Clinical trial results:
A 26 week, randomized, double-blind, parallel-group, active controlled, multicenter, multinational safety study evaluating the risk of serious asthma-related events during treatment with Symbicort®, a fixed combination of inhaled corticosteroid (ICS) (budesonide) and a long acting 2-agonist (LABA) (formoterol) as compared to treatment with ICS (budesonide) alone in adult and adolescent (12 years of age) patients with asthma

Summary

EudraCT number	2011-002790-28
Trial protocol	SK SE CZ BG IT DE GB
Global end of trial date	13 October 2015

Results information

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

Trial information

Trial identification

Sponsor protocol code	D5896C00027

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01444430
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca Research and Development
Sponsor organisation address	AstraZeneca Pepparedsleden 1, Mölndal, Sweden,
Public contact	Carin Jorup, AstraZeneca Research and Development, +46 31 7761000, Carin.Jorup@astrazeneca.com
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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	13 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 October 2015
Global end of trial reached?	Yes
Global end of trial date	13 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was to evaluate whether treatment with SYMBICORT pMDI increases the incidence of serious asthma-related events compared to treatment with budesonide alone in adult and adolescent (≥12 years of age) patients with persistent asthma.

Protection of trial subjects:

Patients were followed at least on a monthly basis by the research site, either by clinic visits or telephone contacts. Criteria for unstable asthma was assessed between study visits on a daily basis via telephone calls to the Interactive Voice Response System (IVRS). In these telephone calls patients recorded missed days of work/school, rescue medication use, asthma symptoms, ability to perform daily activities and night time awakenings. The patient and, if applicable, the patient's parent/legal guardian was trained by the investigational team and also supplied with written instructions on how to enter data and where to turn if problems occurred. A reminder about intake of study medication was given in connection to the IVRS call. The Investigator received an electronic alert to contact patients with unstable asthma. Patients in need of treatment due to an exacerbation could obtain additional medication while remaining on randomized treatment. Site staff reviewed study medication compliance with the patient at each scheduled study visit (Visits 3, 5 and EoT) and monthly telephone contacts and made a note in Medical records. A daily reminder was also addressed via IVRS. If the patient was not compliant, he or she received additional training on how to use the pMDI. In addition to standard protocolized criteria for discontinuation of investigational product, the study included 3 study-specific discontinuation criteria to optimize safety related to asthma exacerbations: - Experience of more than 1 asthma exacerbation within 13 weeks (during the randomized treatment period) or more than 2 asthma exacerbations within 26 weeks (during the randomized treatment period) will necessitate withdrawal. - A patient whose exacerbation is not responding to therapy in the judgment of the investigator or is not responding to 14 days of treatment with systemic corticosteroids. - A patient requires intubation for asthma.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 3515
Country: Number of subjects enrolled	Argentina: 1006
Country: Number of subjects enrolled	France: 50
Country: Number of subjects enrolled	Germany: 91

Country: Number of subjects enrolled	Italy: 109
Country: Number of subjects enrolled	United Kingdom: 132
Country: Number of subjects enrolled	Bulgaria: 624
Country: Number of subjects enrolled	Czech Republic: 267
Country: Number of subjects enrolled	Poland: 827
Country: Number of subjects enrolled	Romania: 402
Country: Number of subjects enrolled	Russian Federation: 788
Country: Number of subjects enrolled	Slovakia: 201
Country: Number of subjects enrolled	Ukraine: 726
Country: Number of subjects enrolled	Brazil: 358
Country: Number of subjects enrolled	Chile: 194
Country: Number of subjects enrolled	Colombia: 71
Country: Number of subjects enrolled	Mexico: 836
Country: Number of subjects enrolled	Panama: 36
Country: Number of subjects enrolled	Peru: 211
Country: Number of subjects enrolled	Philippines: 438
Country: Number of subjects enrolled	South Africa: 552
Country: Number of subjects enrolled	Korea, Republic of: 301
Country: Number of subjects enrolled	India: 433
Country: Number of subjects enrolled	Thailand: 151
Country: Number of subjects enrolled	Vietnam: 141
Worldwide total number of subjects	12460
EEA total number of subjects	2703

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)	1305
Adults (18-64 years)	9752
From 65 to 84 years	1389
85 years and over	14

Subject disposition

Recruitment

Recruitment details:

This study started with an assessment visit where inclusion/exclusion criteria were reviewed and informed consent obtained. Eligible patients were randomized at the next visit. Patients then entered a 26 weeks double-blind treatment period followed by a 1 week follow-up telephone contact. Patients were recruited in 25 countries with 25% in the US.

Pre-assignment

Screening details:

Eligible adult and adolescent patients were stratified at randomization visit (Visit 2) to one of the two dose levels of Symbicort/budesonide based upon assessment of ACQ and prior asthma therapy. Patients received rescue medication (Albuterol or Salbutamol) throughout the study.

Pre-assignment period milestones

Number of subjects started	12460
Number of subjects completed	11693

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Eligibility criteria not fulfilled: 704
Reason: Number of subjects	Consent withdrawn by subject: 34
Reason: Number of subjects	Other: 29

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, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Symbicort

Arm description:

Participants were randomized to one of following treatments: Symbicort pMDI 80/4.5 µg x 2 actuations bid (morning and evening) or Symbicort pMDI 160/4.5 µg x 2 actuations bid (morning and evening).

Arm type	Experimental
Investigational medicinal product name	budesonide/formoterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

pMDI (HFA) for oral inhalation with Actuation Counter Module, 80/4.5µg or 160/4.5µg

Arm title	budesonide

Arm description:

Participants were randomized to one of following treatments: budesonide pMDI 80 µg x 2 actuations bid (morning and evening) or budesonide pMDI 160 µg x 2 actuations bid (morning and evening).

Arm type	Active comparator

Investigational medicinal product name	budesonide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

pMDI (HFA) for oral inhalation with Actuation Counter Module (ACM), 80 µg or 160 µg

Number of subjects in period 1[1]	Symbicort	budesonide
Started	5846	5847
Completed	5785	5766
Not completed	61	81
Adverse event, serious fatal	6	8
Consent withdrawn by subject	53	72
CRF termination module not completed.	-	1
Lost to follow-up	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: AEs were not collected unless they lead to discontinuation or qualified as an SAE.

Baseline characteristics

Reporting groups	
Reporting group title	Symbicort
Reporting group description:	
Participants were randomized to one of following treatments: Symbicort pMDI 80/4.5 µg x 2 actuations bid (morning and evening) or Symbicort pMDI 160/4.5 µg x 2 actuations bid (morning and evening).	
Reporting group title	budesonide
Reporting group description:	
Participants were randomized to one of following treatments: budesonide pMDI 80 µg x 2 actuations bid (morning and evening) or budesonide pMDI 160 µg x 2 actuations bid (morning and evening).	

Reporting group values	Symbicort	budesonide	Total
Number of subjects	5846	5847	11693
Age categorical Units: Subjects			
Adolescents (12-17 years)	632	636	1268
Adults (18-64 years)	4572	4568	9140
From 65 years	642	643	1285
Age Continuous | Units: Years			
arithmetic mean	43.4	43.5	
standard deviation	± 17.4	± 17.3	-
Gender, Male/Female Units: Participants			
Female	3849	3820	7669
Male	1997	2027	4024
Race/Ethnicity, Customized Units: Subjects			
White	4050	4003	8053
Black/African American	396	401	797
Asian	848	907	1755
Native Hawaiian/Pacific Islander	3	3	6
American Indian/Alaska Native	225	207	432
Other	324	326	650

End points

End points reporting groups

Reporting group title	Symbicort
Reporting group description:	
Participants were randomized to one of following treatments: Symbicort pMDI 80/4.5 µg x 2 actuations bid (morning and evening) or Symbicort pMDI 160/4.5 µg x 2 actuations bid (morning and evening).	
Reporting group title	budesonide
Reporting group description:	
Participants were randomized to one of following treatments: budesonide pMDI 80 µg x 2 actuations bid (morning and evening) or budesonide pMDI 160 µg x 2 actuations bid (morning and evening).	

Primary: Time to first event in composite endpoint (asthma-related death, asthma-related intubation or asthma-related hospitalization)

End point title	Time to first event in composite endpoint (asthma-related death, asthma-related intubation or asthma-related hospitalization)
End point description:	
Time to first event included in the composite endpoint (asthma-related death, asthma-related intubation or asthma-related hospitalization), using events adjudicated and confirmed by the Joint Adjudication Committee. Cox proportional hazards model with terms for randomized treatment and strata for incoming control/asthma treatment was used to compare Symbicort and budesonide. Hazard ratios and 95% confidence intervals were estimated.	
End point type	Primary
End point timeframe:	
Up to 27 weeks	

End point values	Symbicort	budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5846	5847		
Units: Participants	43	40		

Statistical analyses

Statistical analysis title	Cox regression
Statistical analysis description:	
Full analysis set (FAS) population comprised of all patients randomized to study drug.	
Comparison groups	budesonide v Symbicort
Number of subjects included in analysis	11693
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.073

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.698
upper limit	1.65

Notes:

[1] - The upper limit of the 95% CI of the hazard ratio will be used to assess statistical non-inferiority (non-inferiority margin=2).

Primary: Time to first event included in the definition of asthma exacerbation

End point title	Time to first event included in the definition of asthma exacerbation

End point description:

Time to first asthma exacerbation, defined as a deterioration of asthma requiring systemic corticosteroids for at least 3 days or an inpatient hospitalization or emergency room visit due to asthma that required systemic corticosteroids. Cox proportional hazards model with terms for randomized treatment and strata for incoming control/asthma treatment was used to compare Symbicort and budesonide. Hazard ratios and 95% confidence intervals were estimated.

End point type	Primary

End point timeframe:

Up to 26 weeks

End point values	Symbicort	budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5846	5847		
Units: Participants	539	633		

Statistical analyses

Statistical analysis title	Cox regression

Statistical analysis description:

The On treatment Analysis set comprised of all randomized patients and included data that corresponded to each patient’s period of exposure to study drug plus 7 days after the last date of study drug treatment.

Comparison groups	Symbicort v budesonide
Number of subjects included in analysis	11693
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.835
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.745
upper limit	0.937

Secondary: Percent of days with no asthma symptoms

End point title	Percent of days with no asthma symptoms

End point description:

Percent of days with no asthma symptoms during the randomized treatment period. Analysis of variance (ANOVA) model including the fixed factors of treatment and strata by incoming control/asthma treatment was used to compare Symbicort and budesonide.

End point type	Secondary

End point timeframe:

Daily up to 26 weeks

End point values	Symbicort	budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5784	5796		
Units: Percentage				
least squares mean (standard error)	81.1 (± 0.4)	76.8 (± 0.4)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

Full analysis set (FAS) population comprised of all patients randomized to study drug and had at least one entry of diary data after randomization.

Comparison groups	Symbicort v budesonide
Number of subjects included in analysis	11580
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.3
upper limit	5.4
Variability estimate	Standard error of the mean
Dispersion value	0.5

Secondary: Percent of days with activity limitation due to asthma

End point title	Percent of days with activity limitation due to asthma

End point description:

Percent of days with activity limitation due to asthma during the randomized treatment period. Analysis of variance (ANOVA) model including the fixed factors of treatment and strata by incoming control/asthma treatment was used to compare Symbicort and budesonide.

End point type	Secondary

End point timeframe:

Daily up to 26 weeks

End point values	Symbicort	budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4895	5045		
Units: Percentage				
least squares mean (standard error)	19.7 (± 0.4)	19.1 (± 0.4)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

Full analysis set (FAS) population comprised of all patients randomized to study drug. The analysis set comprises of all patients with at least one day with asthma symptoms, i.e. the denominator is the number of days with asthma symptoms.

Comparison groups	Symbicort v budesonide
Number of subjects included in analysis	9940
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.272
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	1.7
Variability estimate	Standard error of the mean
Dispersion value	0.6

Secondary: Mean number of puffs of rescue medication per 24 hours

End point title	Mean number of puffs of rescue medication per 24 hours

End point description:

Mean number of puffs of rescue medication per day (24 hours) during the randomized treatment period. Analysis of variance (ANOVA) model including the fixed factors of treatment and strata by incoming control/asthma treatment was used to compare Symbicort and budesonide.

End point type	Secondary

End point timeframe:

Daily up to 26 weeks

End point values	Symbicort	budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5784	5796		
Units: Inhalations/day				
least squares mean (standard error)	0.8 (± 0)	0.9 (± 0)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

Full analysis set (FAS) population comprised of all patients randomized to study drug and had at least one entry of diary data after randomization.

Comparison groups	Symbicort v budesonide
Number of subjects included in analysis	11580
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0

Secondary: Asthma Control Questionnaire (ACQ6)

End point title	Asthma Control Questionnaire (ACQ6)

End point description:

The outcome variable for ACQ6 was the difference between the average of values recorded during the treatment period and the baseline measure. Analysis of covariance (ANCOVA) model, including the fixed factors of treatment and strata by incoming control/asthma treatment and baseline ACQ6 as covariate was used to compare Symbicort and budesonide. The asthma control questionnaire, ACQ6, consists of six questions; all assessed on a 7-point scale from 0 to 6, where 0 represents good control and 6 represents poor control. The overall score is the mean of the responses to each of the six questions.

End point type	Secondary

End point timeframe:

baseline, day 28, day 84, day 182

End point values	Symbicort	budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5701	5698		
Units: ACQ6 overall score change from baseline				
least squares mean (standard error)	-0.7 (± 0.01)	-0.62 (± 0.01)		

Statistical analyses

Statistical analysis title	ANCOVA
Statistical analysis description:	
Full analysis set (FAS) population comprised of all patients randomized to study drug with at least one post-baseline ACQ6 score.	
Comparison groups	Symbicort v budesonide
Number of subjects included in analysis	11399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	-0.06
Variability estimate	Standard error of the mean
Dispersion value	0.01

Secondary: Percent of nights with awakening(s) due to asthma

End point title	Percent of nights with awakening(s) due to asthma
End point description:	
Percent of nights with awakening(s) due to asthma during the randomized treatment period. Analysis of variance (ANOVA) model including the fixed factors of treatment and strata by incoming control/asthma treatment was used to compare Symbicort and budesonide.	
End point type	Secondary
End point timeframe:	
Daily up to 26 weeks	

End point values	Symbicort	budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5784	5796		
Units: Percentage				
least squares mean (standard error)	4 (± 0.2)	4.7 (± 0.2)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

Full analysis set (FAS) population comprised of all patients randomized to study drug and had at least one entry of diary data after randomization.

Comparison groups	Symbicort v budesonide
Number of subjects included in analysis	11580
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.2

Secondary: Time to discontinuation of investigational product due to a protocol defined asthma exacerbation

End point title	Time to discontinuation of investigational product due to a protocol defined asthma exacerbation

End point description:

Time to discontinuation of investigational product due to a protocol defined asthma exacerbation. An asthma exacerbation was defined as a deterioration of asthma requiring systemic corticosteroids for at least 3 days or an inpatient hospitalization or emergency room visit due to asthma that required systemic corticosteroids. Cox proportional hazards model with terms for randomized treatment and strata for incoming control/asthma treatment was used to compare Symbicort and budesonide. Hazard ratios and 95% confidence intervals were estimated.

End point type	Secondary

End point timeframe:

Up to 26 weeks

End point values	Symbicort	budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5846	5847		
Units: Participants	53	71		

Statistical analyses

Statistical analysis title	Cox regression

Statistical analysis description:

The On treatment Analysis set comprised of all randomized patients and included data that corresponded to each patient’s period of exposure to study drug plus 7 days after the last date of study drug treatment.

Comparison groups	Symbicort v budesonide
Number of subjects included in analysis	11693
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.095
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.739
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.518
upper limit	1.055

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and discontinuation of treatment with investigational product due to adverse event (DAEs) were recorded from the time of informed consent through the treatment period and including the follow-up period.

Adverse event reporting additional description:

AEs were not collected unless they lead to discontinuation or qualified as an SAE.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Symbicort

Reporting group description:

Participants were randomized to one of following treatments: Symbicort pMDI 80/4.5 µg x 2 actuations bid (morning and evening) or Symbicort pMDI 160/4.5 µg x 2 actuations bid (morning and evening).

Reporting group title	budesonide

Reporting group description:

Participants were randomized to one of following treatments: budesonide pMDI 80 µg x 2 actuations bid (morning and evening) or budesonide pMDI 160 µg x 2 actuations bid (morning and evening).

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: AEs were not collected unless they lead to discontinuation or qualified as an SAE.

Serious adverse events	Symbicort	budesonide	
Total subjects affected by serious adverse events			
subjects affected / exposed	125 / 5846 (2.14%)	123 / 5847 (2.10%)	
number of deaths (all causes)	6	8	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Astrocytoma malignant			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer female			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			

subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenocarcinoma			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian germ cell teratoma benign			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	2 / 5846 (0.03%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			

subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Hyperemesis gravidarum			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Device dislocation			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-cardiac chest pain			
subjects affected / exposed	1 / 5846 (0.02%)	2 / 5847 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic granulomatous angiitis			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Haemorrhagic ovarian cyst			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menometrorrhagia			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pelvic prolapse			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
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			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	35 / 5846 (0.60%)	36 / 5847 (0.62%)	
occurrences causally related to treatment / all	0 / 38	0 / 39	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (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	1 / 5846 (0.02%)	2 / 5847 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rhinitis allergic			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status asthmaticus			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord disorder			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar I disorder			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Depression			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			

subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart rate irregular			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns second degree			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns first degree			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 5846 (0.02%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Electric shock			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
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	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 5846 (0.02%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Tibia fracture			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			

subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 5846 (0.02%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	3 / 5846 (0.05%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	2 / 5846 (0.03%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 5846 (0.00%)	3 / 5847 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			

subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 5846 (0.03%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery insufficiency			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertensive heart disease			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve stenosis			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
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 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocarditis			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 5846 (0.00%)	2 / 5847 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haematoma			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	0 / 5846 (0.00%)	3 / 5847 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cerebrovascular disorder			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 5846 (0.05%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenopathy mediastinal			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 5846 (0.03%)	2 / 5847 (0.03%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 5846 (0.00%)	3 / 5847 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 5846 (0.02%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive oesophagitis			

subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 5846 (0.03%)	2 / 5847 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 5846 (0.02%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis haemorrhagic			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 5846 (0.02%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dyskinesia			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 5846 (0.02%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 5846 (0.03%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic steatosis			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvi-ureteric obstruction			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
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			
Arthralgia			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			

subjects affected / exposed	0 / 5846 (0.00%)	3 / 5847 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 5846 (0.02%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 5846 (0.00%)	2 / 5847 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 5846 (0.02%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			

subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 5846 (0.02%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysentery			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infection			

subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 5846 (0.00%)	2 / 5847 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaria			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycoplasma infection			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			

subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	1 / 5846 (0.02%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	12 / 5846 (0.21%)	6 / 5847 (0.10%)	
occurrences causally related to treatment / all	0 / 12	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 5846 (0.03%)	3 / 5847 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	2 / 5846 (0.03%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			

subjects affected / exposed	0 / 5846 (0.00%)	2 / 5847 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculous pleurisy			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (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			
Dehydration			
subjects affected / exposed	2 / 5846 (0.03%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 5846 (0.02%)	0 / 5847 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperosmolar hyperglycaemic state			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 5846 (0.00%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	2 / 5846 (0.03%)	1 / 5847 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Symbicort	budesonide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 5846 (0.00%)	0 / 5847 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2011	Revision of sections relating to study committees to clarify that the TDMC was responsible for monitoring the primary safety variable of the study but also all other aspects of safety in the study. Text added to clarify that if a patient was re-screened 3 months or more after the last signing of the ICF, the patient had to re-consent to the study. Additional text added to inclusion criterion 6 to include the ability to read the ACQ6 questionnaire: "Availability and ability to perform the necessary maneuvers and procedures required by the study (eg, read the ACQ6 questionnaire, use a pMDI, and perform daily telephone calls)." Procedures for handling patients incorrectly enrolled or randomized re worded: "Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule."
11 April 2013	Text added to clarify instructions for collection and recording of patient's compliance. Procedures for handling patients incorrectly enrolled or randomized were updated to clarify procedures to be taken by AstraZeneca study team, physician, and investigator where minor violations of inclusion or exclusion criteria were detected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported