Clinical trial results:
A comparison of Symbicort® Maintenance and Reliever Therapy (Symbicort Turbuhaler® 160/4.5 g, one inhalation bid plus as needed) and Symbicort Turbuhaler 160/4.5 g, one inhalation bid plus terbutaline Turbuhaler 0.4 mg/inhalation as needed, for treatment of asthma – a 12-month, randomized, double-blind, parallel group, active-controlled, multinational phase III study in asthmatic patients aged 16 years and above.

Summary

EudraCT number	2008-006869-86
Trial protocol	HU
Global end of trial date	28 May 2012

Results information

Result version number	v1 (current)
This version publication date	01 February 2017
First version publication date	02 August 2015

Trial information

Trial identification

Sponsor protocol code	D589LC00001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	AstraZeneca R&D, SE-221 87 Lund, Sweden,
Public contact	Carin Jorup, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Carin Jorup, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 May 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2012
Global end of trial reached?	Yes
Global end of trial date	28 May 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the efficacy of Symbicort® Maintenance and Reliever Therapy (SMART) (Symbicort Turbuhaler® 160/4.5µg, one inhalation bid plus as needed) with Symbicort Turbuhaler 160/4.5µg, one inhalation bid plus terbutaline Turbuhaler 0.4 mg as needed, as asthma therapy by evaluation of time to first asthma exacerbation.

Protection of trial subjects:

The final study protocol and amendments (Appendix 12.1.1), including the final version of the Informed Consent Form (Appendix 12.1.3), and the Case Report Form (CRF) (Appendix 12.1.2) were approved or given a favourable opinion in writing by an Institutional Review Board (IRB) as appropriate.

The principal investigator at each centre ensured that the patient was given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients were also notified that they were free to discontinue from the study at any time. Patients were given the opportunity to ask questions and allowed time to consider the information provided.

Parents and the legal representatives (if patient was minor) signed and dated informed consent before conducting any procedure specifically for the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 February 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 266
Country: Number of subjects enrolled	Brazil: 95
Country: Number of subjects enrolled	China: 189
Country: Number of subjects enrolled	Costa Rica: 41
Country: Number of subjects enrolled	Hungary: 173
Country: Number of subjects enrolled	India: 249
Country: Number of subjects enrolled	Japan: 400
Country: Number of subjects enrolled	Malaysia: 100
Country: Number of subjects enrolled	Peru: 70
Country: Number of subjects enrolled	Philippines: 198
Country: Number of subjects enrolled	Russian Federation: 144
Country: Number of subjects enrolled	Korea, Republic of: 105
Country: Number of subjects enrolled	Thailand: 61

Worldwide total number of subjects	2091
EEA total number of subjects	173

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)	21
Adults (18-64 years)	1865
From 65 to 84 years	204
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 148 centres in Japan and in 12 other countries in Asia, America and Europe between 16 February 2009 and 23 February 2011.

Pre-assignment

Screening details:

The study consisted of an enrolment visit, a 2-week run-in (standardization) period at Visit 2, randomization at Visit 3, and 5 further visits (Visits 4-8) at 4, 12, 24, 36 and 52 weeks. Subjects received 1 of 2 double-blinded treatments allocated in a random order.

Period 1

Period 1 title	Treatment Period (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 SMART

Arm description:

Symbicort Turbuhaler® 160/4.5 µg/inhalation

Arm type	Experimental
Investigational medicinal product name	Symbicort® Turbuhaler® 160/4.5 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

160/4.5 µg

Arm title	Symbicort + Terbutaline

Arm description:

Symbicort Turbuhaler 160/4.5 µg + terbutaline Turbuhaler 0.4 mg/inhalation

Arm type	Active comparator
Investigational medicinal product name	Symbicort® Turbuhaler® 160/4.5 µg + terbutaline Turbuhaler® 0.4 mg/inhalation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

160/4.5 µg

Number of subjects in period 1	Symbicort SMART	Symbicort + Terbutaline
Started	1049	1042
Completed	956	932
Not completed	93	110
Consent withdrawn by subject	28	34
Adverse event, non-fatal	8	12
Other reasons	20	25
Lost to follow-up	31	26
Protocol deviation	6	13

Baseline characteristics

Reporting groups	
Reporting group title	Symbicort SMART
Reporting group description:	
Symbicort Turbuhaler® 160/4.5 µg/inhalation	
Reporting group title	Symbicort + Terbutaline
Reporting group description:	
Symbicort Turbuhaler 160/4.5 µg + terbutaline Turbuhaler 0.4 mg/inhalation	

Reporting group values	Symbicort SMART	Symbicort + Terbutaline	Total
Number of subjects	1049	1042	2091
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	5	16	21
Adults (18-64 years)	938	927	1865
From 65-84 years	106	98	204
85 years and over	0	1	1
Age Continuous Units: years			
arithmetic mean	45.7	45.6	
full range (min-max)	16 to 84	16 to 85	-
Gender Categorical Units: Subjects			
Female	722	692	1414
Male	327	350	677
Japanese/Non-Japanese Units: Subjects			
Japanese	201	199	400
Non-Japanese	848	843	1691

End points

End points reporting groups	
Reporting group title	Symbicort SMART
Reporting group description:	
Symbicort Turbuhaler® 160/4.5 µg/inhalation	
Reporting group title	Symbicort + Terbutaline
Reporting group description:	
Symbicort Turbuhaler 160/4.5 µg + terbutaline Turbuhaler 0.4 mg/inhalation	

Primary: Total number of asthma exacerbations	
End point title	Total number of asthma exacerbations
End point description:	
Asthma exacerbations, defined as a deterioration in asthma leading to oral GCS treatment,hospitalization, or ER treatment, were recorded, with the primary outcome variable of time tofirst asthma exacerbation and a secondary outcome variable of the total number of	
End point type	Primary
End point timeframe:	
52 weeks	

End point values	Symbicort SMART	Symbicort + Terbutaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1049	1042		
Units: exacerbations	259	363		

Statistical analyses

Statistical analysis title	The time to first asthma exacerbation
Statistical analysis description:	
Cox-proportional hazards model for time to first event	
Comparison groups	Symbicort SMART v Symbicort + Terbutaline
Number of subjects included in analysis	2091
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.695

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.848

Statistical analysis title	Total number of asthma exacerbations
Statistical analysis description:	
Analysis of total number of esthma exacerbations reported per subject.	
Comparison groups	Symbicort SMART v Symbicort + Terbutaline
Number of subjects included in analysis	2091
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Poisson regression
Parameter estimate	Risk ratio (RR)
Point estimate	0.696
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.592
upper limit	0.818

Secondary: Use of as-needed medication	
End point title	Use of as-needed medication
End point description:	
Total daily no. of inhalations during the treatment period	
End point type	Secondary
End point timeframe:	
52 weeks	

End point values	Symbicort SMART	Symbicort + Terbutaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1032	1026		
Units: days				
arithmetic mean (full range (min-max))	1.21 (0 to 9.3)	1.46 (0 to 15)		

Statistical analyses

Statistical analysis title	Change from baseline in use of as-needed med.
Comparison groups	Symbicort SMART v Symbicort + Terbutaline
Number of subjects included in analysis	2058
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	-0.15

Secondary: Morning PEF (L/min)	
End point title	Morning PEF (L/min)
End point description: Mean value during the treatment period	
End point type	Secondary
End point timeframe: 52 weeks	

End point values	Symbicort SMART	Symbicort + Terbutaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1034	1026		
Units: (L/min)				
arithmetic mean (full range (min-max))	331.8 (98 to 752)	324.7 (87 to 725)		

Statistical analyses

Statistical analysis title	Change from baseline in mean morning PEF (L/min)
Comparison groups	Symbicort SMART v Symbicort + Terbutaline
Number of subjects included in analysis	2060
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	9.5

Secondary: Evening PEF (L/min)

End point title	Evening PEF (L/min)
End point description:	
Mean evening PEF during the treatment period	
End point type	Secondary
End point timeframe:	
52 weeks	

End point values	Symbicort SMART	Symbicort + Terbutaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1034	1026		
Units: (L/min)				
arithmetic mean (full range (min-max))	334.2 (96 to 725)	327.8 (85 to 723)		

Statistical analyses

Statistical analysis title	Change from baseline in mean evening PEF(L/min)
Comparison groups	Symbicort SMART v Symbicort + Terbutaline
Number of subjects included in analysis	2060
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	9.3

Secondary: Asthma symptom score

End point title	Asthma symptom score

End point description: Mean Total score(0-6) during the treatment period	
End point type	Secondary
End point timeframe: 52 weeks	

End point values	Symbicort SMART	Symbicort + Terbutaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1034	1025		
Units: average score				
arithmetic mean (full range (min-max))	1.12 (0 to 5.9)	1.22 (0 to 5.5)		

Statistical analyses

Statistical analysis title	Mean asthma symptoms (total score)
Statistical analysis description: Change from baseline in mean asthma symptoms (total)	
Comparison groups	Symbicort SMART v Symbicort + Terbutaline
Number of subjects included in analysis	2059
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	-0.01

Secondary: Nights with awakenings due to asthma symptoms(%)	
End point title	Nights with awakenings due to asthma symptoms(%)
End point description: % nights with awakenings during the treatment period	
End point type	Secondary
End point timeframe: 52 weeks	

End point values	Symbicort SMART	Symbicort + Terbutaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1024	1025		
Units: Proportion of nights				
arithmetic mean (full range (min-max))	15.7 (0 to 100)	15.5 (0 to 100)		

Statistical analyses

Statistical analysis title	% of nights with awakenings due to asthma
Statistical analysis description: Change from baseline in % of nights with awakenings due to asthma	
Comparison groups	Symbicort SMART v Symbicort + Terbutaline
Number of subjects included in analysis	2049
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.68
upper limit	0.07

Secondary: Symptom free days (%)

End point title	Symptom free days (%)
End point description: % of symptom free days during the treatment period	
End point type	Secondary
End point timeframe: 52 weeks	

End point values	Symbicort SMART	Symbicort + Terbutaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1034	1026		
Units: days				
arithmetic mean (full range (min-max))	45.5 (0 to 100)	41.6 (0 to 100)		

Statistical analyses

Statistical analysis title	Change from baseline in % Symptom free days
Comparison groups	Symbicort SMART v Symbicort + Terbutaline
Number of subjects included in analysis	2060
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	6.5

Secondary: Percentage of asthma-control days	
End point title	Percentage of asthma-control days
End point description: % of asthma control days during the treatment period	
End point type	Secondary
End point timeframe: 52 weeks	

End point values	Symbicort SMART	Symbicort + Terbutaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1033	1026		
Units: percentage				
arithmetic mean (full range (min-max))	41.7 (0 to 100)	37.9 (0 to 100)		

Statistical analyses

Statistical analysis title	Change from baseline in % of asthma-control days
Comparison groups	Symbicort SMART v Symbicort + Terbutaline
Number of subjects included in analysis	2059
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	7.1

Secondary: Mean FEV1 (L)

End point title	Mean FEV1 (L)
End point description:	
Mean FEV1 during the treatment period	
End point type	Secondary
End point timeframe:	
52 weeks	

End point values	Symbicort SMART	Symbicort + Terbutaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1049	1042		
Units: Liters				
arithmetic mean (full range (min-max))	2.258 (0.64 to 5.05)	2.222 (0.68 to 5.77)		

Statistical analyses

Statistical analysis title	change from baseline in mean FEV1 (L)
Comparison groups	Symbicort SMART v Symbicort + Terbutaline
Number of subjects included in analysis	2091
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.015
upper limit	0.064

Secondary: Mild asthma exacerbations

End point title	Mild asthma exacerbations

End point description: Patients with at least one mild exacerbation	
End point type	Secondary
End point timeframe: 52 weeks	

End point values	Symbicort SMART	Symbicort + Terbutaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1049	1042		
Units: number of exacerbations	739	825		

Statistical analyses

Statistical analysis title	Time to first mild exacerbation
Comparison groups	Symbicort SMART v Symbicort + Terbutaline
Number of subjects included in analysis	2091
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.811
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.734
upper limit	0.896

Statistical analysis title	Number of mild asthma excerbations (days)
Comparison groups	Symbicort SMART v Symbicort + Terbutaline
Number of subjects included in analysis	2091
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0276
Method	Poisson regression
Parameter estimate	Risk ratio (RR)
Point estimate	0.889
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	0.987

Secondary: ACQ score	
End point title	ACQ score
End point description: Mean overall ACQ score during the treatment period	
End point type	Secondary
End point timeframe: 52 weeks	

End point values	Symbicort SMART	Symbicort + Terbutaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1040	1038		
Units: average score				
arithmetic mean (full range (min-max))	1.162 (0 to 5.88)	1.289 (0 to 4.68)		

Statistical analyses

Statistical analysis title	Change from baseline in mean ACQ score
Comparison groups	Symbicort SMART v Symbicort + Terbutaline
Number of subjects included in analysis	2078
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.124
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.179
upper limit	-0.069

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the run-in visit (visit 2) until visit 8 (52 weeks after randomisation). AEs observed after intake of the investigational product are presented in the summaries below.

Adverse event reporting additional description:

A total of 1201 patients reported non-serious adverse events; 602 on Symbicort SMART, 599 on Symbicort + Terbutaline. Numbers for non-serious AEs in the reporting group table are based on the 5% threshold frequency.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Symbicort + Terbutaline

Reporting group description:

Symbicort Turbuhaler 160/4.5 µg + terbutaline Turbuhaler 0.4 mg/inhalation

Reporting group title	Symbicort SMART

Reporting group description:

Symbicort Turbuhaler® 160/4.5 µg/inhalation

Serious adverse events	Symbicort + Terbutaline	Symbicort SMART	
Total subjects affected by serious adverse events			
subjects affected / exposed	75 / 1042 (7.20%)	43 / 1049 (4.10%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer in situ			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
intestinal adenocarcinoma			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
metastatic neoplasm			

subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 1042 (0.00%)	2 / 1049 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
hypertension			
subjects affected / exposed	1 / 1042 (0.10%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
abortion spontaneous			
subjects affected / exposed	1 / 1042 (0.10%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
abortion threatened			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
premature baby			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (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			
hernia obstructive			

subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
malaise			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyrexia			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
drug hypersensitivity			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (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			
breast calcifications			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dysfunctional uterine bleeding			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (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 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
infertility male			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
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	31 / 1042 (2.98%)	5 / 1049 (0.48%)	
occurrences causally related to treatment / all	0 / 38	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 1042 (0.19%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal septum deviation			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
major depression			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
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			
foot fracture			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
joint injury			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (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 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
muscle strain			

subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
patella fracture			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sternal fracture			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
traumatic brain injury			
subjects affected / exposed	2 / 1042 (0.19%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
cleft lip			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
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 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
angina pectoris			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (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	1 / 1042 (0.10%)	0 / 1049 (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	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
convulsion			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dizziness			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
headache			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
syncope			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
menieres disease			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
cataract			
subjects affected / exposed	1 / 1042 (0.10%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
retinal detachment			

subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 1042 (0.00%)	3 / 1049 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute abdomen			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
colonic polyp			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (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	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastric polyps			

subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
cholelithiasis			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatotoxicity			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
rash			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
haematuria			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
basedows disease			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
back pain			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (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	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
rheumatoid arthritis			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	3 / 1042 (0.29%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 1042 (0.19%)	4 / 1049 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
h1n1 influenza			

subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media chronic			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinusitis			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			

subjects affected / exposed	0 / 1042 (0.00%)	2 / 1049 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 1042 (0.00%)	2 / 1049 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 1049 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
diabetes mellitus			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
type 2 diabetes mellitus			
subjects affected / exposed	2 / 1042 (0.19%)	0 / 1049 (0.00%)	
occurrences causally related to treatment / all	0 / 2	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	Symbicort + Terbutaline	Symbicort SMART	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	350 / 1042 (33.59%)	314 / 1049 (29.93%)	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	75 / 1042 (7.20%)	49 / 1049 (4.67%)	
occurrences (all)	102	60	
Infections and infestations			
Bronchitis			
subjects affected / exposed	78 / 1042 (7.49%)	69 / 1049 (6.58%)	
occurrences (all)	96	87	
Nasopharyngitis			
subjects affected / exposed	133 / 1042 (12.76%)	137 / 1049 (13.06%)	
occurrences (all)	2116	230	
Viral upper respiratory tract infection			
subjects affected / exposed	72 / 1042 (6.91%)	60 / 1049 (5.72%)	
occurrences (all)	87	71	
Pharyngitis			
subjects affected / exposed	58 / 1042 (5.57%)	49 / 1049 (4.67%)	
occurrences (all)	69	65	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2009	Add the explanation that FEV1 predicted normal values for adolescents (age 16 and 17 years) was calculated according to Polgar and reference.
14 July 2009	Add humanised monoclonal antibody to IgE. Change the post- bronchodilatory FEV1 to the pre-bronchodilatory FEV1

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported