Clinical trial results:
A 52-week, Randomized, Double-Blind, Parallel-Group Study of Fluticasone Propionate/Salmeterol DISKUS Combination Product (FSC) 250/50 mcg BID and Fluticasone Propionate (FP) DISKUS 250 mcg BID in Treatment of Subjects with Asthma

Summary

EudraCT number	2015-004883-12
Trial protocol	Outside EU/EEA
Global end of trial date	29 April 2009

Results information

Result version number	v1 (current)
This version publication date	25 January 2017
First version publication date	25 January 2017

Trial information

Trial identification

Sponsor protocol code	ADA109057

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	Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 July 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 April 2009
Global end of trial reached?	Yes
Global end of trial date	29 April 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

TBD

Protection of trial subjects:

No Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 May 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 155
Country: Number of subjects enrolled	Brazil: 39
Country: Number of subjects enrolled	Canada: 45
Country: Number of subjects enrolled	Philippines: 30
Country: Number of subjects enrolled	United States: 359
Worldwide total number of subjects	628
EEA total number of subjects	0

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)	67
Adults (18-64 years)	522
From 65 to 84 years	37

85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 628 subjects were included in the ITT Population: 310 in the FSC DISKUS 250/50 group and 318 in the FP DISKUS 250 group. The majority of subjects in each treatment groups (75% in the FSC DISKUS 250/50 group and 74% in the FP 250 group) completed 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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	FSC DISKUS 250/50 mcg BID

Arm description:

Fluticasone Propionate/Salmeterol DISKUS Combination Product (FSC) 250/50 micrograms (mcg) twice daily (BID) for 52 weeks

Arm type	Active comparator
Investigational medicinal product name	Fluticasone Propionate/Salmeterol Combination (FSC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

Subjects received one inhalation of FSC 250/50 micrograms (mcg) via DISKUS twice daily (BID) for 52 weeks

Arm title	FP DISKUS 250 mcg BID for 52 weeks

Arm description:

Fluticasone Propionate (FP) DISKUS 250 mcg BID for 52 weeks

Arm type	Active comparator
Investigational medicinal product name	Fluticasone Propionate (FP)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

Subjects received one inhalation of FP 250 mcg via DISKUS BID for 52 weeks.

Number of subjects in period 1	FSC DISKUS 250/50 mcg BID	FP DISKUS 250 mcg BID for 52 weeks
Started	310	318
Completed	231	234
Not completed	79	84
Consent withdrawn by subject	18	21
Adverse event, non-fatal	6	9
Other	9	9
Lost to follow-up	14	8
Lack of efficacy	10	9
Protocol deviation	22	28

Baseline characteristics

Reporting groups	
Reporting group title	FSC DISKUS 250/50 mcg BID
Reporting group description:	
Fluticasone Propionate/Salmeterol DISKUS Combination Product (FSC) 250/50 micrograms (mcg) twice daily (BID) for 52 weeks	
Reporting group title	FP DISKUS 250 mcg BID for 52 weeks
Reporting group description:	
Fluticasone Propionate (FP) DISKUS 250 mcg BID for 52 weeks	

Reporting group values	FSC DISKUS 250/50 mcg BID	FP DISKUS 250 mcg BID for 52 weeks	Total
Number of subjects	310	318	628
Age categorical Units: Subjects			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	40.9	39.6	
standard deviation	± 15.71	± 16.56	-
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	186	181	367
Male	124	137	261
Race/Ethnicity, Customized Units: Subjects			
White	254	262	516
African American	29	27	56
Asian	20	25	45
American Indian	2	0	2
Other	5	4	9

End points

End points reporting groups

Reporting group title	FSC DISKUS 250/50 mcg BID
Reporting group description:	
Fluticasone Propionate/Salmeterol DISKUS Combination Product (FSC) 250/50 micrograms (mcg) twice daily (BID) for 52 weeks	
Reporting group title	FP DISKUS 250 mcg BID for 52 weeks
Reporting group description:	
Fluticasone Propionate (FP) DISKUS 250 mcg BID for 52 weeks	

Primary: Mean change from baseline in pre-dose FEV1 over Weeks 1-52

End point title	Mean change from baseline in pre-dose FEV1 over Weeks 1-52
End point description:	
Pulmonary function was measured by forced expiratory volume in one second (FEV1), which is the volume of air exhaled from the lungs in one second. Change from baseline was calculated as the average of the Week 1 through Week 52 values minus the baseline value. Intent-to-Treat (ITT) Population: all participants randomized to study drug who had at least one on-treatment FEV1.	
End point type	Primary
End point timeframe:	
Baseline and Week 1 through Week 52	

End point values	FSC DISKUS 250/50 mcg BID	FP DISKUS 250 mcg BID for 52 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303[1]	304[2]		
Units: Liters				
arithmetic mean (standard error)	0.16 (± 0.017)	0.12 (± 0.02)		

Notes:

[1] - Intent-to-Treat (ITT) Population

[2] - Intent-to-Treat (ITT) Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FSC DISKUS 250/50 mcg BID v FP DISKUS 250 mcg BID for 52 weeks
Number of subjects included in analysis	607
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.09
Method	ANCOVA
Parameter estimate	Least Squares Mean
Point estimate	0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.09

Secondary: Mean change from baseline in AM PEF over Weeks 1-52

End point title	Mean change from baseline in AM PEF over Weeks 1-52

End point description:

Morning (AM) peak expiratory flow (PEF) is defined as the maximum volume of air exhaled in liters per minute. Change from baseline was calculated as the average of the Week 1 through Week 52 values minus the baseline value.

End point type	Secondary

End point timeframe:

Baseline and Week 1 through Week 52

End point values	FSC DISKUS 250/50 mcg BID	FP DISKUS 250 mcg BID for 52 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305[3]	310[4]		
Units: Liters/minute (L/min)				
arithmetic mean (standard error)	27.7 (± 2.85)	14.6 (± 2.49)		

Notes:

[3] - Participants in the ITT Population who had a minimum of 1 week PEF values.

[4] - Participants in the ITT Population who had a minimum of 1 week PEF values.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in the percentage of symptom-free days over Weeks 1-52

End point title	Mean change from baseline in the percentage of symptom-free days over Weeks 1-52

End point description:

A symptom-free day was defined as a day without asthma symptoms, as measured via the daily asthma symptom score (measuring symptoms during the day and previous night) on a 6-point scale (ranging from 0 to 5). A symptom score of 0=no symptoms, 1=symptoms for one short period, 2=symptoms for two or more short periods, 3=symptoms that did not affect normal daily activities, 4=symptoms that did affect normal daily activities, 5=symptoms so severe that daily activities could not be performed. Change from baseline was calculated as the average of the Week 1-Week 52 values minus the baseline value.

End point type	Secondary

End point timeframe:

Baseline and Week 1 through Week 52

End point values	FSC DISKUS 250/50 mcg BID	FP DISKUS 250 mcg BID for 52 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305[5]	310[6]		
Units: Percentage of symptom-free days				
arithmetic mean (standard error)	37.4 (± 2.03)	28.9 (± 1.82)		

Notes:

[5] - Participants in the ITT Population for which at least 1 week of diary data were provided.

[6] - Participants in the ITT Population for which at least 1 week of diary data were provided.

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of asthma attacks per participant per year

End point title	Rate of asthma attacks per participant per year

End point description:

The rate of asthma attacks was defined as the mean number of attacks per participant per year. An asthma attack was defined as a >=20% decrease in AM PEF, a >=70% increase in albuterol use, or the occurrence of an asthma exacerbation requiring oral steroids or hospitalization.

End point type	Secondary

End point timeframe:

Week 1 through Week 52

End point values	FSC DISKUS 250/50 mcg BID	FP DISKUS 250 mcg BID for 52 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	310[7]	318[8]		
Units: attacks per participant per year				
arithmetic mean (confidence interval 95%)	2.63 (2.17 to 3.19)	2.73 (2.26 to 3.31)		

Notes:

[7] - ITT Population

[8] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All on-treatment serious adverse events (SAEs) and non-serious AEs were collected from the start of the run-in period (Day -14 to -21) until the end of the follow up period (approximately 53 weeks).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	FP DISKUS 250 mcg BID for 52 weeks

Reporting group description:

Fluticasone Propionate (FP) DISKUS 250 mcg BID for 52 weeks

Reporting group title	FSC DISKUS 250/50 mcg BID

Reporting group description:

Fluticasone Propionate/Salmeterol DISKUS Combination Product (FSC) 250/50 micrograms (mcg) twice daily (BID) for 52 weeks

Serious adverse events	FP DISKUS 250 mcg BID for 52 weeks	FSC DISKUS 250/50 mcg BID	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 318 (2.20%)	6 / 310 (1.94%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 318 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 318 (0.31%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 318 (0.31%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			

subjects affected / exposed	1 / 318 (0.31%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 318 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 318 (0.31%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 318 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 318 (0.31%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Large intestine perforation			
subjects affected / exposed	1 / 318 (0.31%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast cancer			
subjects affected / exposed	1 / 318 (0.31%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ovarian cyst			

subjects affected / exposed	0 / 318 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 318 (0.63%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 318 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cholecystitis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	FP DISKUS 250 mcg BID for 52 weeks	FSC DISKUS 250/50 mcg BID	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	201 / 318 (63.21%)	184 / 310 (59.35%)	
Nervous system disorders			
Headache			
subjects affected / exposed	60 / 318 (18.87%)	51 / 310 (16.45%)	
occurrences (all)	188	153	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	18 / 318 (5.66%)	19 / 310 (6.13%)	
occurrences (all)	21	21	
Oropharyngeal pain			
subjects affected / exposed	19 / 318 (5.97%)	23 / 310 (7.42%)	
occurrences (all)	21	28	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	24 / 318 (7.55%)	23 / 310 (7.42%)	
occurrences (all)	33	28	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	55 / 318 (17.30%)	45 / 310 (14.52%)	
occurrences (all)	77	60	
Nasopharyngitis			
subjects affected / exposed	70 / 318 (22.01%)	54 / 310 (17.42%)	
occurrences (all)	108	75	
Bronchitis			
subjects affected / exposed	38 / 318 (11.95%)	34 / 310 (10.97%)	
occurrences (all)	61	43	
Influenza			
subjects affected / exposed	21 / 318 (6.60%)	15 / 310 (4.84%)	
occurrences (all)	22	15	
Sinusitis			
subjects affected / exposed	40 / 318 (12.58%)	33 / 310 (10.65%)	
occurrences (all)	45	47	
Rhinitis			
subjects affected / exposed	18 / 318 (5.66%)	23 / 310 (7.42%)	
occurrences (all)	35	39	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2007	Amendment provided clarifications for the following: 1. Definition of "7 days prior to randomization" for the randomization criteria 2. Asthma Medication History inclusion criterion 3. Respiratory Tract Infections and Concurrent Medications exclusion criteria 4. Asthma Withdrawal criteria 5. Permitted and prohibited medications 6. Re-screening and screen failures 7. Calculation of percent predicted FEV1 8. Treatment for an asthma exacerbation and additional guidelines

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported