Clinical trial results:
A randomized, multi-center, parallel group, double blind, study to assess the safety of QMF Twisthaler® (500/400g) and mometasone furoate Twisthaler® (400g) in adolescent and adult patients with persistent asthma.

Summary

EudraCT number	2009-011539-10
Trial protocol	CZ HU SK
Global end of trial date	06 May 2011

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	07 August 2015

Trial information

Trial identification

Sponsor protocol code	CQMF149A2210

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00941798
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 May 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 May 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to compare the time to first serious asthma exacerbation resulting in hospitalisation, intubation or death in the subjects treated with the study drug either once daily QMF149 500/400 microgram (µg) or mometasone furoate (MF) 400 µg.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed. Rescue medication was allowed as recommended by the treating physician based on asthma management standard of care. Short acting β2- adrenergic agonists (salbutamol/albuterol) were permitted for the treatment of asthma exacerbations during the study. The investigator provided follow-up medical care for all subjects who were prematurely withdrawn from the study, or referred them for appropriate ongoing care.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 July 2009
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	Slovakia: 133
Country: Number of subjects enrolled	Czech Republic: 194
Country: Number of subjects enrolled	Colombia: 59
Country: Number of subjects enrolled	Brazil: 64
Country: Number of subjects enrolled	India: 223
Country: Number of subjects enrolled	Korea, Republic of: 52
Country: Number of subjects enrolled	Peru: 104
Country: Number of subjects enrolled	United States: 578
Country: Number of subjects enrolled	Hungary: 101
Worldwide total number of subjects	1508
EEA total number of subjects	428

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)	66
Adults (18-64 years)	1357
From 65 to 84 years	85
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 174 centres in 9 countries.

Pre-assignment

Screening details:

2282 subjects screened, 1519 subjects randomized and 1518 received study drug.11 randomized patients were excluded from all analysis population (i.e. FAS, PPS, Safety Set, and PK Set) because one patient was not treated, three patients did not sign the informed consent form, 7 patients from center 39 where Ethics Committee did not approve Amend 1.

Period 1

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

Blinding implementation details:

The identity of the treatments was concealed by the use of study drugs that were all identical in appearence of packaging, labeling and schedule. Unblinding was allowed only in case of subjects emergencies and at the conclusion of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: QMF149

Arm description:

Subjects were administered with QMF149 (Indacaterol maleate 500 µg/mometasone furoate 400 µg), once daily (o.d) in evening via Twisthaler® (a multi-dose powder inhaler).

Arm type	Experimental
Investigational medicinal product name	Indacaterol maleate/mometasone furoate
Investigational medicinal product code	QMF149
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

QMF149 (Indacaterol maleate 500 µg/mometasone furoate 400 µg) was administered o.d via Twisthaler®.

Arm title	Cohort 2: Mometasone furoate

Arm description:

Subjects were administered with MF 400 µg, o.d in evening via Twisthaler (a multi-dose powder inhaler).

Arm type	Experimental
Investigational medicinal product name	Mometasone furoate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal powder
Routes of administration	Inhalation use

Dosage and administration details:

MF 400 µg was administered o.d via Twisthaler.

Number of subjects in period 1	Cohort 1: QMF149	Cohort 2: Mometasone furoate
Started	749	759
Full analysis set	749	759
Treated subjects	749	759
Completed	555	574
Not completed	194	185
Abnormal laboratory value(s)	1	2
Consent withdrawn by subject	72	74
Subject's inability to use the device	6	1
Adverse event, non-fatal	43	23
Death	-	1
Unsatisfactory therapeutic effect	10	17
Administrative problems	13	23
Lost to follow-up	29	23
Abnormal test procedure result(s)	3	1
Protocol deviation	17	20

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: QMF149
Reporting group description:	
Subjects were administered with QMF149 (Indacaterol maleate 500 µg/mometasone furoate 400 µg), once daily (o.d) in evening via Twisthaler® (a multi-dose powder inhaler).	
Reporting group title	Cohort 2: Mometasone furoate
Reporting group description:	
Subjects were administered with MF 400 µg, o.d in evening via Twisthaler (a multi-dose powder inhaler).	

Reporting group values	Cohort 1: QMF149	Cohort 2: Mometasone furoate	Total
Number of subjects	749	759	1508
Age categorical Units: Subjects			
< 18 years	31	35	66
18 - 64 years	675	682	1357
>= 65 years	43	42	85
Age continuous Units: years			
arithmetic mean	42.4	42.3	
standard deviation	± 14.75	± 14.58	-
Gender categorical Units: Subjects			
Female	436	449	885
Male	313	310	623

End points

End points reporting groups

Reporting group title	Cohort 1: QMF149

Reporting group description:

Subjects were administered with QMF149 (Indacaterol maleate 500 µg/mometasone furoate 400 µg), once daily (o.d) in evening via Twisthaler® (a multi-dose powder inhaler).

Reporting group title	Cohort 2: Mometasone furoate

Reporting group description:

Subjects were administered with MF 400 µg, o.d in evening via Twisthaler (a multi-dose powder inhaler).

Primary: Time to first serious asthma exacerbation

End point title	Time to first serious asthma exacerbation

End point description:

Time to first serious asthma exacerbation was defined as the number of days from start of treatment up to the first date when an asthma exacerbation becomes serious (i.e. the date of hospitalisation, intubation or death, whichever occurred first). Subjects who did not experience a serious asthma exacerbation were censored at their last follow-up date. The analysis was performed in full analysis set (FAS), defined as all randomised subjects who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From randomisation up to Month 21

End point values	Cohort 1: QMF149	Cohort 2: Mometasone furoate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	749	759		
Units: Months				
median (full range (min-max))	13.3 (0 to 19.6)	13.4 (0 to 20.3)		

Statistical analyses

Statistical analysis title	Time to first serious asthma exacerbation

Statistical analysis description:

The Cox proportional hazards regression model was used to analyse serious asthma exacerbation stratified by asthma related hospitalization, asthma worsening and African American subjects.

Comparison groups	Cohort 1: QMF149 v Cohort 2: Mometasone furoate

Number of subjects included in analysis	1508
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.076 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.31
Confidence interval	
level	90 %
sides	1-sided
lower limit	0.08

Notes:

[1] - The one-sided p-value was based on the hypothesis 'Hazard ratio QMF149 / MF >=1' vs. the alternative 'Hazard ratio QMF149 / MF <1. A hazard ratio <1 favors QMF149.

Secondary: Incidence of serious asthma exacerbation resulting in hospitalisation, intubation or death

End point title	Incidence of serious asthma exacerbation resulting in hospitalisation, intubation or death

End point description:

The incidence rate of the first serious asthma exacerbation was defined as the number of subjects with at least one serious asthma exacerbations over the course of the study. A serious asthma exacerbation was one that resulted in hospitalisation, intubation or death. The analysis was performed in FAS population.

End point type	Secondary

End point timeframe:

From randomisation up to Month 21

End point values	Cohort 1: QMF149	Cohort 2: Mometasone furoate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	749	759		
Units: Subjects	2	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with asthma exacerbations that required treatment with systemic corticosteroids

End point title	Number of subjects with asthma exacerbations that required treatment with systemic corticosteroids

End point description:

Number of subjects with asthma exacerbations that required treatment with systemic corticosteroids (oral or parenteral) during the study was estimated. Subjects who did not experience an asthma exacerbation requiring treatment with systemic corticosteroids were censored at their last follow-up date. The analysis was performed in FAS population.

End point type	Secondary

End point timeframe:

From randomisation up to Month 21

End point values	Cohort 1: QMF149	Cohort 2: Mometasone furoate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	749	759		
Units: Subjects	124	171		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with at least one asthma worsening

End point title	Number of subjects with at least one asthma worsening

End point description:

Asthma worsening was evaluated based on following criteria, 1; decrease in peak expiratory flow (PEF) greater than or equal to (≥) 20 percent (%) from mean baseline on ≥ 3 consecutive days, 2; night-time symptom score ≥ 2 on ≥ 2 consecutive nights, 3; decrease in forced expiration volume in 1 second (FEV1) ≥ 20% from baseline at evening visits, 4; daytime symptom score of 3 or 4 on ≥ 2 consecutive days, 5; requiring an urgent unscheduled visit for medical care, 6; 24 hour rescue medication use ≥ 8 puffs on ≥ 2 consecutive days and 7; any other clinically important symptoms included pre-specified MedDRA preferred terms. The analysis was performed in FAS population.

End point type	Secondary

End point timeframe:

From randomisation up to Month 21

End point values	Cohort 1: QMF149	Cohort 2: Mometasone furoate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	749	759		
Units: Subjects	533	637		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in trough forced expiration volume in 1 second (trough FEV1) to Month 21

End point title	Change from baseline in trough forced expiration volume in 1 second (trough FEV1) to Month 21

End point description:

Trough FEV1 was defined as the volume of air expired in 1 second. Trough FEV1 was assessed as a pulmonary function by using spirometry tests in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) criteria. Change from baseline in trough FEV1 measured at 15 minutes before dosing was analysed. Trough FEV1 measurements within 6 hours of rescue medication use were excluded from analysis. Positive change from baseline indicated improvement. The analysis was performed in FAS population. Here, "Number of subjects analysed" signifies those subjects evaluable for trough FEV1 at specified time points for each arm, respectively.

End point type	Secondary

End point timeframe:

From randomisation up to Month 21

End point values	Cohort 1: QMF149	Cohort 2: Mometasone furoate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	674	699		
Units: Liter (L)				
least squares mean (standard error)	0.06 (± 0.025)	-0.07 (± 0.024)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in forced expiration volume in 1 second (FEV1) to Month 21

End point title	Change from baseline in forced expiration volume in 1 second (FEV1) to Month 21

End point description:

FEV1 was defined as the volume of air expired in 1 second. FEV1 was assessed as a pulmonary function by using spirometry tests in accordance with ATS/ERS criteria. FEV1 data taken within 6 hours of rescue medication was excluded from the analysis. Positive change from baseline indicated improvement. The analysis was performed in FAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

From randomisation up to Month 21

End point values	Cohort 1: QMF149	Cohort 2: Mometasone furoate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	749	759		
Units: Litres				
least squares mean (standard error)				
5 minutes post-dose (n = 578, 607)	0.09 (± 0.018)	-0.04 (± 0.018)		
30 minutes post-dose (n = 576, 605)	0.12 (± 0.02)	-0.05 (± 0.02)		

1 hour post-dose (n = 575, 602)	0.13 (± 0.021)	-0.06 (± 0.021)		
2 hours post-dose (n = 568, 601)	0.14 (± 0.022)	-0.05 (± 0.022)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in forced vital capacity (FVC) to Month 21

End point title	Change from baseline in forced vital capacity (FVC) to Month 21

End point description:

FVC was defined as the maximum volume of air exhaled with maximally forced effort from a position of maximal inspiration. FVC was determined from spirometry tests in accordance with ATS/ERS criteria. FVC data taken within 6 hours of rescue medication was excluded from the analysis. Negative change from baseline indicated improvement. The analysis was performed in FAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

From randomisation up to Month 21

End point values	Cohort 1: QMF149	Cohort 2: Mometasone furoate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	749	759		
Units: Litres				
least squares mean (standard error)				
5 minutes post-dose (n = 578, 607)	-0.03 (± 0.023)	-0.11 (± 0.023)		
30 minutes post-dose (n = 576, 605)	-0.03 (± 0.025)	-0.13 (± 0.024)		
1 hour post-dose (n = 575, 602)	-0.01 (± 0.025)	-0.13 (± 0.025)		
2 hours post-dose (n = 568, 601)	-0.02 (± 0.026)	-0.13 (± 0.026)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in morning peak expiratory flow (PEF) and evening trough PEF averaged to Month 21

End point title	Change from baseline in morning peak expiratory flow (PEF) and evening trough PEF averaged to Month 21

End point description:

PEF was measured at every morning and evening prior to study medication use except evenings on the day of clinic visits. The baseline value was defined as the average over the last 14 days prior to start of

treatment. Positive change from baseline indicated improvement. The analysis was performed in FAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

From randomisation up to Month 21

End point values	Cohort 1: QMF149	Cohort 2: Mometasone furoate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	749	759		
Units: Liters per second				
least squares mean (standard error)				
Morning PEF (n = 730, 746)	0.43 (± 0.075)	0 (± 0.075)		
Evening PEF (n = 731, 748)	0.27 (± 0.076)	-0.15 (± 0.075)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in percentage of days with no asthma symptoms during the morning, daytime and night-time to Month 21

End point title	Change from baseline in percentage of days with no asthma symptoms during the morning, daytime and night-time to Month 21

End point description:

The percentage of days with no asthma symptoms during morning, daytime and night time was estimated. Baseline was the last 14 days prior to start of treatment. Positive change from baseline indicated improvement. The analysis was performed in FAS. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

From randomisation up to Month 21

End point values	Cohort 1: QMF149	Cohort 2: Mometasone furoate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	749	759		
Units: Percentage of days				
least squares mean (standard error)				
Morning (n = 730, 746)	22.3 (± 2.17)	18.4 (± 2.17)		
Daytime (n = 731, 749)	27.1 (± 2.96)	19.5 (± 2.95)		
Night-time (n = 730, 746)	23.6 (± 2.69)	17.3 (± 2.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in average asthma symptom score to Month 21

End point title	Change from baseline in average asthma symptom score to Month 21

End point description:

The average total asthma symptom score was defined as the daily sum of morning asthma symptom score (score range 0-1), daytime asthma symptom scores (score range 0-4) and night-time asthma symptom scores (score range 0-4) and the score range of total asthma symptom score was from 0 to 9. Baseline was the last 14 days prior to start of treatment. Negative change from baseline indicated improvement. The analysis was performed in FAS. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

From randomisation up to Month 21

End point values	Cohort 1: QMF149	Cohort 2: Mometasone furoate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	749	759		
Units: Units on a scale				
least squares mean (standard error)				
Total (n = 708, 733)	-1.22 (± 0.088)	-0.94 (± 0.088)		
Daytime (n = 731, 749)	-0.5 (± 0.043)	-0.39 (± 0.043)		
Night-time (n = 730, 746)	-0.46 (± 0.037)	-0.36 (± 0.037)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in percentage of days with no rescue medication use to Month 21

End point title	Change from baseline in percentage of days with no rescue medication use to Month 21

End point description:

Percentage of days with no rescue medication use during 24 hours, daytime and night-time was estimated. Baseline was the last 14 days prior to start of treatment. The analysis was performed in FAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each

group, respectively.

End point type	Secondary

End point timeframe:

From randomisation up to Month 21

End point values	Cohort 1: QMF149	Cohort 2: Mometasone furoate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	749	759		
Units: Percentage of days				
least squares mean (standard error)				
24 hours (n = 669, 696)	29.1 (± 2.88)	17.9 (± 2.88)		
Daytime (n = 692, 711)	23.6 (± 2.74)	13.8 (± 2.74)		
Night-time (n = 691, 708)	24.6 (± 2.69)	14.5 (± 2.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in asthma control questionnaire (ACQ) at Month 21

End point title	Change from baseline in asthma control questionnaire (ACQ) at Month 21

End point description:

The ACQ was a seven-item disease-specific instrument used to assess asthma control in subjects. The ACQ score ranges from 0 = good control of asthma to 6 = poor control of asthma. A negative change in score indicated improvement in asthma control. The analysis was performed in FAS population. Here, "Number of subjects analysed" signifies those subjects evaluable for ACQ at specified time points for each arm, respectively.

End point type	Secondary

End point timeframe:

From randomisation up to Month 21

End point values	Cohort 1: QMF149	Cohort 2: Mometasone furoate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	675	687		
Units: Units on a scale				
least squares mean (standard error)	-0.55 (± 0.052)	-0.32 (± 0.052)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events (AEs), AEs related to study drug, serious adverse events (SAEs), AE/SAEs leading to discontinuation and deaths during the study

End point title	Number of subjects with adverse events (AEs), AEs related to study drug, serious adverse events (SAEs), AE/SAEs leading to discontinuation and deaths during the study

End point description:

An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not related to study drug. A SAE was defined as an event which was fatal or life threatening, required or prolonged hospitalisation, was significantly or permanently disabling or incapacitating, constituted a congenital anomaly or a birth defect, or encompassed any other clinically significant event that could jeopardize the subject or require medical or surgical intervention to prevent one of the aforementioned outcomes. Treatment related AEs were defined as AEs that were suspected to be related to study treatment as per investigator. Based on the severity, AEs were categorised into 3 types as mild, moderate and severe. Death was a fatal event leading to permanent cessations of all vital functions of the body. The analysis was performed in safety set, defined as all the subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

From randomisation up to Month 21

End point values	Cohort 1: QMF149	Cohort 2: Mometasone furoate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	749	759		
Units: Subjects				
AEs	554	557		
Mild AEs	230	201		
Moderate AEs	275	294		
Severe AEs	49	62		
AEs related to study drug	269	81		
SAEs	30	44		
Death	0	1		
Discontinued due to AE(s)	44	25		
Discontinued due to SAE(s)	7	7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	MF
Reporting group description:	
MF	
Reporting group title	QMF149
Reporting group description:	
QMF149	

Serious adverse events	MF	QMF149	
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 759 (5.80%)	30 / 749 (4.01%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			

subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondroma			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (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	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	1 / 759 (0.13%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Inguinal hernia repair			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pregnancy			
subjects affected / exposed	1 / 759 (0.13%)	3 / 749 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 759 (0.26%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 759 (0.26%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Colpocele			

subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian mass			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
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	9 / 759 (1.19%)	2 / 749 (0.27%)	
occurrences causally related to treatment / all	1 / 10	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 759 (0.26%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus polyp			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Electrocardiogram T wave inversion			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (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			
Concussion			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus lesion			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal compression fracture			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (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	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
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 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			

subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 759 (0.13%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery occlusion			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radicular pain			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Thrombocytopenia			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia obstructive			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	2 / 759 (0.26%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 759 (0.00%)	2 / 749 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting			
subjects affected / exposed	0 / 759 (0.00%)	2 / 749 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 759 (0.00%)	2 / 749 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
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			
Intervertebral disc disorder			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			

subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (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			
Abscess intestinal			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 759 (0.26%)	2 / 749 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 759 (0.26%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
External ear cellulitis			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaria			
subjects affected / exposed	0 / 759 (0.00%)	1 / 749 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			

subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (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 / 759 (0.53%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 759 (0.13%)	0 / 749 (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	MF	QMF149	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	407 / 759 (53.62%)	456 / 749 (60.88%)	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	269 / 759 (35.44%)	195 / 749 (26.03%)	
occurrences (all)	478	327	
Cough			
subjects affected / exposed	63 / 759 (8.30%)	266 / 749 (35.51%)	
occurrences (all)	71	441	
Infections and infestations			
Bronchitis			
subjects affected / exposed	58 / 759 (7.64%)	39 / 749 (5.21%)	
occurrences (all)	76	45	
Nasopharyngitis			

subjects affected / exposed	106 / 759 (13.97%)	112 / 749 (14.95%)	
occurrences (all)	150	159	
Sinusitis			
subjects affected / exposed	52 / 759 (6.85%)	55 / 749 (7.34%)	
occurrences (all)	64	74	
Upper respiratory tract infection			
subjects affected / exposed	96 / 759 (12.65%)	83 / 749 (11.08%)	
occurrences (all)	123	107	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2011	1. Clarification for the premature study drug discontinuation due to prohibited concomitant medication was provided . 2. The primary safety endpoint was ammended from "time to the first serious asthma exacerbation" to "rate of serious asthma exacerbations". The new key secondary analysis was added for secondary objective to compare the rate of the first serious asthma exacerbations resulting in hospitalization, intubation, or death of subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported