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	2015-004892-61
Trial protocol	Outside EU/EEA
Global end of trial date	15 May 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	ADA109055

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 July 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 May 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

TBD

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 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: 123
Country: Number of subjects enrolled	Brazil: 38
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Philippines: 99
Country: Number of subjects enrolled	United States: 654
Worldwide total number of subjects	937
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)	147
Adults (18-64 years)	756
From 65 to 84 years	33

85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 937 subjects were screened for this study; 316 (34%) failed screening and were not randomized to double-blind treatment. The majority (82%) of Screen Failures were unable to fulfill the study eligibility criteria.

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 for 52 weeks

Arm description:

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

Arm type	Experimental
Investigational medicinal product name	Fluticasone propionate/Salmeterol xinofoate 250/50 microgram (mcg) fixed dose combination (FDC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

FSC 250/50 mcg one inhalation twice daily (in the morning, and in the evening, approximately 12 hours apart)

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

Dosage and administration details:

FP 250 mcg one inhalation twice daily (in the morning, and in the evening, approximately 12 hours apart)

Number of subjects in period 1[1]	FSC DISKUS 250/50 mcg BID for 52 weeks	FP DISKUS 250 mcg BID for 52 weeks
Started	306	315
Completed	225	242
Not completed	81	73
Consent withdrawn by subject	26	25
Adverse event, non-fatal	10	3
Other	12	7
Lost to follow-up	6	9
Lack of efficacy	6	4
Protocol deviation	21	25

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: A total of 937 subjects were screened for this study; 316 (34%) failed screening and were not randomized to double-blind treatment.

Baseline characteristics

Reporting groups	
Reporting group title	FSC DISKUS 250/50 mcg BID for 52 weeks
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 for 52 weeks	FP DISKUS 250 mcg BID for 52 weeks	Total
Number of subjects	306	315	621
Age categorical Units: Subjects			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	36.8	39.3	
standard deviation	± 15.52	± 15.52	-
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	191	201	392
Male	115	114	229
Race/Ethnicity, Customized Units: Subjects			
White	197	208	405
African American	63	61	124
Asian	39	41	80
American Indian	3	4	7
Other	4	1	5

End points

End points reporting groups

Reporting group title	FSC DISKUS 250/50 mcg BID for 52 weeks
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 by forced expiratory volume in one second (FEV1) over Weeks 1-52

End point title	Mean change from baseline in pre-dose by forced expiratory volume in one second (FEV1) over Weeks 1-52
End point description:	
Pulmonary function was measured by 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.	
End point type	Primary
End point timeframe:	
Baseline and Week 1 through Week 52	

End point values	FSC DISKUS 250/50 mcg BID for 52 weeks	FP DISKUS 250 mcg BID for 52 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	306[1]	315[2]		
Units: Liters				
arithmetic mean (standard error)	0.2 (± 0.017)	0.09 (± 0.015)		

Notes:

[1] - Intent-to-Treat (ITT) Population: all participants randomized to study drug.

[2] - Intent-to-Treat (ITT) Population: all participants randomized to study drug.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FP DISKUS 250 mcg BID for 52 weeks v FSC DISKUS 250/50 mcg BID for 52 weeks
Number of subjects included in analysis	621
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	0.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.15

Secondary: Mean change from baseline in Morning (AM) peak expiratory flow (PEF) over Weeks 1-52

End point title	Mean change from baseline in Morning (AM) peak expiratory flow (PEF) over Weeks 1-52

End point description:

Morning 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 for 52 weeks	FP DISKUS 250 mcg BID for 52 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	299[3]	313[4]		
Units: Liters/minute (L/min)				
arithmetic mean (standard error)	23.6 (± 2.47)	9.8 (± 2.4)		

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 for 52 weeks	FP DISKUS 250 mcg BID for 52 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	299[5]	313[6]		
Units: Percentage of symptom-free days				
arithmetic mean (standard error)	37.1 (± 2.02)	28.5 (± 1.9)		

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 for 52 weeks	FP DISKUS 250 mcg BID for 52 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	306[7]	315[8]		
Units: attacks per participant per year				
arithmetic mean (confidence interval 95%)	1.87 (1.36 to 2.59)	2.14 (1.55 to 2.96)		

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 AE data from the time of subject consent until the follow-up period (approximately 53 weeks) were collected.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	FSC DISKUS 250/50 mcg BID for 52 weeks

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

Serious adverse events	FSC DISKUS 250/50 mcg BID for 52 weeks	FP DISKUS 250 mcg BID for 52 weeks	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 306 (4.58%)	9 / 315 (2.86%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	1 / 306 (0.33%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	1 / 306 (0.33%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Phlebitis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 306 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 315 (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			
Cerebrovascular accident			
subjects affected / exposed	0 / 306 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 306 (0.33%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	1 / 306 (0.33%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia, obstructive			

subjects affected / exposed	0 / 306 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 306 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 306 (0.98%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 306 (0.00%)	1 / 315 (0.32%)	
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			
Arthritis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 306 (0.65%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amoebic dysentery			

subjects affected / exposed	1 / 306 (0.33%)	0 / 315 (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	0 / 306 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 306 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 315 (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	FSC DISKUS 250/50 mcg BID for 52 weeks	FP DISKUS 250 mcg BID for 52 weeks	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	183 / 306 (59.80%)	203 / 315 (64.44%)	
Nervous system disorders			
Headache			
subjects affected / exposed	56 / 306 (18.30%)	59 / 315 (18.73%)	
occurrences (all)	158	128	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	27 / 306 (8.82%)	19 / 315 (6.03%)	
occurrences (all)	32	24	
Oropharyngeal Pain			
subjects affected / exposed	14 / 306 (4.58%)	20 / 315 (6.35%)	
occurrences (all)	15	23	
Rhinitis Allergic			

subjects affected / exposed	13 / 306 (4.25%)	18 / 315 (5.71%)	
occurrences (all)	17	27	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	20 / 306 (6.54%)	14 / 315 (4.44%)	
occurrences (all)	52	17	
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	62 / 306 (20.26%)	96 / 315 (30.48%)	
occurrences (all)	89	135	
Nasopharyngitis			
subjects affected / exposed	54 / 306 (17.65%)	56 / 315 (17.78%)	
occurrences (all)	87	83	
Bronchitis			
subjects affected / exposed	20 / 306 (6.54%)	31 / 315 (9.84%)	
occurrences (all)	21	35	
Influenza			
subjects affected / exposed	22 / 306 (7.19%)	25 / 315 (7.94%)	
occurrences (all)	24	27	
Sinusitis			
subjects affected / exposed	17 / 306 (5.56%)	27 / 315 (8.57%)	
occurrences (all)	22	38	

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: • Definition of "7 days prior to randomization" for the randomization criteria • Asthma Medication History inclusion criterion • Respiratory Tract Infections and Concurrent Medications exclusion criteria • Asthma Withdrawal criteria • Permitted and prohibited medications • Re-screening and screen failures • Calculation of percent predicted FEV1 • 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