Clinical trial results:
FFA115285: A randomised, double-blind, double-dummy, placebo controlled multi-centre study to evaluate the efficacy and safety of fluticasone furoate inhalation powder and fluticasone propionate inhalation powder in the treatment of asthma in adults and adolescents not currently treated with inhaled corticosteroids.

Summary

EudraCT number	2011-001900-36
Trial protocol	NL PL
Global end of trial date	26 September 2012

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	07 February 2015

Trial information

Trial identification

Sponsor protocol code	FFA115285

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 8664357343,
Scientific contact	GSK Response Center, GlaxoSmithKline, +1 8664357343,

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	29 October 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 September 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of inhaled fluticasone furoate 50 mcg administered once daily in the evening in adolescent and adult subjects 12 years of age and older with persistent asthma over a 24-week treatment period.

Protection of trial subjects:

Participant withdrawal due to lack of efficacy was required when:

A participant’s clinic FEV1 fell below the FEV1 stability limit value calculated at Visit 2;

In the 7 days immediately preceding any contact, the subject experienced: at least 4 days in which the AM or PM PEF fell below the PEF stability limit calculated at Visit 2 and/or at least 3 days in which >=12 inhalations/day of albuterol/salbutamol were used;

A participant experienced a protocol-defined severe asthma exacerbation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 53
Country: Number of subjects enrolled	United States: 232
Country: Number of subjects enrolled	Netherlands: 38
Country: Number of subjects enrolled	Poland: 86
Country: Number of subjects enrolled	Mexico: 96
Country: Number of subjects enrolled	Peru: 150
Worldwide total number of subjects	655
EEA total number of subjects	124

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	96
Adults (18-64 years)	525
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants (par.) meeting eligibility criteria at the Screening visit entered a 2-week Run-in Period for Baseline safety evaluations and to obtain measures of asthma status. Participants were then randomized to a 24-week Treatment Period. A total of 655 participants were screened; 351 were randomized, and 347 received >=1 dose of 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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo via a dry powder inhaler (DPI) once daily (OD) in the evening plus placebo via a different DPI twice daily (BID) for 24 weeks. In addition, all participants were provided with albuterol/salbutamol aerosol to be used as rescue medication as needed.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received placebo via a dry powder inhaler (DPI) once daily (OD) in the evening plus placebo via a different DPI twice daily (BID) for 24 weeks.

Arm title	FF 50 µg OD

Arm description:

Participants received fluticasone furoate (FF) 50 micrograms (µg) inhalation powder via a DPI OD in the evening plus placebo via a different DPI BID for 24 weeks. In addition, all participants were provided with albuterol/salbutamol aerosol to be used as rescue medication as needed.

Arm type	Experimental
Investigational medicinal product name	FF 50 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received fluticasone furoate (FF) 50 micrograms (µg) inhalation powder via a DPI OD in the evening plus placebo via a different DPI BID for 24 weeks.

Arm title	FP 100 µg BID

Arm description:

Participants received fluticasone propionate (FP) 100 µg BID via a DPI plus placebo via a different DPI OD in the evening for 24 weeks. In addition, all participants were provided with albuterol/salbutamol aerosol to be used as rescue medication as needed.

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

Dosage and administration details:

Participants received fluticasone propionate (FP) 100 µg BID via a DPI plus placebo via a different DPI OD in the evening for 24 weeks.

Number of subjects in period 1[1]	Placebo	FF 50 µg OD	FP 100 µg BID
Started	115	117	115
Completed	77	91	95
Not completed	38	26	20
Consent withdrawn by subject	6	8	4
Physician decision	3	1	1
Adverse event, non-fatal	2	1	2
Lost to follow-up	1	1	3
Lack of efficacy	23	14	9
Protocol deviation	3	1	1

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 655 participants were screened; 351 were randomized, and 347 received >=1 dose of study treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo via a dry powder inhaler (DPI) once daily (OD) in the evening plus placebo via a different DPI twice daily (BID) for 24 weeks. In addition, all participants were provided with albuterol/salbutamol aerosol to be used as rescue medication as needed.	
Reporting group title	FF 50 µg OD
Reporting group description:	
Participants received fluticasone furoate (FF) 50 micrograms (µg) inhalation powder via a DPI OD in the evening plus placebo via a different DPI BID for 24 weeks. In addition, all participants were provided with albuterol/salbutamol aerosol to be used as rescue medication as needed.	
Reporting group title	FP 100 µg BID
Reporting group description:	
Participants received fluticasone propionate (FP) 100 µg BID via a DPI plus placebo via a different DPI OD in the evening for 24 weeks. In addition, all participants were provided with albuterol/salbutamol aerosol to be used as rescue medication as needed.	

Reporting group values	Placebo	FF 50 µg OD	FP 100 µg BID
Number of subjects	115	117	115
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	37.6	35.4	36.2
standard deviation	± 18.03	± 14.64	± 16.95
Gender categorical Units: Subjects			
Female	81	72	76
Male	34	45	39
Race, Customized Units: Subjects			
White - White/Caucasian/European Heritage	52	55	54
American Indian or Alaska Native	31	30	34
Mixed Race	22	17	18
African American/African Heritage	9	14	9
Asian - East Asian Heritage	1	1	0

Reporting group values	Total		
Number of subjects	347		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical Units: Subjects			
Female	229		
Male	118		
Race, Customized Units: Subjects			
White - White/Caucasian/European Heritage	161		
American Indian or Alaska Native	95		
Mixed Race	57		
African American/African Heritage	32		
Asian - East Asian Heritage	2		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo via a dry powder inhaler (DPI) once daily (OD) in the evening plus placebo via a different DPI twice daily (BID) for 24 weeks. In addition, all participants were provided with albuterol/salbutamol aerosol to be used as rescue medication as needed.	
Reporting group title	FF 50 µg OD
Reporting group description:	
Participants received fluticasone furoate (FF) 50 micrograms (µg) inhalation powder via a DPI OD in the evening plus placebo via a different DPI BID for 24 weeks. In addition, all participants were provided with albuterol/salbutamol aerosol to be used as rescue medication as needed.	
Reporting group title	FP 100 µg BID
Reporting group description:	
Participants received fluticasone propionate (FP) 100 µg BID via a DPI plus placebo via a different DPI OD in the evening for 24 weeks. In addition, all participants were provided with albuterol/salbutamol aerosol to be used as rescue medication as needed.	

Primary: Change from Baseline in clinic visit evening (pre-bronchodilator and pre-dose) forced expiratory volume in one second (FEV1) at the end of the 24-week treatment period

End point title	Change from Baseline in clinic visit evening (pre-bronchodilator and pre-dose) forced expiratory volume in one second (FEV1) at the end of the 24-week treatment period
End point description:	
FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. Evening clinic visit FEV1 is defined as the clinic visit (pre-bronchodilator and pre-dose) FEV1 measurement taken at the Week 24 clinic visit. Pre-dose and pre-rescue albuterol/salbutamol trough FEV1 were measured electronically by spirometry in the evening at the Baseline through Week 24 clinic visits. The highest of 3 technically acceptable measurements was recorded. Baseline was the pre-dose value obtained at Visit 2. Change from Baseline was calculated as the Week 24 value minus the Baseline value. Analysis was performed using analysis of covariance (ANCOVA) with covariates of Baseline, region, sex, age, and treatment. The last observation carried forward (LOCF) method was used to impute missing data, in which the last non-missing, pre-dose, post-Baseline, on-treatment measurement at scheduled clinic visits was used to impute the missing measurements.	
End point type	Primary
End point timeframe:	
Baseline and Week 24	

End point values	Placebo	FF 50 µg OD	FP 100 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111[1]	116[2]	112[3]	
Units: Liters				
least squares mean (standard error)	0.089 (± 0.0331)	0.126 (± 0.0323)	0.191 (± 0.0328)	

Notes:

[1] - Intent-to-Treat (ITT) Population: all par. randomized to treatment who received >=1 dose.

[2] - Intent-to-Treat (ITT) Population: all par. randomized to treatment who received >=1 dose.

[3] - Intent-to-Treat (ITT) Population: all par. randomized to treatment who received >=1 dose.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo v FF 50 µg OD
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.43
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.055
upper limit	0.128

Statistical analysis title	Analysis 2
Comparison groups	Placebo v FP 100 µg BID
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.194

Secondary: Change from Baseline in the percentage of rescue-free 24-hour (hr) periods over the 24-week treatment period

End point title	Change from Baseline in the percentage of rescue-free 24-hour (hr) periods over the 24-week treatment period

End point description:

The number of inhalations of rescue bronchodilator, albuterol/salbutamol inhalation aerosol, used during the day and night was recorded by the participants in a daily electronic diary (eDiary). A 24-hour period in which a participant’s responses to both the morning and evening assessments indicated no use of rescue medication was considered to be rescue free. A 24-hour period was considered as missing if both day time and night time values were missing or if one of the day time or night time values were missing and the other value indicated no use of rescue medication. The Baseline value is the average of the

values over the last 7 days of the daily eDiary prior to the randomization of the participant. Change from Baseline was calculated as the averaged value during the 24-week Treatment Period minus the Baseline value. Analysis was performed using ANCOVA with covariates of Baseline, region, sex, age, and treatment.

End point type	Secondary

End point timeframe:

From Baseline up to Week 24

End point values	Placebo	FF 50 µg OD	FP 100 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	114[4]	116[5]	113[6]	
Units: Percentage of rescue-free 24-hr periods				
least squares mean (standard error)	21.1 (± 3.2)	28.9 (± 3.17)	31.7 (± 3.21)	

Notes:

[4] - ITT Population. Only those participants available at the specified time points were analyzed.

[5] - ITT Population. Only those participants available at the specified time points were analyzed.

[6] - ITT Population. Only those participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in daily evening (PM) peak expiratory flow (PEF) averaged over the 24-week treatment period

End point title	Change from Baseline in daily evening (PM) peak expiratory flow (PEF) averaged over the 24-week treatment period

End point description:

PEF is a measure of lung function and is defined as the maximum airflow during a forced expiration beginning with the lungs fully inflated. PEF was measured by the participants using a hand-held electronic peak flow meter each morning and evening prior to the dose of study medication and any rescue albuterol/salbutamol inhalation aerosol use. Change from Baseline (defined as the average of the values of the last 7 days prior to randomization of the participants) was calculated as the value of the averaged daily trough PM PEF over the 24-week Treatment Period minus the Baseline value. Analysis was performed using ANCOVA with covariates of Baseline, region, sex, age, and treatment.

End point type	Secondary

End point timeframe:

From Baseline up to Week 24

End point values	Placebo	FF 50 µg OD	FP 100 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	114[7]	116[8]	113[9]	
Units: Liters/minute (L/min)				
least squares mean (standard error)	7.6 (± 4.08)	24.9 (± 4.04)	12 (± 4.09)	

Notes:

[7] - ITT Population. Only those participants available at the specified time points were analyzed.

[8] - ITT Population. Only those participants available at the specified time points were analyzed.

[9] - ITT Population. Only those participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in daily morning (AM) PEF averaged over the 24-week treatment period

End point title	Change from Baseline in daily morning (AM) PEF averaged over the 24-week treatment period

End point description:

PEF is a measure of lung function and is defined as the maximum airflow during a forced expiration beginning with the lungs fully inflated. PEF was measured by the participants using a hand-held electronic peak flow meter each morning and evening prior to the dose of study medication and any rescue albuterol/salbutamol inhalation aerosol use. Change from Baseline (defined as the last 7 days prior to randomization of the participants) was calculated as the value of the averaged daily AM PEF over the 24-week Treatment Period minus the Baseline value. Analysis was performed using ANCOVA with covariates of Baseline, region, sex, age, and treatment.

End point type	Secondary

End point timeframe:

From Baseline up to Week 24

End point values	Placebo	FF 50 µg OD	FP 100 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	114[10]	116[11]	113[12]	
Units: L/min				
least squares mean (standard error)	10.8 (± 3.85)	30 (± 3.81)	21.4 (± 3.86)	

Notes:

[10] - ITT Population. Only those participants available at the specified time points were analyzed.

[11] - ITT Population. Only those participants available at the specified time points were analyzed.

[12] - ITT Population. Only those participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the percentage of symptom-free 24-hour (hr) periods during the 24-week treatment period

End point title	Change from Baseline in the percentage of symptom-free 24-hour (hr) periods during the 24-week treatment period

End point description:

Asthma symptoms were recorded in a daily eDiary by the participants every day in the morning and evening before taking any rescue or study medication and before the peak expiratory flow measurement. A 24-hour period in which a participant's responses to both the morning and evening assessments indicated no symptoms was considered to be symptom free. A 24-hour period was considered as missing if both the day time and night time data were missing or if one was symptom-free but the other was missing. The Baseline value was the average of the values of the last 7 days of the daily eDiary prior to the randomization of the participant. Change from Baseline was calculated as the averaged value during the 24-week Treatment Period minus the Baseline value. Analysis was performed using ANCOVA with covariates of Baseline, region, sex, age, and treatment.

End point type	Secondary

End point timeframe:

From Baseline up to Week 24

End point values	Placebo	FF 50 µg OD	FP 100 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	114[13]	116[14]	113[15]	
Units: Percentage of symptom-free 24-hr periods				
least squares mean (standard error)	16.8 (± 2.88)	25.1 (± 2.85)	24.3 (± 2.88)	

Notes:

[13] - ITT Population. Only those participants available at the specified time points were analyzed.

[14] - ITT Population. Only those participants available at the specified time points were analyzed.

[15] - ITT Population. Only those participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who withdrew due to lack of efficacy during the 24-week treatment period

End point title	Number of participants who withdrew due to lack of efficacy during the 24-week treatment period

End point description:

The reason for withdrawal was lack of efficacy if a participant was withdrawn due to: clinic FEV1 falling below the FEV1 stability limit; participant experiencing at least 4 days of AM or PM PEF falling below the PEF stability limit and/or at least 3 days of >=12 inhalations/day of albuterol/salbutamol usage during the 7 days immediately preceding any contact; or the occurrence of an asthma exacerbation, defined as the deterioration of asthma requiring the use of systemic (oral, parenteral, or depot) corticosteroids for at least 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. The FEV1 stability limit was calculated as the best pre-salbutamol/albuterol FEV1 at Visit 2 * 80%. The PEF stability limit was calculated as the mean AM PEF from the available 7 consecutive days preceding Visit 2 * 80%.

End point type	Secondary

End point timeframe:

From the first dose of the study medication until Week 24/Early Withdrawal

End point values	Placebo	FF 50 µg OD	FP 100 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115[16]	117[17]	115[18]	
Units: participants	23	14	9	

Notes:

[16] - ITT Population

[17] - ITT Population

[18] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment adverse events (AEs), defined as those events occurring while participants were on treatment, up to and including the day after the last dose (up to 24 weeks), are reported.

Adverse event reporting additional description:

Serious AEs (SAEs) and non-serious AEs were collected in the ITT, comprised of all participants randomized to treatment who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo via a dry powder inhaler (DPI) once daily (OD) in the evening plus placebo via a different DPI twice daily (BID) for 24 weeks. In addition, all participants were provided with albuterol/salbutamol aerosol to be used as rescue medication as needed.

Reporting group title	FF 50 µg OD

Reporting group description:

Participants received fluticasone furoate (FF) 50 micrograms (µg) inhalation powder via a DPI OD in the evening plus placebo via a different DPI BID for 24 weeks. In addition, all participants were provided with albuterol/salbutamol aerosol to be used as rescue medication as needed.

Reporting group title	FP 100 µg BID

Reporting group description:

Participants received fluticasone propionate (FP) 100 µg BID via a DPI plus placebo via a different DPI OD in the evening for 24 weeks. In addition, all participants were provided with albuterol/salbutamol aerosol to be used as rescue medication as needed.

Serious adverse events	Placebo	FF 50 µg OD	FP 100 µg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 115 (2.61%)	0 / 117 (0.00%)	1 / 115 (0.87%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Reproductive system and breast disorders			
Premenstrual syndrome			
subjects affected / exposed	1 / 115 (0.87%)	0 / 117 (0.00%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	1 / 115 (0.87%)	0 / 117 (0.00%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 117 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 117 (0.00%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Placebo	FF 50 µg OD	FP 100 µg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 115 (31.30%)	38 / 117 (32.48%)	39 / 115 (33.91%)
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 115 (11.30%)	17 / 117 (14.53%)	12 / 115 (10.43%)
occurrences (all)	17	25	19
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	6 / 115 (5.22%)	0 / 117 (0.00%)	2 / 115 (1.74%)
occurrences (all)	6	0	2
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	4 / 115 (3.48%)	2 / 117 (1.71%)	1 / 115 (0.87%)
occurrences (all)	4	2	1
Infections and infestations			
Influenza			
subjects affected / exposed	4 / 115 (3.48%)	4 / 117 (3.42%)	6 / 115 (5.22%)
occurrences (all)	4	4	7
Upper respiratory tract infection			

subjects affected / exposed	3 / 115 (2.61%)	6 / 117 (5.13%)	6 / 115 (5.22%)
occurrences (all)	3	7	6
Pharyngitis			
subjects affected / exposed	10 / 115 (8.70%)	7 / 117 (5.98%)	5 / 115 (4.35%)
occurrences (all)	12	8	6
Nasopharyngitis			
subjects affected / exposed	6 / 115 (5.22%)	8 / 117 (6.84%)	12 / 115 (10.43%)
occurrences (all)	6	10	13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2011	The number of withdrawals due to lack of efficacy was changed from an 'other' endpoint to a secondary endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported