Clinical trial results:
A 6-month safety and benefit study of inhaled fluticasone propionate/ salmeterol combination versus inhaled fluticasone propionate in the treatment of 6,200 pediatric subjects 4-11 years old with persistent asthma

Summary

EudraCT number	2011-001643-79
Trial protocol	HU GB LV CZ LT ES AT SE BE DK NL BG IT FI SK DE
Global end of trial date	03 November 2015

Results information

Result version number	v2 (current)
This version publication date	12 November 2016
First version publication date	15 May 2016
Version creation reason	• Correction of full data set Changes required per study team changes to the ctgov summary to get summaries consistent.

Trial information

Trial identification

Sponsor protocol code	SAS115358

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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	15 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate whether the addition of a long-acting beta-adrenoceptor agonist (LABA) to an inhaled corticosteroid (ICS) (Fluticasone propionate/salmeterol combination [FSC]) therapy is non-inferior in terms of risk of serious asthma-related events (asthma-related hospitalizations, endotracheal intubations, and deaths) compared with ICS alone (Fluticasone Propionate [FP]) in pediatric subjects (age 4-11 years) with persistent asthma.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 November 2011
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	Canada: 97
Country: Number of subjects enrolled	United States: 2796
Country: Number of subjects enrolled	Argentina: 251
Country: Number of subjects enrolled	Chile: 151
Country: Number of subjects enrolled	Mexico: 38
Country: Number of subjects enrolled	Peru: 220
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Bulgaria: 252
Country: Number of subjects enrolled	Croatia: 45
Country: Number of subjects enrolled	Czech Republic: 24
Country: Number of subjects enrolled	Germany: 52
Country: Number of subjects enrolled	Hungary: 132
Country: Number of subjects enrolled	Italy: 31
Country: Number of subjects enrolled	Latvia: 70
Country: Number of subjects enrolled	Lithuania: 15
Country: Number of subjects enrolled	Poland: 299
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Russian Federation: 271

Country: Number of subjects enrolled	Serbia: 131
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Ukraine: 177
Country: Number of subjects enrolled	United Kingdom: 33
Country: Number of subjects enrolled	South Africa: 700
Country: Number of subjects enrolled	Australia: 25
Country: Number of subjects enrolled	Korea, Republic of: 99
Country: Number of subjects enrolled	Malaysia: 82
Country: Number of subjects enrolled	Philippines: 52
Country: Number of subjects enrolled	Taiwan: 93
Country: Number of subjects enrolled	Thailand: 70
Worldwide total number of subjects	6250
EEA total number of subjects	997

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)	6249
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 6250 participants were enrolled and randomized to study treatments; total 6208 participants took at least one dose of study drug.

Pre-assignment

Screening details:

Participants aged between 4 to 11 years having asthma, defined by the regional asthma guidelines for at least 6 months, having history of at least one occurrence of treatment with systemic corticosteroid and with no change in asthma therapy for the last 4 weeks from first visit were enrolled for the study.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Fluticasone propionate/salmeterol combination (FSC)

Arm description:

Participants were randomized to either FSC or FP, and the treatment dose was based on participants' asthma control status. There was no intent to compare the dosage levels received, therefore participants were combined for comparison regardless of dosage. In this treatment arm, participants received one of following treatments: FSC 100/50 microgram (µg) or FSC 250/50 µg as one inhalation twice daily (BID) (approximately 12 hours apart) via Dry powder inhaler (DPI) during the 6 month treatment period. Rescue medication (albuterol/salbutamol) via metered dose inhaler (MDI) was permitted during study treatment.

Arm type	Experimental
Investigational medicinal product name	Fluticasone Propionate 100 micrograms (µg) and salmeterol 50 µg inhalation powder
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

1 inhalation twice daily (morning and evening) via dry powder inhaler

Investigational medicinal product name	Fluticasone Propionate 250 µg and salmeterol 50 µg inhalation powder
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

1 inhalation twice daily (morning and evening) via dry powder inhaler

Arm title	Fluticasone propionate (FP)

Arm description:

Participants were randomized to either FSC or FP, and the treatment dose was based on participants' asthma control status. There was no intent to compare the dosage levels received, therefore participants were combined for comparison regardless of dosage. In this treatment arm, participants received one of the following treatments: FP 100 µg or FP 250 µg as one inhalation BID (approximately 12 hours apart) via DPI during the 6 month treatment period. Rescue medication (albuterol/salbutamol) via MDI was permitted during study treatment.

Arm type	Active comparator
Investigational medicinal product name	Fluticasone Propionate 100 µg inhalation powder
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

1 inhalation twice daily (morning and evening) via dry powder inhaler

Investigational medicinal product name	Fluticasone Propionate 250 µg inhalation powder
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

1 inhalation twice daily (morning and evening) via dry powder inhaler

Number of subjects in period 1[1]	Fluticasone propionate/salmeterol combination (FSC)	Fluticasone propionate (FP)
Started	3107	3101
Completed	2724	2751
Not completed	383	350
Consent withdrawn by subject	245	226
Asthma Exacerbation	34	35
Adverse event, non-fatal	24	23
Lost to follow-up	7	7
Lack of efficacy	5	6
Protocol deviation	68	53

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: The worldwide number enrolled was calculated from the 'Randomization Population', and included participants who were randomized to but never used study treatment whereas the number of subjects reported to be in the baseline period represents the 'Intent-to-Treat Population' which included only those randomized participants who took study treatment.

Baseline characteristics

Reporting groups

Reporting group title	Fluticasone propionate/salmeterol combination (FSC)

Reporting group description:

Participants were randomized to either FSC or FP, and the treatment dose was based on participants' asthma control status. There was no intent to compare the dosage levels received, therefore participants were combined for comparison regardless of dosage. In this treatment arm, participants received one of following treatments: FSC 100/50 microgram (µg) or FSC 250/50 µg as one inhalation twice daily (BID) (approximately 12 hours apart) via Dry powder inhaler (DPI) during the 6 month treatment period. Rescue medication (albuterol/salbutamol) via metered dose inhaler (MDI) was permitted during study treatment.

Reporting group title	Fluticasone propionate (FP)

Reporting group description:

Participants were randomized to either FSC or FP, and the treatment dose was based on participants' asthma control status. There was no intent to compare the dosage levels received, therefore participants were combined for comparison regardless of dosage. In this treatment arm, participants received one of the following treatments: FP 100 µg or FP 250 µg as one inhalation BID (approximately 12 hours apart) via DPI during the 6 month treatment period. Rescue medication (albuterol/salbutamol) via MDI was permitted during study treatment.

Reporting group values	Fluticasone propionate/salmeterol combination (FSC)	Fluticasone propionate (FP)	Total
Number of subjects	3107	3101	6208
Age categorical			
Units: Subjects			
Age continuous			
Population: Randomization			
Units: years			
arithmetic mean	7.6	7.6	
standard deviation	± 2.21	± 2.2	-
Gender categorical			
Units: Subjects			
Female	1187	1227	2414
Male	1920	1874	3794
Race, Customized			
Units: Subjects			
African American / African Heritage	539	511	1050
American Indian or Alaskan Native	144	118	262
Asian - Central / South Asian Heritage	30	37	67
Asian - East Asian Heritage	96	112	208
Japanese Heritage	1	0	1
Asian - South East Asian Heritage	122	108	230
Native Hawaiian or Other Pacific Islander	5	1	6
White - Arabic / North African Heritage	13	15	28
White - White / Caucasian / European Heritage	1985	2017	4002
Mixed Race	167	180	347

Missing	5	2	7

End points

End points reporting groups

Reporting group title	Fluticasone propionate/salmeterol combination (FSC)

Reporting group description:

Participants were randomized to either FSC or FP, and the treatment dose was based on participants' asthma control status. There was no intent to compare the dosage levels received, therefore participants were combined for comparison regardless of dosage. In this treatment arm, participants received one of following treatments: FSC 100/50 microgram (µg) or FSC 250/50 µg as one inhalation twice daily (BID) (approximately 12 hours apart) via Dry powder inhaler (DPI) during the 6 month treatment period. Rescue medication (albuterol/salbutamol) via metered dose inhaler (MDI) was permitted during study treatment.

Reporting group title	Fluticasone propionate (FP)

Reporting group description:

Participants were randomized to either FSC or FP, and the treatment dose was based on participants' asthma control status. There was no intent to compare the dosage levels received, therefore participants were combined for comparison regardless of dosage. In this treatment arm, participants received one of the following treatments: FP 100 µg or FP 250 µg as one inhalation BID (approximately 12 hours apart) via DPI during the 6 month treatment period. Rescue medication (albuterol/salbutamol) via MDI was permitted during study treatment.

Primary: Number of participants experiencing an event in the composite safety endpoint of serious asthma outcomes (asthma-related hospitalization, asthma-related endotracheal intubation, or asthma-related death)

End point title	Number of participants experiencing an event in the composite safety endpoint of serious asthma outcomes (asthma-related hospitalization, asthma-related endotracheal intubation, or asthma-related death)

End point description:

Composite endpoint was defined as clinically relevant endpoint that is constructed from combinations of other clinically relevant endpoints of serious asthma outcomes (i.e., asthma-related hospitalization, asthma-related endotracheal intubation, or asthma-related death). Hospitalization was defined as an inpatient stay or a >=24-hour stay in an observation area in an emergency department or other equivalent facility. Time to first event in the composite endpoint of serious asthma-related outcomes over the 6-month study treatment period was analyzed using a Cox proportional hazards regression model. An estimate of absolute risk difference and its corresponding 95% confidence interval (CI) were also included. The Intent-to-Treat (ITT) Population included all participants randomized to study drug and who took study treatment.

End point type	Primary

End point timeframe:

From Day 1 up to 6 months

End point values	Fluticasone propionate/salmeterol combination (FSC)	Fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3107[1]	3101[2]		
Units: Participants	27	21		

Notes:
[1] - ITT Population
[2] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Estimated for Hazard ratio	
Comparison groups	Fluticasone propionate/salmeterol combination (FSC) v Fluticasone propionate (FP)
Number of subjects included in analysis	6208
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.006
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.285
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.726
upper limit	2.272

Notes:
[3] - The non-inferiority comparison was statistically significant if the upper bound of the two-sided 95% CI falls below 2.675, the non-inferiority margin, and the non-inferiority test one-sided p-value <0.025.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Estimated for Absolute risk difference	
Comparison groups	Fluticasone propionate/salmeterol combination (FSC) v Fluticasone propionate (FP)
Number of subjects included in analysis	6208
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	0.0019
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0024
upper limit	0.0063

Primary: Number of participants with at least one asthma exacerbation over the 6-month study treatment period

End point title	Number of participants with at least one asthma exacerbation over the 6-month study treatment period

End point description:

Number of participants with asthma exacerbation over the 6-month study treatment period are presented. Participants from mITT population with screening childhood asthma control test (C-ACT) scores of 20 or higher, one exacerbation in the previous year, and either low-dose inhaled corticosteroid (ICS) + one or more adjunctive therapy or medium-dose ICS monotherapy or medium-dose ICS and one or more adjunctive therapy as prior asthma therapy were included for this endpoint. Time to first exacerbation analyzed using a cox proportional hazards regression model. The number of asthma exacerbations were compared between treatments using a negative binomial regression model. The modified Intent-to-Treat (mITT) Population consisted of the ITT participants with a different data cut-off for supportive analyses of the primary composite safety endpoint.

End point type	Primary

End point timeframe:

From Day 1 up to 6 months

End point values	Fluticasone propionate/salmeterol combination (FSC)	Fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3107[4]	3101[5]		
Units: Participants	265	309		

Notes:

[4] - mITT Population

[5] - mITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Fluticasone propionate/salmeterol combination (FSC) v Fluticasone propionate (FP)
Number of subjects included in analysis	6208
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.859
Method	Regression, Cox

Secondary: Number of participants experiencing asthma-related deaths over the 6-month study treatment period

End point title	Number of participants experiencing asthma-related deaths over the 6-month study treatment period

End point description:

Number of participants experiencing asthma-related death over the 6-month study treatment period are presented.

End point type	Secondary

End point timeframe:

From Day 1 up to 6 months

End point values	Fluticasone propionate/salmeterol combination (FSC)	Fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3107[6]	3101[7]		
Units: Participants	0	0		

Notes:

[6] - ITT Population

[7] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants experiencing asthma-related endotracheal intubations over the 6-month study treatment period

End point title	Number of participants experiencing asthma-related endotracheal intubations over the 6-month study treatment period

End point description:

Intubation is defined as endotracheal intubation with ventilation (mechanical or by hand). The number of participants experiencing asthma-related endotracheal intubations over the 6-month study treatment period are presented.

End point type	Secondary

End point timeframe:

From Day 1 up to 6 months

End point values	Fluticasone propionate/salmeterol combination (FSC)	Fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3107[8]	3101[9]		
Units: Participants	0	0		

Notes:

[8] - ITT Population

[9] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants experiencing asthma-related hospitalizations over the 6-month study treatment period

End point title	Number of participants experiencing asthma-related hospitalizations over the 6-month study treatment period

End point description:

Hospitalization is defined as a >=24-hour stay as an inpatient or in an observation ward. The number of participants experiencing asthma-related hospitalizations over the 6-month study treatment period are presented.

End point type	Secondary

End point timeframe:

From Day 1 up to 6 months

End point values	Fluticasone propionate/salmeterol combination (FSC)	Fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3107[10]	3101[11]		
Units: Participants	27	21		

Notes:

[10] - ITT Population

[11] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants withdrawn from study treatment due to asthma exacerbation over the 6-month study treatment period

End point title	Number of participants withdrawn from study treatment due to asthma exacerbation over the 6-month study treatment period

End point description:

An exacerbation is defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days (up to 10 days) or a single depot corticosteroid injection. Number of participants experiencing at least one exacerbation from mITT population were included for this endpoint. The number of participants withdrawn from study treatment due to asthma exacerbation over the 6-month study treatment period are presented.

End point type	Secondary

End point timeframe:

From Day 1 up to 6 months

End point values	Fluticasone propionate/salmeterol combination (FSC)	Fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265[12]	309[13]		
Units: Participants	33	35		

Notes:

[12] - mITT Population

[13] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of rescue-free days over the 6-month study treatment period

End point title	Percentage of rescue-free days over the 6-month study treatment period

End point description:

Rescue-free days were days without use of rescue albuterol/salbutamol (other than pre-exercise treatment) over the 6-month study treatment period. The mean percentages of rescue-free days over the months 1-6 (defined as treatment days 2-182) are summarized. Number of participants over treatment days 2-182 from mITT Population were included for this endpoint.

End point type	Secondary

End point timeframe:

From Day 1 up to 6 months

End point values	Fluticasone propionate/salmeterol combination (FSC)	Fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3049[14]	3036[15]		
Units: Percentage of rescue-free days				
arithmetic mean (standard error)	83 (± 0.5)	81.9 (± 0.52)		

Notes:

[14] - mITT Population

[15] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of asthma control days over the 6-month study treatment period

End point title	Percentage of asthma control days over the 6-month study treatment period

End point description:

An asthma control day is one on which rescue albuterol/salbutamol use was recorded as 0, no night time awakenings were recorded, no asthma exacerbations were recorded, no work, school, or daycare days were missed by caregiver or participant due to asthma, coughing symptom score was <=1 and wheezing symptom score was 0. The mean percentages of asthma control days over the months 1-6 (defined as treatment days 2-182) are summarized. Number of participants over treatment days 2-182 from mITT Population were included for this endpoint.

End point type	Secondary

End point timeframe:

From Day 1 up to 6 months

End point values	Fluticasone propionate/salmeterol combination (FSC)	Fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2936[16]	2935[17]		
Units: Percentage of asthma control days				

arithmetic mean (standard error)	74.8 (± 0.57)	73.4 (± 0.58)		

Notes:

[16] - mITT Population

[17] - mITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of study medication until follow-up (up to 6 months).

Adverse event reporting additional description:

Due to the extensive safety database of FSC, FP, and albuterol/salbutamol, and the outcomes of interest in this study, the only non-serious AEs that were collected in this study are those that lead to study drug discontinuation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Fluticasone propionate/salmeterol combination (FSC)

Reporting group description:

Participants were randomized to either FSC or FP, and the treatment dose was based on participants' asthma control status. There was no intent to compare the dosage levels received, therefore participants were combined for comparison regardless of dosage. In this treatment arm, participants received one of following treatments: FSC 100/50 microgram (µg) or FSC 250/50 µg as one inhalation twice daily (BID) (approximately 12 hours apart) via Dry powder inhaler (DPI) during the 6 month treatment period. Rescue medication (albuterol/salbutamol) via metered dose inhaler (MDI) was permitted during study treatment.

Reporting group title	Fluticasone propionate (FP)

Reporting group description:

Participants were randomized to either FSC or FP, and the treatment dose was based on participants' asthma control status. There was no intent to compare the dosage levels received, therefore participants were combined for comparison regardless of dosage. In this treatment arm, participants received one of the following treatments: FP 100 µg or FP 250 µg as one inhalation BID (approximately 12 hours apart) via DPI during the 6 month treatment period. Rescue medication (albuterol/salbutamol) via MDI was permitted during study treatment.

Serious adverse events	Fluticasone propionate/salmeterol combination (FSC)	Fluticasone propionate (FP)	
Total subjects affected by serious adverse events			
subjects affected / exposed	56 / 3107 (1.80%)	54 / 3101 (1.74%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Effusion			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Anaphylactic shock			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	23 / 3107 (0.74%)	13 / 3101 (0.42%)	
occurrences causally related to treatment / all	4 / 23	1 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyperreactivity			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (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	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
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			
Concussion			
subjects affected / exposed	1 / 3107 (0.03%)	2 / 3101 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal bite			

subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative fever			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (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 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt malfunction			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fractured base			

subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 3107 (0.03%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 3107 (0.00%)	2 / 3101 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 3107 (0.03%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Constipation			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (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			
Henoch-Schonlein purpura			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (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 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract disorder			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
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			
Synovitis			

subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	11 / 3107 (0.35%)	8 / 3101 (0.26%)	
occurrences causally related to treatment / all	0 / 11	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	3 / 3107 (0.10%)	2 / 3101 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 3107 (0.03%)	2 / 3101 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 3107 (0.03%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 3107 (0.00%)	2 / 3101 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 3107 (0.03%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	1 / 3107 (0.03%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			

subjects affected / exposed	1 / 3107 (0.03%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 3107 (0.00%)	2 / 3101 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 3107 (0.03%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
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 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bullous impetigo			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema infected			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (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 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudocroup			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral myositis			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral tonsillitis			

subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (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			
Metabolic disorder			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Fluticasone propionate/salmeterol combination (FSC)	Fluticasone propionate (FP)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 3107 (1.00%)	39 / 3101 (1.26%)	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 3107 (0.03%)	1 / 3101 (0.03%)	
occurrences (all)	1	1	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 3107 (0.06%)	2 / 3101 (0.06%)	
occurrences (all)	2	2	
Tremor			
subjects affected / exposed	2 / 3107 (0.06%)	0 / 3101 (0.00%)	
occurrences (all)	3	0	
Dizziness			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences (all)	0	1	
Psychomotor hyperactivity			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest discomfort			

subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences (all)	0	1	
Eye disorders			
Eye swelling			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	15 / 3107 (0.48%)	23 / 3101 (0.74%)	
occurrences (all)	15	23	
Cough			
subjects affected / exposed	2 / 3107 (0.06%)	2 / 3101 (0.06%)	
occurrences (all)	2	2	
Wheezing			
subjects affected / exposed	1 / 3107 (0.03%)	1 / 3101 (0.03%)	
occurrences (all)	1	1	
Bronchospasm			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences (all)	0	1	
Pharyngeal inflammation			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences (all)	0	1	
Rhinitis allergic			

subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 3107 (0.03%)	1 / 3101 (0.03%)	
occurrences (all)	1	1	
Eczema			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences (all)	0	1	
Pityriasis rosea			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 3107 (0.06%)	0 / 3101 (0.00%)	
occurrences (all)	2	0	
Irritability			
subjects affected / exposed	1 / 3107 (0.03%)	1 / 3101 (0.03%)	
occurrences (all)	1	1	
Abnormal behaviour			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Juvenile idiopathic arthritis			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences (all)	0	1	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 3107 (0.03%)	1 / 3101 (0.03%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 3107 (0.06%)	0 / 3101 (0.00%)	
occurrences (all)	2	0	
Bronchitis			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences (all)	0	1	

Lower respiratory tract infection			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 3107 (0.00%)	1 / 3101 (0.03%)	
occurrences (all)	0	1	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	1 / 3107 (0.03%)	0 / 3101 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported