



Clinical trial results:

SAS115359, a Safety and Efficacy Study of Inhaled Fluticasone Propionate/Salmeterol Combination versus Inhaled Fluticasone Propionate in the Treatment of Adolescent and Adult Subjects with Asthma

Summary

EudraCT number	2011-001644-29
Trial protocol	GB AT DE ES LT SE LV HU CZ BE NL PL IT DK SK FI BG
Global end of trial date	23 June 2015

Results information

Result version number	v1
This version publication date	12 June 2016
First version publication date	12 June 2016

Trial information

Trial identification

Sponsor protocol code	115359
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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	26 October 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess whether the risk of serious asthma-related events (asthma-related hospitalizations, endotracheal intubations, and deaths) in adolescents and adults (12 years of age and older) taking inhaled fluticasone propionate/salmeterol combination is the same as those taking inhaled fluticasone propionate alone.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 November 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: 5224
Country: Number of subjects enrolled	Canada: 79
Country: Number of subjects enrolled	Argentina: 401
Country: Number of subjects enrolled	Chile: 79
Country: Number of subjects enrolled	Colombia: 8
Country: Number of subjects enrolled	Mexico: 11
Country: Number of subjects enrolled	Peru: 178
Country: Number of subjects enrolled	Austria: 47
Country: Number of subjects enrolled	Belgium: 22
Country: Number of subjects enrolled	Bulgaria: 263
Country: Number of subjects enrolled	Croatia: 19
Country: Number of subjects enrolled	Czech Republic: 217
Country: Number of subjects enrolled	Denmark: 29
Country: Number of subjects enrolled	Germany: 624
Country: Number of subjects enrolled	Hungary: 174
Country: Number of subjects enrolled	Italy: 86
Country: Number of subjects enrolled	Latvia: 106
Country: Number of subjects enrolled	Lithuania: 97
Country: Number of subjects enrolled	Poland: 551
Country: Number of subjects enrolled	Romania: 45

Country: Number of subjects enrolled	Russian Federation: 1035
Country: Number of subjects enrolled	Serbia: 183
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Spain: 161
Country: Number of subjects enrolled	Ukraine: 480
Country: Number of subjects enrolled	United Kingdom: 59
Country: Number of subjects enrolled	South Africa: 951
Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Indonesia: 227
Country: Number of subjects enrolled	Korea, Republic of: 131
Country: Number of subjects enrolled	Malaysia: 60
Country: Number of subjects enrolled	Philippines: 81
Country: Number of subjects enrolled	Taiwan: 31
Worldwide total number of subjects	11679
EEA total number of subjects	2503

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)	1230
Adults (18-64 years)	9181
From 65 to 84 years	1268
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study duration was 29 weeks, comprised of a randomization visit followed by a treatment period of 26 weeks and a 1-week follow-up phone call. Subjects were assessed for eligibility at screening up to 15 days prior to randomization.

Pre-assignment

Screening details:

Eligible adolescent and adult participants with asthma were stratified based on current asthma medication and a Asthma Control Questionnaire (ACQ-6) score and randomized 1:1 to double-blind study treatment. A total of 11751 were enrolled; however, 72 were randomized but did not receive study treatment.

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 received one of following treatments: FSC 100/50 microgram (µg) or FSC 250/50 µg or FSC 500/50 µg as one inhalation twice daily (BID) via Dry powder inhaler (DPI) for 26 weeks. Rescue medication (albuterol/salbutamol) via metered dose inhaler (MDI) was permitted during study treatment. Participants were instructed to stop using their current asthma medication.

Arm type	Experimental
Investigational medicinal product name	Fluticasone propionate/salmeterol combination (FSC) 100/50 mcg, FSC 250/50 mcg, and FSC 500/50 mcg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation was administered via DPI twice daily (BID) (approximately 12 hours apart)

Arm title	Fluticasone propionate (FP)
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Arm description:

Participants received one of the following treatments: FP 100 µg or FP 250 µg or FP 500 µg as one inhalation BID via DPI for 26 weeks. Rescue medication (albuterol/salbutamol) via metered dose inhaler (MDI) was permitted during study treatment. Participants were instructed to stop using their current asthma medication.

Arm type	Active comparator
Investigational medicinal product name	Fluticasone Propionate (FP) 100 mcg, FP 250 mcg, FP 500 mcg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation was administered via DPI twice daily (BID) (approximately 12 hours apart)

Number of subjects in period 1	Fluticasone propionate/salmeter ol combination (FSC)	Fluticasone propionate (FP)
Started	5834	5845
Completed	5823	5831
Not completed	11	14
Consent withdrawn by subject	8	8
Death	3	6

Baseline characteristics

Reporting groups

Reporting group title	Fluticasone propionate/salmeterol combination (FSC)
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Reporting group description:

Participants received one of following treatments: FSC 100/50 microgram (µg) or FSC 250/50 µg or FSC 500/50 µg as one inhalation twice daily (BID) via Dry powder inhaler (DPI) for 26 weeks. Rescue medication (albuterol/salbutamol) via metered dose inhaler (MDI) was permitted during study treatment. Participants were instructed to stop using their current asthma medication.

Reporting group title	Fluticasone propionate (FP)
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Reporting group description:

Participants received one of the following treatments: FP 100 µg or FP 250 µg or FP 500 µg as one inhalation BID via DPI for 26 weeks. Rescue medication (albuterol/salbutamol) via metered dose inhaler (MDI) was permitted during study treatment. Participants were instructed to stop using their current asthma medication.

Reporting group values	Fluticasone propionate/salmeterol combination (FSC)	Fluticasone propionate (FP)	Total
Number of subjects	5834	5845	11679
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	43.4 ± 17.45	43.4 ± 17.28	-
Gender categorical Units: Subjects			
Female	3851	3898	7749
Male	1983	1947	3930
Customized, Race Units: Subjects			
Missing	3	3	6
African American/African Heritage	870	856	1726
American Indian/Alaska native	109	116	225
Asian-Central/South Asian Heritage	36	45	81
Asian-East Asian Heritage	94	88	182
Japanese Heritage	4	3	7
Asian-South East Asian Heritage	234	224	458
Native Hawaiian or other Pacific Islander	8	10	18
White-Arabic/North African Heritage	22	21	43
White-White/Caucasian/European Heritage	4352	4388	8740
Multiple	102	91	193

End points

End points reporting groups

Reporting group title	Fluticasone propionate/salmeterol combination (FSC)
Reporting group description: Participants received one of following treatments: FSC 100/50 microgram (µg) or FSC 250/50 µg or FSC 500/50 µg as one inhalation twice daily (BID) via Dry powder inhaler (DPI) for 26 weeks. Rescue medication (albuterol/salbutamol) via metered dose inhaler (MDI) was permitted during study treatment. Participants were instructed to stop using their current asthma medication.	
Reporting group title	Fluticasone propionate (FP)
Reporting group description: Participants received one of the following treatments: FP 100 µg or FP 250 µg or FP 500 µg as one inhalation BID via DPI for 26 weeks. Rescue medication (albuterol/salbutamol) via metered dose inhaler (MDI) was permitted during study treatment. Participants were instructed to stop using their current asthma medication.	

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. Probability of having event was summarized with Kaplan-Meier estimates. Hazard ratio, confidence interval, and p-value are from a stratified Cox proportional hazard model, using randomization stratum as the stratification factor. The 95% CI provided in the table is actually the 95. Intent to treat (ITT) Population comprised of all participants randomized to study drug and who took study drug.	
End point type	Primary
End point timeframe: From Day 1 up to 26 weeks	

End point values	Fluticasone propionate/sal meterol combination (FSC)	Fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5834	5845		
Units: Participants				
number (not applicable)	34	33		

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	11679
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	= 0.003
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.638
upper limit	1.662

Notes:

[1] - The non-inferiority comparison is statistically significant if the upper bound of the two-sided 95% CI falls below 2, 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	11679
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	0.0002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0026
upper limit	0.0029

Primary: Number of participants experiencing at least one asthma exacerbation

End point title	Number of participants experiencing at least one asthma exacerbation
End point description:	
An asthma exacerbation is defined as a deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least three days or an inpatient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. Modified intent to treat (mITT) Population comprised of participants included in the ITT population that correspond to each participant's period of exposure to study drug plus seven days after the last date of study drug treatment.	
End point type	Primary
End point timeframe:	
From Day 1 up to 26 weeks	

End point values	Fluticasone propionate/sal meterol combination (FSC)	Fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5834	5845		
Units: Participants				
number (not applicable)	480	597		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Analysis of time to first exacerbation in efficacy subgroup: Subjects not well-controlled on prior ICS or non-LABA therapy

Comparison groups	Fluticasone propionate/salmeterol combination (FSC) v Fluticasone propionate (FP)
Number of subjects included in analysis	11679
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.203
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.834
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.103

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Analysis of time to first exacerbation in efficacy subgroup: Subjects not well-controlled on prior ICS+LABA therapy

Comparison groups	Fluticasone propionate/salmeterol combination (FSC) v Fluticasone propionate (FP)
Number of subjects included in analysis	11679
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.188
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.839

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.645
upper limit	1.09

Statistical analysis title	Statistical Analysis 3
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Statistical analysis description:

Analysis of time to first exacerbation in efficacy subgroup: Subjects controlled on prior ICS+LABA therapy

Comparison groups	Fluticasone propionate/salmeterol combination (FSC) v Fluticasone propionate (FP)
Number of subjects included in analysis	11679
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.764
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.645
upper limit	0.905

Statistical analysis title	Statistical Analysis 4
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Statistical analysis description:

Analysis of time to first exacerbation in efficacy subgroup: Subjects controlled on prior ICS therapy

Comparison groups	Fluticasone propionate/salmeterol combination (FSC) v Fluticasone propionate (FP)
Number of subjects included in analysis	11679
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.071
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.682
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.451
upper limit	1.034

Statistical analysis title	Statistical Analysis 5
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Statistical analysis description:

Analysis of number of asthma exacerbations in efficacy subgroup: Subjects not well-controlled on prior ICS or non-LABA therapy

Comparison groups	Fluticasone propionate/salmeterol combination (FSC) v Fluticasone propionate (FP)
Number of subjects included in analysis	11679
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.373
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.878
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.659
upper limit	1.17

Statistical analysis title	Statistical Analysis 6
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Statistical analysis description:

Analysis of number of asthma exacerbations in efficacy subgroup: Subjects not well-controlled on prior ICS+LABA therapy

Comparison groups	Fluticasone propionate/salmeterol combination (FSC) v Fluticasone propionate (FP)
Number of subjects included in analysis	11679
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.271
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.864
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.665
upper limit	1.122

Statistical analysis title	Statistical Analysis 7
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Statistical analysis description:

Analysis of number of asthma exacerbations in efficacy subgroup: Subjects controlled on prior ICS+LABA therapy

Comparison groups	Fluticasone propionate/salmeterol combination (FSC) v Fluticasone propionate (FP)
Number of subjects included in analysis	11679
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.755
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.637
upper limit	0.895

Statistical analysis title	Statistical Analysis 8
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Statistical analysis description:

Analysis of number of asthma exacerbations in efficacy subgroup: Subjects controlled on prior ICS therapy

Comparison groups	Fluticasone propionate/salmeterol combination (FSC) v Fluticasone propionate (FP)
Number of subjects included in analysis	11679
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.075
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.687

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.454
upper limit	1.04

Secondary: Number of participants experiencing at least one asthma related hospitalization, endotracheal intubation and death

End point title	Number of participants experiencing at least one asthma related hospitalization, endotracheal intubation and death
End point description: Hospitalization was defined as an inpatient stay or a >=24-hour stay in an observation area in an emergency department or other equivalent facility.	
End point type	Secondary
End point timeframe: From Day 1 up to 26 weeks	

End point values	Fluticasone propionate/sal meterol combination (FSC)	Fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5834 ^[2]	5845 ^[3]		
Units: Participants				
number (not applicable)				
Hospitalization	34	33		
Endotracheal intubation	0	2		
Death	0	0		

Notes:

[2] - ITT Population

[3] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participant withdrawals from study treatment due to asthma exacerbation

End point title	Number of participant withdrawals from study treatment due to asthma exacerbation
End point description: An asthma exacerbation is defined as a deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least three days or an inpatient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.	
End point type	Secondary
End point timeframe: From Day 1 up to 26 weeks	

End point values	Fluticasone propionate/sal meterol combination (FSC)	Fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5834 ^[4]	5845 ^[5]		
Units: Participants				
number (not applicable)	66	84		

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	11679
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.123
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.776
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.562
upper limit	1.071

Secondary: Mean rescue medication (albuterol/salbutamol) use as puffs per 24 hours

End point title	Mean rescue medication (albuterol/salbutamol) use as puffs per 24 hours
End point description:	
Rescue medication included albuterol/salbutamol used to treat acute asthma were reported as puffs per 24 hours over a period of 6 months.	
End point type	Secondary
End point timeframe:	
From Day 1 up to 26 weeks	

End point values	Fluticasone propionate/sal meterol combination (FSC)	Fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5677 ^[6]	5673 ^[7]		
Units: Number of Puffs				
arithmetic mean (standard error)	0.9 (± 0.018)	1.09 (± 0.02)		

Notes:

[6] - mITT Population. Only those participants available at specified timepoint were analysed.

[7] - mITT Population. Only those participants available at specified timepoint were analysed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Efficacy subgroup: Subjects not well-controlled on prior ICS or non-LABA therapy	
Comparison groups	Fluticasone propionate/salmeterol combination (FSC) v Fluticasone propionate (FP)
Number of subjects included in analysis	11350
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Mean difference (final values)
Point estimate	-0.263
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.385
upper limit	-0.141

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Efficacy subgroup: Subjects not well-controlled on prior ICS+LABA therapy	
Comparison groups	Fluticasone propionate/salmeterol combination (FSC) v Fluticasone propionate (FP)
Number of subjects included in analysis	11350
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003
Method	Regression, Cox
Parameter estimate	Mean difference (final values)
Point estimate	-0.222
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.369
upper limit	-0.076

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Efficacy subgroup: Subjects controlled on prior ICS+LABA therapy	
Comparison groups	Fluticasone propionate/salmeterol combination (FSC) v Fluticasone propionate (FP)
Number of subjects included in analysis	11350
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Mean difference (final values)
Point estimate	-0.172
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.238
upper limit	-0.106

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Efficacy subgroup: Subjects controlled on prior ICS therapy	
Comparison groups	Fluticasone propionate/salmeterol combination (FSC) v Fluticasone propionate (FP)
Number of subjects included in analysis	11350
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.251
Method	Regression, Cox
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.216
upper limit	0.056

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious events (AEs) were collected from post-randomization, throughout the treatment period of 26 weeks up to a 1-week follow-up phone call (27 Weeks).

Adverse event reporting additional description:

All SAEs are presented and Non-serious AEs were collected from the members of mITT population up until the participants' withdrawal from study treatment, only non-serious AEs that lead to withdrawal of study treatment were collected

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Fluticasone propionate (FP)
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Reporting group description:

Participants received one of following treatments: FP 100 µg or FP 250 µg or FP 500 µg as one inhalation (BID) via (DPI) for 26 weeks. Rescue medication (albuterol/salbutamol) via metered dose inhaler (MDI) was permitted during study treatment. Participants were instructed to stop using their current asthma medication.

Reporting group title	Fluticasone propionate/salmeterol combination (FSC)
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Reporting group description:

Participants received one of following treatments: FSC 100/50 microgram (µg) or FSC 250/50 µg or FSC 500/50 µg as one inhalation twice daily (BID) via Dry powder inhaler (DPI) for 26 weeks. Rescue medication (albuterol/salbutamol) via metered dose inhaler (MDI) was permitted during study treatment. Participants were instructed to stop using their current asthma medication.

Serious adverse events	Fluticasone propionate (FP)	Fluticasone propionate/salmeterol combination (FSC)	
Total subjects affected by serious adverse events			
subjects affected / exposed	125 / 5845 (2.14%)	134 / 5834 (2.30%)	
number of deaths (all causes)	6	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic neoplasm			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Anaplastic astrocytoma			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer stage II			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal oncocytoma			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 5845 (0.02%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Hypertension			
subjects affected / exposed	0 / 5845 (0.00%)	2 / 5834 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery occlusion			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (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			
Abortion spontaneous			
subjects affected / exposed	4 / 5845 (0.07%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blighted ovum			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ectopic pregnancy			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Stillbirth			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (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	4 / 5845 (0.07%)	2 / 5834 (0.03%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (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			
Anaphylactic reaction			
subjects affected / exposed	1 / 5845 (0.02%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Allergic granulomatous angiitis			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (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			
Fallopian tube cyst			

subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cervical squamous metaplasia			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	1 / 5845 (0.02%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 5845 (0.09%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Status asthmaticus			
subjects affected / exposed	2 / 5845 (0.03%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			

subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	28 / 5845 (0.48%)	30 / 5834 (0.51%)	
occurrences causally related to treatment / all	3 / 30	2 / 32	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 5845 (0.03%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress			
subjects affected / exposed	0 / 5845 (0.00%)	2 / 5834 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bulimia nervosa			

subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnambulism			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	2 / 5845 (0.03%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Coagulation time prolonged			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 5845 (0.00%)	2 / 5834 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 5845 (0.00%)	2 / 5834 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Clavicle fracture			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heat exhaustion			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delayed recovery from anaesthesia			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament injury			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			

subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Radius fracture			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic liver injury			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 5845 (0.02%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hereditary angioedema			

subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 5845 (0.00%)	3 / 5834 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 5845 (0.03%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 5845 (0.00%)	2 / 5834 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (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 / 5845 (0.03%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (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	1 / 5845 (0.02%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prinzmetal angina			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (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			
Ischaemic stroke			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical cord compression			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal subdural haematoma			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 5845 (0.02%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 5845 (0.02%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 5845 (0.03%)	2 / 5834 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 5845 (0.05%)	4 / 5834 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Hemiparesis			

subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
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			
Anaemia			
subjects affected / exposed	1 / 5845 (0.02%)	3 / 5834 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	2 / 5845 (0.03%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			

subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			

subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 5845 (0.02%)	2 / 5834 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			

subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 5845 (0.03%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (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			
Nephrolithiasis			
subjects affected / exposed	0 / 5845 (0.00%)	2 / 5834 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst			

subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (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			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 5845 (0.00%)	2 / 5834 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone cyst			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (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	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal osteoarthritis			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (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 / 5845 (0.02%)	2 / 5834 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
subjects affected / exposed	3 / 5845 (0.05%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 5845 (0.00%)	3 / 5834 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 5845 (0.00%)	2 / 5834 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typhoid fever			
subjects affected / exposed	0 / 5845 (0.00%)	2 / 5834 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute tonsillitis			

subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural abscess			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (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	2 / 5845 (0.03%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Helicobacter gastritis			

subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillitis			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	8 / 5845 (0.14%)	8 / 5834 (0.14%)	
occurrences causally related to treatment / all	2 / 9	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingo-oophoritis			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (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	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sialoadenitis			

subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viraemia			
subjects affected / exposed	1 / 5845 (0.02%)	0 / 5834 (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 / 5845 (0.02%)	0 / 5834 (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	1 / 5845 (0.02%)	0 / 5834 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 5845 (0.02%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 5845 (0.02%)	1 / 5834 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	0 / 5845 (0.00%)	3 / 5834 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 5845 (0.00%)	2 / 5834 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 5845 (0.00%)	1 / 5834 (0.02%)	
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: 1 %

Non-serious adverse events	Fluticasone propionate (FP)	Fluticasone propionate/salmeterol combination (FSC)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 5845 (1.28%)	46 / 5834 (0.79%)	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	75 / 5845 (1.28%)	46 / 5834 (0.79%)	
occurrences (all)	75	47	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2012	Removed the inclusion of adolescent subjects ($12 \leq \text{ages} < 18$) for France.
06 November 2013	Removed Table 1
06 February 2014	Updated GSK Case Management contact information.
07 May 2014	Updated Sponsor's medical monitor contact information and minor typographical corrections.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported