Clinical trial results:
A randomised, double-blind, parallel group, multicentre study of Fluticasone Furoate/GW642444 Inhalation Powder, Fluticasone Furoate Inhalation Powder alone, and Fluticasone Propionate alone in the treatment of persistent asthma in adults and adolescents

Summary

EudraCT number	2010-019594-14
Trial protocol	DE PL Outside EU/EEA
Global end of trial date	18 October 2011

Results information

Result version number	v1
This version publication date	26 February 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	0HZA106829

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01134042
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	02 December 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 October 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the efficacy and safety of Fluticasone Furoate (FF)/GW642444 Inhalation Powder 200 microgram (mcg)/25 mcg administered once daily each evening to FF Inhalation Powder 200 mcg administered alone once daily each evening in adolescent and adult subjects 12 years of age and older with persistent bronchial asthma over a 24 week treatment period.

Protection of trial subjects:

The following steps were taken to protect trial participants:
1). Only participants meeting all of the inclusion criteria and none of the exclusion criteria were randomized to investigational medication.
2). All participants enrolled into the study were provided rescue medication for use as necessary.
3). The investigator or treating physician could have unblinded a participant's treatment assignment in the case of an emergency, when knowledge of the study treatment was essential for the appropriate clinical management or welfare of the participant.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 June 2010
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	Romania: 241
Country: Number of subjects enrolled	Japan: 106
Country: Number of subjects enrolled	Poland: 163
Country: Number of subjects enrolled	Germany: 122
Country: Number of subjects enrolled	Russian Federation: 246
Country: Number of subjects enrolled	United States: 328
Worldwide total number of subjects	1206
EEA total number of subjects	526

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)	65
Adults (18-64 years)	991
From 65 to 84 years	150
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 4-week Run-in Period for completion of Baseline (BL) safety evaluations and to obtain BL measures of asthma status. Par. were then randomized to a 24-week Treatment Period. 1206 par. were screened, 587 were randomized, and 586 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	FF 200 µg OD

Arm description:

Participants received FF 200 microgram (µg) inhalation powder via a Dry Powder Inhaler (DPI) once daily (OD) in the evening plus placebo via the DISKUS/ACCUHALER twice daily (BID), for 24 weeks. Additionally participants were provided with albuterol/salbutamol inhalation aerosol to be used as rescue medication as needed.

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

Dosage and administration details:

200 µg once daily

Arm title	FF/VI 200/25 µg OD

Arm description:

Participants received Fluticasone Furoate/Vilanterol (FF/VI) 200/25 µg inhalation powder via a DPI OD in the evening plus placebo via the DISKUS/ACCUHALER BID, for 24 weeks. Additionally participants were provided with albuterol/salbutamol inhalation aerosol to be used as rescue medication as needed.

Arm type	Experimental
Investigational medicinal product name	fluticasone furoate/vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

200 µg/25 µg once daily

Arm title	FP 500 µg BID

Arm description:

Participants received Fluticasone Propionate (FP) 500 µg inhalation powder via the DISKUS/ACCUHALER BID plus placebo via a DPI OD in the evening, for 24 weeks. Additionally participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication as needed.

Arm type	Active comparator
Investigational medicinal product name	fluticasone propionate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

500 µg twice daily

Number of subjects in period 1[1]	FF 200 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID
Started	194	197	195
Completed	146	169	161
Not completed	48	28	34
Physician decision	4	8	1
Consent withdrawn by subject	13	4	7
Adverse event, non-fatal	3	7	2
Lost to follow-up	2	-	1
Lack of efficacy	21	6	18
Protocol deviation	5	3	5

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: Baseline data were collected in members of the Intent-to-Treat (ITT) Population, comprised of all participants who were randomized to treatment who received at least one dose of study medication. Randomized participants were assumed to have received study medication unless definitive evidence to the contrary existed. A total of 1206 participants were screened (enrolled), 587 were randomized, and 586 received at least one dose of study medication.

Baseline characteristics

Reporting groups	
Reporting group title	FF 200 µg OD
Reporting group description:	
Participants received FF 200 microgram (µg) inhalation powder via a Dry Powder Inhaler (DPI) once daily (OD) in the evening plus placebo via the DISKUS/ACCUHALER twice daily (BID), for 24 weeks. Additionally participants were provided with albuterol/salbutamol inhalation aerosol to be used as rescue medication as needed.	
Reporting group title	FF/VI 200/25 µg OD
Reporting group description:	
Participants received Fluticasone Furoate/Vilanterol (FF/VI) 200/25 µg inhalation powder via a DPI OD in the evening plus placebo via the DISKUS/ACCUHALER BID, for 24 weeks. Additionally participants were provided with albuterol/salbutamol inhalation aerosol to be used as rescue medication as needed.	
Reporting group title	FP 500 µg BID
Reporting group description:	
Participants received Fluticasone Propionate (FP) 500 µg inhalation powder via the DISKUS/ACCUHALER BID plus placebo via a DPI OD in the evening, for 24 weeks. Additionally participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication as needed.	

Reporting group values	FF 200 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID
Number of subjects	194	197	195
Age categorical			
Units: Subjects			
Age continuous			
Baseline data were collected in members of the Intent-to-Treat (ITT) Population, comprised of all participants who were randomized to treatment who received at least one dose of study medication. Randomized participants were assumed to have received study medication unless definitive evidence to the contrary existed.			
Units: years			
arithmetic mean	44.6	46.6	47.3
standard deviation	± 14.33	± 15.05	± 14.06
Gender categorical			
Baseline data were collected in members of the Intent-to-Treat (ITT) Population, comprised of all participants who were randomized to treatment who received at least one dose of study medication. Randomized participants were assumed to have received study medication unless definitive evidence to the contrary existed.			
Units: Subjects			
Female	113	116	116
Male	81	81	79
Race, Customized			
Baseline data were collected in members of the Intent-to-Treat (ITT) Population, comprised of all participants who were randomized to treatment who received at least one dose of study medication. Randomized participants were assumed to have received study medication unless definitive evidence to the contrary existed.			
Units: Subjects			
African American/African Heritage (HER)	16	16	19
American Indian or Alaska Native	0	0	1
Japanese/East Asian HER/South East Asian HER	12	15	13
White	165	165	162

African American/African Heritage and White	1	1	0

Reporting group values	Total		
Number of subjects	586		
Age categorical Units: Subjects			

Age continuous			
Baseline data were collected in members of the Intent-to-Treat (ITT) Population, comprised of all participants who were randomized to treatment who received at least one dose of study medication. Randomized participants were assumed to have received study medication unless definitive evidence to the contrary existed.			
Units: years arithmetic mean standard deviation	 -		
Gender categorical			
Baseline data were collected in members of the Intent-to-Treat (ITT) Population, comprised of all participants who were randomized to treatment who received at least one dose of study medication. Randomized participants were assumed to have received study medication unless definitive evidence to the contrary existed.			
Units: Subjects			
Female Male	345 241		
Race, Customized			
Baseline data were collected in members of the Intent-to-Treat (ITT) Population, comprised of all participants who were randomized to treatment who received at least one dose of study medication. Randomized participants were assumed to have received study medication unless definitive evidence to the contrary existed.			
Units: Subjects			
African American/African Heritage (HER) American Indian or Alaska Native Japanese/East Asian HER/South East Asian HER White African American/African Heritage and White	51 1 40 492 2		

End points

End points reporting groups

Reporting group title	FF 200 µg OD

Reporting group description:

Participants received FF 200 microgram (µg) inhalation powder via a Dry Powder Inhaler (DPI) once daily (OD) in the evening plus placebo via the DISKUS/ACCUHALER twice daily (BID), for 24 weeks. Additionally participants were provided with albuterol/salbutamol inhalation aerosol to be used as rescue medication as needed.

Reporting group title	FF/VI 200/25 µg OD

Reporting group description:

Participants received Fluticasone Furoate/Vilanterol (FF/VI) 200/25 µg inhalation powder via a DPI OD in the evening plus placebo via the DISKUS/ACCUHALER BID, for 24 weeks. Additionally participants were provided with albuterol/salbutamol inhalation aerosol to be used as rescue medication as needed.

Reporting group title	FP 500 µg BID

Reporting group description:

Participants received Fluticasone Propionate (FP) 500 µg inhalation powder via the DISKUS/ACCUHALER BID plus placebo via a DPI OD in the evening, for 24 weeks. Additionally participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication as needed.

Primary: Change from Baseline in clinic visit trough (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 trough (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. Trough FEV1 is defined as the clinic visit (pre-bronchodilator and pre-dose) FEV1 measurement taken at the clinic visit while still on treatment. Pre-dose and pre-rescue albuterol/salbutamol trough FEV1 was measured electronically by spirometry in the evening at the Baseline (BL) through Week 24 clinic visits. The highest of 3 technically acceptable measurements was recorded. BL was the pre-dose value obtained at Visit 3. Change from BL was calculated as the Week 24 value minus the Baseline value. The analysis was performed using an Analysis of Covariance (ANCOVA) model with covariates of BL trough FEV1, country, sex, age, and treatment group.The last observation carried forward (LOCF) method was used to impute missing data, in which the last non-missing post-BL 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	FF 200 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	186[1]	187[2]	190[3]	
Units: Liters				
least squares mean (standard error)	0.201 (± 0.0303)	0.394 (± 0.0302)	0.183 (± 0.03)	

Notes:

[1] - Intent-to-Treat (ITT) Population: randomized participants who received >=1 dose of study medication

[2] - Intent-to-Treat (ITT) Population: randomized participants who received >=1 dose of study medication

[3] - Intent-to-Treat (ITT) Population: randomized participants who received >=1 dose of study medication

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
This is a comparison of FF/VI 200/25 µg OD v FF 200 µg OD	
Comparison groups	FF 200 µg OD v FF/VI 200/25 µg OD
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.193
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.108
upper limit	0.277

Statistical analysis title	Statistical Analysis 2
Comparison groups	FF/VI 200/25 µg OD v FP 500 µg BID
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.127
upper limit	0.294

Statistical analysis title	Statistical Analysis 3
Comparison groups	FF 200 µg OD v FP 500 µg BID

Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Mean difference (final values)
Point estimate	0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.066
upper limit	0.102

Notes:

[4] - Non-inferiority is demonstrated if the lower limit of the confidence interval (CI: 0.025, 1-sided significance level) for the mean difference in change from Baseline in clinic visit trough FEV1 of FF 200 µg OD versus FP 500 µg BID was greater than -125 milliliters.

Primary: Change from Baseline in weighted mean serial FEV1 over 0-24 hours post-dose at Week 24

End point title	Change from Baseline in weighted mean serial FEV1 over 0-24 hours post-dose at Week 24

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. Serial FEV1 measurements were taken electronically by spirometry at the Baseline and Week 24 clinic visits. Weighted mean was calculated using the 24-hour serial FEV1 measurements that included the pre-dose assessment (within 5 minutes prior to dosing) and the post-dose assessments after 5, 15, and 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23, and 24 hours. At each time point, the highest of 3 technically acceptable measurements was recorded. Baseline was the value obtained at Visit 3. Change from Baseline was calculated as the average Week 24 FEV1 value minus the Baseline value.

End point type	Primary

End point timeframe:

Baseline and Week 24

End point values	FF 200 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83[5]	89[6]	86[7]	
Units: Liters				
least squares mean (standard error)	0.328 (± 0.0493)	0.464 (± 0.047)	0.258 (± 0.0483)	

Notes:

[5] - ITT Population. Data were calculated in participants for whom serial FEV1 at Week 24 was performed.

[6] - ITT Population. Data were calculated in participants for whom serial FEV1 at Week 24 was performed.

[7] - ITT Population. Data were calculated in participants for whom serial FEV1 at Week 24 was performed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	FF 200 µg OD v FF/VI 200/25 µg OD

Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.048
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.136
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.27

Statistical analysis title	Statistical Analysis 2
Comparison groups	FP 500 µg BID v FF/VI 200/25 µg OD
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.206
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.073
upper limit	0.339

Secondary: Change from Baseline in the percentage of rescue-free and symptom-free 24-hour periods during the 24-week Treatment Period

End point title	Change from Baseline in the percentage of rescue-free and symptom-free 24-hour periods during 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). Similarly, asthma symptoms were recorded in a daily eDairy 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 use of rescue medication/symptoms was considered to be rescue free/symptom free. The Baseline value was derived from 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.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1-24

End point values	FF 200 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	193[8]	197[9]	194[10]	
Units: Percentage of periods				
least squares mean (standard error)				
Rescue-free 24-hour periods	26.6 (± 2.45)	38.2 (± 2.42)	31.9 (± 2.45)	
Symptom-free 24-hour periods	21 (± 2.32)	29.3 (± 2.29)	24.5 (± 2.31)	

Notes:

[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.

[10] - 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 total Asthma Quality of Life Questionnaire (AQLQ) (+12) score at Week 12 and Week 24

End point title	Change from Baseline in the total Asthma Quality of Life Questionnaire (AQLQ) (+12) score at Week 12 and Week 24

End point description:

The AQLQ is a disease-specific, self-administered quality of life questionnaire used to evaluate the impact of asthma treatments on the quality of life of asthma sufferers. The AQLQ for 12 years and older (AQLQ [+12]) is a modified version of the AQLQ for use in asthma patients between the age of 12 and 70. The AQLQ contains 32 items in 4 domains: activity limitation (11 items), symptoms (12 items), emotional function (5 items), and environmental stimuli (4 items). For the 32 items on the questionnaire, the response format consists of a seven-point scale, where a value of 1 indicates “total impairment” and a value of 7 indicates “no impairment.” The AQLQ total score is defined as the average of the scores from all 32 questions; thus, the total score ranges from 1 (indicates "total impairment") to 7 (indicates "no impairment"). Baseline was the total score obtained at Visit 3. Change from Baseline was calculated as the total score at Weeks 12 and 24 minus the total score at Baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 12, and Week 24

End point values	FF 200 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	194[11]	197[12]	195[13]	
Units: Scores on a scale				
least squares mean (standard error)				
Week 12, n=154, 180, 163	0.66 (± 0.061)	0.74 (± 0.056)	0.74 (± 0.059)	
Week 24, n=140, 167, 156	0.88 (± 0.071)	0.93 (± 0.065)	0.9 (± 0.068)	

Notes:

[11] - ITT Population. Available participants were analyzed (represented by n=X, X, X in category titles).

[12] - ITT Population. Available participants were analyzed (represented by n=X, X, X in category titles).

[13] - ITT Population. Available participants were analyzed (represented by n=X, X, X in category titles).

Statistical analyses

No statistical analyses for this end point

Secondary: Clinic visit 12-hour post-dose FEV1at Week 24

End point title	Clinic visit 12-hour post-dose FEV1at Week 24

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. 12-hour post-dose FEV1 measurements were taken electronically by spirometry at the Week 24 clinic visit. The highest of 3 technically acceptable measurements was recorded.

End point type	Secondary

End point timeframe:

Week 24

End point values	FF 200 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82[14]	93[15]	87[16]	
Units: Liters				
arithmetic mean (standard deviation)	2.611 (± 0.8437)	2.683 (± 0.9758)	2.262 (± 0.7786)	

Notes:

[14] - ITT Population. Data were analyzed in participants for whom serial FEV1 at Week 24 was performed.
[15] - ITT Population. Data were analyzed in participants for whom serial FEV1 at Week 24 was performed.
[16] - ITT Population. Data were analyzed in participants for whom serial FEV1 at Week 24 was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in weighted mean serial FEV1 over 0 to 4 hours post-dose at Week 24

End point title	Change from Baseline in weighted mean serial FEV1 over 0 to 4 hours post-dose at Week 24

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. Serial FEV1 measurements were taken electronically by spirometry at Baseline. Weighted mean was calculated using the 4-hour serial FEV1 measurements that included the pre-dose assessment (within 5 minutes prior to dosing) and post-dose assessments after 5, 15, and 30 minutes and 1, 2, 3, and 4 hours. At each time point, the highest of 3 technically acceptable measurements was recorded. Baseline was the value obtained at Visit 3. Change from Baseline was calculated as the average Week 24 FEV1 value minus the Baseline value.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	FF 200 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83[17]	89[18]	86[19]	
Units: Liters				
arithmetic mean (standard deviation)	0.363 (± 0.469)	0.492 (± 0.5671)	0.256 (± 0.4679)	

Notes:

[17] - ITT Population. Data were calculated in participants for whom serial FEV1 at Week 24 was performed.
[18] - ITT Population. Data were calculated in participants for whom serial FEV1 at Week 24 was performed.
[19] - ITT Population. Data were calculated in participants for whom serial FEV1 at Week 24 was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in daily morning trough (AM) and evening (PM) Peak Expiratory Flow (PEF) averaged over the first 12 weeks and 24 weeks of the 24-week Treatment Period

End point title	Mean change from Baseline in daily morning trough (AM) and evening (PM) Peak Expiratory Flow (PEF) averaged over the first 12 weeks and 24 weeks of 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. Trough PEF is the PEF measured approximately 24 hours after the last administration of study drug. Change from Baseline (defined as the last 7 days prior to randomization of the participants) was calculated as the value of the averaged daily trough AM/PM PEF over 12 weeks and 24 weeks of the 24-week Treatment Period (at Weeks 12 and 24) minus the Baseline value. ITT Population. Different participants may have been analyzed at different time points, wo the overall number of participants analyzed reflects everyone in the ITT Population.

End point type	Secondary

End point timeframe:

From Baseline up to Week 12 and Week 24

End point values	FF 200 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	194[20]	197[21]	195[22]	
Units: Liters/minute (L/min)				
least squares mean (standard error)				
AM PEF, Week 1 to 12, n=193, 197, 195	15.1 (± 2.82)	48.1 (± 2.78)	17.1 (± 2.8)	
AM PEF, Week 1 to 24, n=193, 197, 195	18.2 (± 2.97)	51.8 (± 2.94)	18.8 (± 2.95)	
PM PEF, Week 1 to 12, 192, 197, 194	7.5 (± 2.8)	36.6 (± 2.75)	12.6 (± 2.78)	
PM PEF, Week 1 to 24, 192, 197, 194	9.1 (± 2.98)	39.8 (± 2.93)	13.6 (± 2.96)	

Notes:

[20] - ITT Population. Available participants were analyzed (represented by n=X, X, X in category titles).
[21] - ITT Population. Available participants were analyzed (represented by n=X, X, X in category titles).
[22] - ITT Population. Available participants were analyzed (represented by n=X, X, X in category titles).

Statistical analyses

No statistical analyses for this end point

Secondary: The number of participants who withdrew due to lack of efficacy during the 24-week Treatment Period

End point title	The number of participants who withdrew due to lack of efficacy during the 24-week Treatment Period

End point description:

The number of participants whose primary reason for withdrawal was lack of efficacy was analyzed.

End point type	Secondary

End point timeframe:

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

End point values	FF 200 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	194[23]	197[24]	195[25]	
Units: Participants	21	6	18	

Notes:

[23] - ITT Population

[24] - ITT Population

[25] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Asthma Control Test (ACT) scores at Week 12 and Week 24

End point title	Change from Baseline in the Asthma Control Test (ACT) scores at Week 12 and Week 24

End point description:

The ACT is a 5-item questionnaire developed as a measure of the participant's asthma control. Questions are designed to be self-completed by the participant and include the following: In the past 4 weeks, "How much of the time did your asthma keep you from getting as much done at work, school or at home?", "How often have you had shortness of breath?", "How often did your asthma symptoms wake you up at night or earlier than usual in the morning?", "How often have you used your rescue inhaler or nebulizer medication (such as albuterol)?" and "How would you rate your asthma control"? The ACT total score is defined as the sum of the scores from all 5 questions, provided all questions have been answered; thus, the total score ranges from 5 (poor control of asthma) to 25 (complete control of asthma). A score of 20 or higher indicates well-controlled asthma. Change from Baseline was calculated as the total score at Week 12 and Week 24 minus the total score at Baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 12, and Week 24

End point values	FF 200 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	194[26]	197[27]	195[28]	
Units: Scores on a scale				
least squares mean (standard error)				
Week 12, n=164, 183, 169	3.9 (± 0.29)	4.8 (± 0.27)	3.9 (± 0.28)	
Week 24, n=147, 170, 162	5.2 (± 0.3)	5.5 (± 0.28)	4.7 (± 0.29)	

Notes:

[26] - ITT Population. Available participants were analyzed (represented by n=X, X, X in category titles).

[27] - ITT Population. Available participants were analyzed (represented by n=X, X, X in category titles).

[28] - ITT Population. Available participants were analyzed (represented by n=X, X, X in category titles).

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated Global Assessment of Change Questionnaire responses at Weeks 4, 12, and 24

End point title	Number of participants with the indicated Global Assessment of Change Questionnaire responses at Weeks 4, 12, and 24

End point description:

At the end of Week 4, Week 8, and Week 24/Early Withdrawal, the Global Assessment of Change Questionnaire that assesses changes in asthma symptoms (AS) and rescue medication use (RMU) was completed by the participants. The number of participants who chose the following answers to the questionnaire were determined: much better, somewhat better, a little better, the same, a little worse, somewhat worse, much worse (to assess the changes in asthma symptoms); much less often, somewhat less often, a little less often, the same, a little more often, somewhat more often, much more often (to assess the changes in the frequency of rescue medication use). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the ITT Population.

End point type	Secondary

End point timeframe:

Week 4, Week 12, and Week 24

End point values	FF 200 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	194[29]	197[30]	195[31]	
Units: Participants				
Week 4, AS: Much better, n=174, 191, 180	37	58	35	
Week 4, AS: Somewhat better, n=174, 191, 180	47	65	49	
Week 4, AS: A little better, n=174, 191, 180	43	34	40	
Week 4, AS: The same, n=174, 191, 180	35	25	44	
Week 4, AS: A little worse, n=174, 191, 180	8	7	6	
Week 4, AS: Somewhat worse, n=174, 191, 180	2	2	3	
Week 4, AS: Much worse, n=174, 191, 180	2	0	3	

Week 4, RMU: Much less often, n=174, 191, 180	49	71	42	
Week 4, RMU: Somewhat less often, n=174, 191, 180	29	48	41	
Week 4, RMU: A little less often, n=174, 191, 180	42	38	45	
Week 4, RMU: The same, n=174, 191, 180	34	27	37	
Week 4, RMU: A little more often, n=174, 191, 180	14	4	9	
Week 4, RMU: Somewhat more often, n=174, 191, 180	5	2	3	
Week 4, RMU: Much more often, n=174, 191, 180	1	1	3	
Week 12, AS: Much better, n=162, 183, 165	60	78	54	
Week 12, AS: Somewhat better, n=162, 183, 165	43	51	52	
Week 12, AS: A little better, n=162, 183, 165	27	33	34	
Week 12, AS: The same, n=162, 183, 165	23	15	16	
Week 12, AS: A little worse, n=162, 183, 165	8	5	6	
Week 12, AS: Somewhat worse, n=162, 183, 165	0	1	3	
Week 12, AS: Much worse, n=162, 183, 165	1	0	0	
Week 12, RMU: Much less often, n=162, 183, 164	66	93	59	
Week12, RMU: Somewhat less often, n=162, 183, 164	31	36	37	
Week12, RMU: A little less often, n=162, 183, 164	28	24	40	
Week12, RMU: The same, n=162, 183, 164	26	24	20	
Week12, RMU: A little more often, n=162, 183, 164	7	8	6	
Week12, RMU: Somewhat more often, n=162, 183, 164	2	0	1	
Week12, RMU: Much more often, n=162, 183, 164	2	1	1	
Week 24, AS: Much better, n=146, 168, 162	64	89	62	
Week 24, AS: Somewhat better, n=146, 168, 162	43	37	52	
Week 24, AS: A little better, n=146, 168, 162	22	23	17	
Week 24, AS: The same, n=146, 168, 162	11	14	23	
Week 24, AS: A little worse, n=146, 168, 162	3	4	4	
Week 24, AS: Somewhat worse, n=146, 168, 162	2	1	2	
Week 24, AS: Much worse, n=146, 168, 162	1	0	2	
Week 24, RMU: Much less often, n=146, 168, 162	68	87	69	
Week 24, RMU: Somewhat less often, n=146, 168, 162	33	38	37	
Week 24, RMU: A little less often, n=146, 168, 162	29	22	26	

Week 24, RMU: The same, n=146, 168, 162	12	16	19	
Week 24, RMU: A little more often, n=146, 168, 162	1	3	8	
Week 24, RMU: Somewhat more often, n=146, 168, 162	3	1	1	
Week 24, RMU: Much more often, n=146, 168, 162	0	1	2	

Notes:

[29] - ITT Population. Available participants were analyzed (represented by n=X, X, X in category titles).

[30] - ITT Population. Available participants were analyzed (represented by n=X, X, X in category titles).

[31] - ITT Population. Available participants were analyzed (represented by n=X, X, X in category titles).

Statistical analyses

No statistical analyses for this end point

Secondary: Number of the indicated unscheduled asthma-related healthcare visits during the Treatment Period

End point title	Number of the indicated unscheduled asthma-related healthcare visits during the Treatment Period

End point description:

All unscheduled asthma-related visits to a physician's office, visits to urgent care, visits to the emergency department, and hospitalizations (ICU=intensive care unit; GW=general ward) associated with severe asthma exacerbations or other asthma-related healthcare issues were recorded.

End point type	Secondary

End point timeframe:

From Baseline up to Week 24/Withdrawal Visit

End point values	FF 200 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	194[32]	197[33]	195[34]	
Units: Number of visits				
arithmetic mean (standard deviation)				
Number of Home Visits (Day)	0 (± 0.07)	0 (± 0)	0 (± 0)	
Number of Home Visits (Night)	0 (± 0)	0 (± 0)	0 (± 0)	
Number of Physician Office/Practice Visits	0 (± 0.1)	0 (± 0)	0.1 (± 0.45)	
Number of Urgent Care/Outpatient Clinic Visits	0 (± 0)	0 (± 0)	0 (± 0)	
Number of Emergency Room Visits	0 (± 0.07)	0 (± 0)	0 (± 0)	
Number of Inpatient Hospitalization Days (ICU)	0 (± 0)	0 (± 0)	0 (± 0)	
Number of Inpatient Hospitalization (GW) Days	0 (± 0.29)	0 (± 0)	0 (± 0)	

Notes:

[32] - ITT Population

[33] - ITT Population

[34] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected from the start of study medication to the end of the the treatment period (up to Week 24).

Adverse event reporting additional description:

An on-therapy AE or SAE is defined as an AE with an onset on or after the start date of study medication, but not later than one day after the last date of study medication. SAEs and AEs were collected in members of the ITT Population, comprised of all participants randomized to treatment, who received at least one dose of the study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	FF 200 µg OD

Reporting group description:

Participants received FF 200 microgram (µg) inhalation powder via a Dry Powder Inhaler (DPI) once daily (OD) in the evening plus placebo via the DISKUS/ACCUHALER twice daily (BID), for 24 weeks. Additionally participants were provided with albuterol/salbutamol inhalation aerosol to be used as rescue medication as needed.

Reporting group title	FF/VI 200/25 µg OD

Reporting group description:

Participants received Fluticasone Furoate/Vilanterol (FF/VI) 200/25 µg inhalation powder via a DPI OD in the evening plus placebo via the DISKUS/ACCUHALER BID, for 24 weeks. Additionally participants were provided with albuterol/salbutamol inhalation aerosol to be used as rescue medication as needed.

Reporting group title	FP 500 µg BID

Reporting group description:

Participants received Fluticasone Propionate (FP) 500 µg inhalation powder via the DISKUS/ACCUHALER BID plus placebo
via a DPI OD in the evening, for 24 weeks. Additionally participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication as needed.

Serious adverse events	FF 200 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 194 (0.52%)	6 / 197 (3.05%)	2 / 195 (1.03%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid cancer			
subjects affected / exposed	0 / 194 (0.00%)	1 / 197 (0.51%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Limb traumatic amputation			
subjects affected / exposed	0 / 194 (0.00%)	1 / 197 (0.51%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 194 (0.00%)	0 / 197 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 194 (0.00%)	1 / 197 (0.51%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 194 (0.00%)	1 / 197 (0.51%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 194 (0.52%)	0 / 197 (0.00%)	0 / 195 (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
Haemoptysis			
subjects affected / exposed	0 / 194 (0.00%)	0 / 197 (0.00%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 194 (0.00%)	1 / 197 (0.51%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 194 (0.00%)	1 / 197 (0.51%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	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	FF 200 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 194 (34.02%)	62 / 197 (31.47%)	73 / 195 (37.44%)
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 194 (6.70%)	11 / 197 (5.58%)	15 / 195 (7.69%)
occurrences (all)	21	12	25
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	2 / 194 (1.03%)	6 / 197 (3.05%)	4 / 195 (2.05%)
occurrences (all)	2	6	5
Oropharyngeal pain			
subjects affected / exposed	8 / 194 (4.12%)	4 / 197 (2.03%)	7 / 195 (3.59%)
occurrences (all)	10	5	7
Cough			
subjects affected / exposed	6 / 194 (3.09%)	3 / 197 (1.52%)	13 / 195 (6.67%)
occurrences (all)	6	3	14
Infections and infestations			
Rhinitis			
subjects affected / exposed	2 / 194 (1.03%)	1 / 197 (0.51%)	7 / 195 (3.59%)
occurrences (all)	2	1	7
Pharyngitis			
subjects affected / exposed	2 / 194 (1.03%)	4 / 197 (2.03%)	6 / 195 (3.08%)
occurrences (all)	2	4	7
Sinusitis			
subjects affected / exposed	7 / 194 (3.61%)	3 / 197 (1.52%)	4 / 195 (2.05%)
occurrences (all)	7	3	5
Bronchitis			
subjects affected / exposed	6 / 194 (3.09%)	7 / 197 (3.55%)	6 / 195 (3.08%)
occurrences (all)	6	7	6

Influenza			
subjects affected / exposed	8 / 194 (4.12%)	5 / 197 (2.54%)	7 / 195 (3.59%)
occurrences (all)	9	5	8
Respiratory tract infection viral			
subjects affected / exposed	7 / 194 (3.61%)	7 / 197 (3.55%)	7 / 195 (3.59%)
occurrences (all)	9	8	8
Nasopharyngitis			
subjects affected / exposed	27 / 194 (13.92%)	25 / 197 (12.69%)	39 / 195 (20.00%)
occurrences (all)	34	33	60

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported