms of the short-term growth rate of the right lower leg, measured by knemometry, in children with documented mild to moderate asthma.

Protection of trial subjects:

This study was conducted in compliance to the study protocol, and in accordance with the provisions of the guidelines of the World Medical Association Declaration of Helsinki in its revised edition (Tokyo, Japan, 2004), the guidelines of International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) (CPMP/ICH/135/95) and "Clinical Investigation of Medicinal Products in the Paediatric Population" (CPMP/ICH/2711/99), designated Standard Operating Procedures (SOPs), and with local laws and regulations relevant to the use of new and/or further development of therapeutic agents in the country of conduct. This study was also conducted in compliance with European Union (EU) Regulation 1901/2006. The study was conducted with due attention to the rights of children. Written consent to participate in the study was given by all participants' parents/guardian prior to any study procedures being performed and after they had read an Information Sheet about the study, and received a verbal explanation by the Investigator or his study nurses (who all had paedagogical skills) about the nature of the study, its purpose, procedures, expected duration and benefits, the necessity of having both parents consent and all examinations and treatment, sprays and spacers included in the study and risks of participation. The written consent obtained also included permission for the investigator to contact the participants' General Practitioner for details of previous medical history.

Background therapy:

Participants were allowed to take short-acting beta agonist (SABA) therapy throughout the study (during 2-week run-in period, 2-week wash-out period, and both treatment periods [2 weeks each]).

Evidence for comparator: -

Actual start date of recruitment	08 September 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 64
Worldwide total number of subjects	64
EEA total number of subjects	64

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)	64
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted at single centre in Denmark. After screening and 2-week run-in period, a total of 64 participants were randomized and treated in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence 1: Qvar Then Beclazone

Arm description:

Participants received Qvar (Beclometasone dipropionate) 100 mcg BD in first treatment period (Week 0 to Week 2) and Beclazone (Beclometasone dipropionate/Clorofluorocarbon [CFC] formulation) 200 mcg BD in second treatment period (Week 4 to Week 6). There was a 2-week washout period (Week 2 to Week 4) between both treatment periods.

Arm type	Experimental
Investigational medicinal product name	Qvar
Investigational medicinal product code	
Other name	Beclometasone dipropionate
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

Qvar was administered via pressurised metered dose inhaler (pMDI) (Qvar® IVAX with an AeroChamber® spacer) containing 200 doses of 50 mcg.

Investigational medicinal product name	Beclazone
Investigational medicinal product code	
Other name	Beclometasone dipropionate/CFC formulation
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

Beclazone was administered via pMDI (with a Volumatic™ spacer) containing 200 doses of 100 mcg.

Arm title	Sequence 2: Beclazone Then Qvar
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Arm description:

Participants received Beclazone 200 mcg BD in first treatment period (Week 0 to Week 2) and Qvar 100 mcg BD in second treatment period (Week 4 to Week 6). There was a 2-week washout period (Week 2 to Week 4) between both treatment periods.

Arm type	Experimental
Investigational medicinal product name	Qvar
Investigational medicinal product code	
Other name	Beclometasone dipropionate
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

Qvar was administered via pMDI (Qvar® IVAX with an AeroChamber® spacer) containing 200 doses of 50 mcg.

Investigational medicinal product name	Beclazone
Investigational medicinal product code	
Other name	Beclometasone dipropionate/CFC formulation
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

Beclazone was administered via pMDI (with a Volumatic™ spacer) containing 200 doses of 100 mcg.

Number of subjects in period 1	Sequence 1: Qvar Then Beclazone	Sequence 2: Beclazone Then Qvar
Started	32	32
Safety population	32	32
Completed	31	32
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups

Reporting group title	Sequence 1: Qvar Then Beclazone
Reporting group description:	
Participants received Qvar (Beclometasone dipropionate) 100 mcg BD in first treatment period (Week 0 to Week 2) and Beclazone (Beclometasone dipropionate/Clorofluorocarbon [CFC] formulation) 200 mcg BD in second treatment period (Week 4 to Week 6). There was a 2-week washout period (Week 2 to Week 4) between both treatment periods.	
Reporting group title	Sequence 2: Beclazone Then Qvar
Reporting group description:	
Participants received Beclazone 200 mcg BD in first treatment period (Week 0 to Week 2) and Qvar 100 mcg BD in second treatment period (Week 4 to Week 6). There was a 2-week washout period (Week 2 to Week 4) between both treatment periods.	

Reporting group values	Sequence 1: Qvar Then Beclazone	Sequence 2: Beclazone Then Qvar	Total
Number of subjects	32	32	64
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)	32	32	64
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	8.0	8.3	-
standard deviation	± 1.92	± 1.99	
Gender Categorical			
Units: Subjects			
Female	7	6	13
Male	25	26	51
Race			
Units: Subjects			
White	30	31	61
Asian	1	1	2
Other	1	0	1

End points

End points reporting groups

Reporting group title	Sequence 1: Qvar Then Beclazone
Reporting group description: Participants received Qvar (Beclometasone dipropionate) 100 mcg BD in first treatment period (Week 0 to Week 2) and Beclazone (Beclometasone dipropionate/Clorofluorocarbon [CFC] formulation) 200 mcg BD in second treatment period (Week 4 to Week 6). There was a 2-week washout period (Week 2 to Week 4) between both treatment periods.	
Reporting group title	Sequence 2: Beclazone Then Qvar
Reporting group description: Participants received Beclazone 200 mcg BD in first treatment period (Week 0 to Week 2) and Qvar 100 mcg BD in second treatment period (Week 4 to Week 6). There was a 2-week washout period (Week 2 to Week 4) between both treatment periods.	
Subject analysis set title	Qvar
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received Qvar 100 mcg BD either in first treatment period (Week 0 to Week 2) or in second treatment period (Week 4 to Week 6).	
Subject analysis set title	Beclazone
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received Beclazone 200 mcg BD either in first treatment period (Week 0 to Week 2) or in second treatment period (Week 4 to Week 6).	
Subject analysis set title	Run-in
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants were only allowed to take SABA therapy as required during 2-week run-in period.	
Subject analysis set title	Qvar
Subject analysis set type	Safety analysis
Subject analysis set description: Participants received Qvar 100 mcg BD either in first treatment period (Week 0 to Week 2) or in second treatment period (Week 4 to Week 6).	
Subject analysis set title	Beclazone
Subject analysis set type	Safety analysis
Subject analysis set description: Participants received Beclazone 200 mcg BD either in first treatment period (Week 0 to Week 2) or in second treatment period (Week 4 to Week 6).	

Primary: Short-Term Lower Leg Growth Rate (LLGR) During the Two Active Treatments

End point title	Short-Term Lower Leg Growth Rate (LLGR) During the Two Active Treatments
End point description: Short-term LLGR was measured by knemometry of the right lower leg after 2 weeks of treatment, and was calculated for each participant and for each treatment period in millimetres per week (mm/week). Four measurements were taken at each visit, with summaries and analysis based on the mean of the last three results. The LLGR was then determined from the change in growth measurement and number of days in each period, i.e. $LLGR \text{ (mm/week)} = ([\text{length in mm \{end\}} - \text{length in mm \{start\}}]/[\text{date \{end\}} - \text{date \{start\}}] + 1) * 7$. Analysis was performed on intent-to treat (ITT) population included all randomised participants who received at least one administration of one of the treatments and with an available evaluation of the primary variable in at least one of the treatment periods.	
End point type	Primary
End point timeframe: Treatments periods (Week 0 to Week 2; and Week 4 to Week 6)	

End point values	Qvar	Beclazone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63	63		
Units: mm/week				
arithmetic mean (standard deviation)	0.27 (± 0.214)	0.23 (± 0.178)		

Statistical analyses

Statistical analysis title	Qvar versus Beclazone
Statistical analysis description:	
Actual number of participants analysed=63. Analysis was performed using a linear mixed effects model-period and treatment was included as fixed effects, participant was included as a random effect, lower leg length at the start of the interval was added as a covariate.	
Comparison groups	Qvar v Beclazone
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.1

Notes:

[1] - The residual variance from the model was used to calculate lower limit of the 2 sided 95% confidence interval (CI) for the mean difference. Non-inferiority was concluded if lower limit of the 2 sided 95% CI was greater than -0.12 mm/week.

Secondary: LLGR During Each of the Two Active Treatments Compared With LLGR During Run-in

End point title	LLGR During Each of the Two Active Treatments Compared With LLGR During Run-in
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End point description:

Short-term LLGR was measured by knemometry of the right lower leg, and was calculated for each participant and for run-in period and each treatment period in mm/week. Four measurements were taken at each visit, with summaries and analysis based on the mean of the last three results. The LLGR was then determined from the change in growth measurement and number of days in each period, i.e. $LLGR \text{ (mm/week)} = ([\text{length in mm \{end\}} - \text{length in mm \{start\}}] / [\text{date \{end\}} - \text{date \{start\}}] + 1) * 7$.

Analysis was performed on ITT population included all randomised participants who received at least one administration of one of the treatments and with an available evaluation of the primary variable in at least one of the treatment periods.

End point type	Secondary
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End point timeframe:

Run-in period (Week -2 to Week 0), Treatment periods (Week 0 to Week 2; and Week 4 to Week 6)

End point values	Qvar	Beclazone	Run-in	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	63	63	63	
Units: mm/week				
arithmetic mean (standard deviation)	0.27 (\pm 0.214)	0.23 (\pm 0.178)	0.36 (\pm 0.166)	

Statistical analyses

No statistical analyses for this end point

Secondary: 24-Hour Urine Free Cortisol/Creatinine Levels During the Two Active Treatments

End point title	24-Hour Urine Free Cortisol/Creatinine Levels During the Two Active Treatments
End point description:	
Participants collected 24-hour urine at the end of each treatment period. Urine samples were analysed for free cortisol and creatinine at a central laboratory. Mean cortisol (nanomole [nmol])/creatinine (millimole [mmol]) ratio was reported. Analysis was performed on ITT population included all randomised participants who received at least one administration of one of the treatments and with an available evaluation of the primary variable in at least one of the treatment periods. Here, 'Number of subjects analyzed' signifies participants who were evaluable for this endpoint.	
End point type	Secondary
End point timeframe:	
Treatments periods (Week 0 to Week 2; and Week 4 to Week 6)	

End point values	Qvar	Beclazone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: nmol/mmol				
arithmetic mean (standard deviation)	7.13 (\pm 10.035)	6.13 (\pm 3.100)		

Statistical analyses

No statistical analyses for this end point

Secondary: 24-Hour Urine Free Cortisol/Creatinine Levels During Each of the Two Active Treatments Compared With Run-in Levels

End point title	24-Hour Urine Free Cortisol/Creatinine Levels During Each of the Two Active Treatments Compared With Run-in Levels
End point description:	
Participants collected 24-hour urine at the end of run-in period and each treatment period. Urine	

samples were analysed for free cortisol and creatinine at a central laboratory. Mean cortisol (nmol)/creatinine (mmol) ratio was reported. Analysis was performed on ITT population included all randomised participants who received at least one administration of one of the treatments and with an available evaluation of the primary variable in at least one of the treatment periods. Here, 'Number of subjects analyzed' signifies participants who were evaluable for this endpoint.

End point type	Secondary
End point timeframe:	
Run-in period (Week -2 to Week 0), Treatment periods (Week 0 to Week 2; and Week 4 to Week 6)	

End point values	Qvar	Beclazone	Run-in	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	62	61	61	
Units: nmol/mmol				
arithmetic mean (standard deviation)	7.13 (\pm 10.035)	6.13 (\pm 3.100)	6.73 (\pm 3.445)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Days With Rescue Medication

End point title	Percentage of Days With Rescue Medication
End point description:	
<p>Participants were instructed to use the provided SABA (e.g. salbutamol) as needed during the run-in, treatment and washout periods. The daily use of rescue medication (number of SABA puffs) was recorded by the participants on their diary cards twice daily in the morning and in the evening. The number of puffs taken during the night was recorded on the diary card each morning on awakening while the number of puffs taken during the day was recorded each evening before taking the study drug. The percentage of days rescue medication taken was calculated as: (Number of days with puffs greater than [$>$] 0/Number of days in period) * 100. For the calculation of percentages, days with missing results were assumed as a day with rescue medication. Analysis was performed on ITT population included all randomised participants who received at least one administration of one of the treatments and with an available evaluation of the primary variable in at least one of the treatment periods.</p>	
End point type	Secondary
End point timeframe:	
Week -2 to Week 6	

End point values	Qvar	Beclazone	Run-in	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	63	63	63	
Units: percentage of days				
arithmetic mean (standard deviation)	4.39 (\pm 11.945)	6.70 (\pm 17.317)	14.00 (\pm 24.333)	

Statistical analyses

No statistical analyses for this end point

Secondary: Average Number of Puffs Taken Per Day

End point title	Average Number of Puffs Taken Per Day
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End point description:

Participants were instructed to use the provided SABA (e.g. salbutamol) as needed during the run-in, treatment and washout periods. The daily use of rescue medication (number of SABA puffs) was recorded by the participants on their diary cards twice daily in the morning and in the evening. The number of puffs taken during the night was recorded on the diary card each morning on awakening while the number of puffs taken during the day was recorded each evening before taking the study drug. The average number of puffs per day was calculated as: Total number of puffs in period/Total number of days in period. For the calculation of percentages, days with missing results were assumed as a day with rescue medication. Analysis was performed on ITT population included all randomised participants who received at least one administration of one of the treatments and with an available evaluation of the primary variable in at least one of the treatment periods.

End point type	Secondary
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End point timeframe:

Week -2 to Week 6

End point values	Qvar	Beclazone	Run-in	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	63	63	63	
Units: puffs per day				
arithmetic mean (standard deviation)	0.15 (± 0.680)	0.13 (± 0.421)	0.25 (± 0.576)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Run-in (Week -2) in Peak Expiratory Flow (PEF) at the End of Treatment (Week 6)

End point title	Change From Run-in (Week -2) in Peak Expiratory Flow (PEF) at the End of Treatment (Week 6)
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End point description:

PEF was measured by participants at home using a portable, hand-held peak flow meter. During each measurement session (in the morning, before the intake of the study medication) the participant performed 3 blows and the best out of three PEF parameter results was recorded by the participant or their parents/guardians as necessary on the daily diary card. Participants recorded their best AM and PM PEF result (Liters per minute [L/min]) in the diary cards. Average AM and PM PEF were calculated using all available results in each period. Analysis was performed on ITT population included all randomised participants who received at least one administration of one of the treatments and with an available evaluation of the primary variable in at least one of the treatment periods. Here, 'n' signifies participants analyzed for this endpoint for specified categories.

End point type	Secondary
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End point timeframe:

Week -2, Week 6

End point values	Qvar	Beclazone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63	63		
Units: L/min				
arithmetic mean (standard deviation)				
Change from Run-in AM PEF (n=61,61)	9.19 (± 24.714)	8.49 (± 22.869)		
Change from Run-in PM PEF (n=61,61)	9.31 (± 23.692)	7.34 (± 18.833)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) (Including Asthma Exacerbations)

End point title	Number of Participants With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) (Including Asthma Exacerbations)
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End point description:

AE was defined as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. Serious AEs include death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event that jeopardized the participant and required medical intervention to prevent 1 of the outcomes listed in this definition. Treatment-emergent AEs were AEs that commenced after exposure to study treatment. A summary of serious and all other non-serious AEs regardless of causality is located in the Reported Adverse Events module. Analysis was performed on safety population included all randomised participants who received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

Treatments periods (Week 0 to Week 2; and Week 4 to Week 6)

End point values	Qvar	Beclazone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	63		
Units: participants				
AEs	8	6		
SAEs	0	0		

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatments periods (Week 0 to Week 2; and Week 4 to Week 6)

Adverse event reporting additional description:

Safety population included all randomised participants who received at least one dose of study medication.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.0
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Reporting groups

Reporting group title	Beclazone
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Reporting group description:

Participants received Beclazone 200 mcg BD either in first treatment period (Week 0 to Week 2) or in second treatment period (Week 4 to Week 6).

Reporting group title	Qvar
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Reporting group description:

Participants received Qvar 100 mcg BD either in first treatment period (Week 0 to Week 2) or in second treatment period (Week 4 to Week 6).

Serious adverse events	Beclazone	Qvar	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Beclazone	Qvar	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 63 (9.52%)	8 / 64 (12.50%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Psychomotor hyperactivity			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Periorbital oedema			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Pharyngitis			
subjects affected / exposed	1 / 63 (1.59%)	2 / 64 (3.13%)	
occurrences (all)	1	2	
Asthma			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Pharyngolaryngeal pain			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 June 2008	- Amendments to the text of study procedures, Visit 1 screening in response to the request by the Danish Ethics committee. - Amendments to the text of following sections were made in response to the request by the Danish Medicines Agency: Lung function measurements with spirometer, recording and reporting AEs, protocol synopsis visit schedule- protocol synopsis, study design, randomization and blinding, primary variable. - Amendments to the text of following sections were made at the request of the Investigator following review of Danish translation by email: Protocol synopsis, inclusion criteria, exclusion criteria, treatment, primary objective, selection and withdrawal of participants.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported