Clinical trial results:
HZA106827: A randomised, double-blind, placebo-controlled (with rescue medication), parallel group multicentre study of Fluticasone Furoate/GW642444 Inhalation Powder and Fluticasone Furoate Inhalation Powder alone in the treatment of persistent asthma in adults and adolescents.

Summary

EudraCT number	2010-019590-15
Trial protocol	DE RO Outside EU/EEA
Global end of trial date	19 October 2011

Results information

Result version number	v1 (current)
This version publication date	22 February 2016
First version publication date	04 June 2015

Trial information

Trial identification

Sponsor protocol code	HZA106827

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01165138
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000431-PIP01-08
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	15 December 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 October 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to compare the efficacy and safety of FF/GW642444 Inhalation Powder 100mcg/25mcg and FF 100mcg both administered once daily in the evening in adolescent and adult subjects 12 years of age and older with persistent bronchial asthma over a 12 week treatment period.

Protection of trial subjects:

The following steps were taken to protect trial subjects:
1). Only subjects meeting all of the inclusion criteria and none of the exclusion criteria were randomized to investigational medication.
2). All subjects enrolled into the study were provided rescue medication for use as necessary.
3). Subject lung function, as measured by AM and PM PEF was monitored for stability through the use of a daily electronic diary.
4) Both safety and efficacy parameters were also assessed by the investigator regularly in the clinic to minimise any potential risks to the patients.
5). The investigator or treating physician may unblind a subject's treatment assignment in the case of an emergency, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 August 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	Poland: 167
Country: Number of subjects enrolled	Romania: 157
Country: Number of subjects enrolled	Germany: 126
Country: Number of subjects enrolled	United States: 363
Country: Number of subjects enrolled	Ukraine: 146
Country: Number of subjects enrolled	Japan: 151
Worldwide total number of subjects	1110
EEA total number of subjects	450

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)	149
Adults (18-64 years)	865
From 65 to 84 years	96
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants meeting eligibility criteria at the Screening visit completed a 4-week Run-in Period for Baseline safety evaluations and measures of asthma status. Participants were then randomized to a 12-week Treatment Period. 1110 participants were screened, 610 were randomized, and 609 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 (par.) received placebo once daily (OD) in the evening from the dry powder inhaler (DPI) for 12 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

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:

Once daily via Ellipta Device

Arm title	FF 100 µg OD

Arm description:

Participants received Fluticasone Furoate (FF) 100 microgram (µg) inhalation powder OD in the evening from the DPI for 12 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

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

Dosage and administration details:

100 µg once daily via Ellipta Device

Arm title	FF/VI 100/25 µg OD

Arm description:

Participants received FF/Vilanterol (VI) 100/25 µg inhalation powder OD in the evening from the DPI for 12 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

Arm type	Experimental

Investigational medicinal product name	FF/VI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

100/25 µg once daily via Ellipta Device

Number of subjects in period 1[1]	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD
Started	203	205	201
Completed	151	185	179
Not completed	52	20	22
Physician decision	6	7	6
Consent withdrawn by subject	6	6	3
Adverse event, non-fatal	1	-	2
Lost to follow-up	-	1	2
Lack of efficacy	32	6	7
Protocol deviation	7	-	2

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: Only those enrolled participants who received >=1 dose of study treatment are reported to be in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants (par.) received placebo once daily (OD) in the evening from the dry powder inhaler (DPI) for 12 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.	
Reporting group title	FF 100 µg OD
Reporting group description:	
Participants received Fluticasone Furoate (FF) 100 microgram (µg) inhalation powder OD in the evening from the DPI for 12 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.	
Reporting group title	FF/VI 100/25 µg OD
Reporting group description:	
Participants received FF/Vilanterol (VI) 100/25 µg inhalation powder OD in the evening from the DPI for 12 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.	

Reporting group values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD
Number of subjects	203	205	201
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	38.1	40.4	40.7
standard deviation	± 16.49	± 16.78	± 16.38
Gender categorical Units: Subjects			
Female	111	126	116
Male	92	79	85
Race, Customized Units: Subjects			
African American/African Heritage	14	16	13
American Indian or Alaska Native	0	1	0
Asian - Japanese Heritage	19	16	15
Asian - South East Asian Heritage	0	0	1
White - Arabic/North African Heritage	0	1	0
White - White/Caucasian/European Heritage	169	170	172
Mixed Race	1	1	0

Reporting group values	Total		
Number of subjects	609		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	353		
Male	256		
Race, Customized Units: Subjects			
African American/African Heritage	43		
American Indian or Alaska Native	1		
Asian - Japanese Heritage	50		
Asian - South East Asian Heritage	1		
White - Arabic/North African Heritage	1		
White - White/Caucasian/European Heritage	511		
Mixed Race	2		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants (par.) received placebo once daily (OD) in the evening from the dry powder inhaler (DPI) for 12 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.	
Reporting group title	FF 100 µg OD
Reporting group description:	
Participants received Fluticasone Furoate (FF) 100 microgram (µg) inhalation powder OD in the evening from the DPI for 12 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.	
Reporting group title	FF/VI 100/25 µg OD
Reporting group description:	
Participants received FF/Vilanterol (VI) 100/25 µg inhalation powder OD in the evening from the DPI for 12 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.	

Primary: Mean change from Baseline (BL) in clinic visit trough (pre-bronchodilator and pre-dose) forced expiratory volume in one second (FEV1) at Week 12

End point title	Mean change from Baseline (BL) in clinic visit trough (pre-bronchodilator and pre-dose) forced expiratory volume in one second (FEV1) at Week 12
End point description:	
Pulmonary function was measured by FEV1, 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 BL through Week 12 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 12 value minus the BL value. The analysis was performed using an Analysis of Covariance (ANCOVA) model with covariates of BL trough FEV1, region, 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. ITT, Intent-to-Treat.	
End point type	Primary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	193[1]	203[2]	200[3]	
Units: Liters				
least squares mean (standard error)	0.196 (± 0.031)	0.332 (± 0.0302)	0.368 (± 0.0304)	

Notes:

[1] - ITT Population. Only those participants with non-missing covariates and post-BL data were analyzed.

[2] - ITT Population. Only those participants with non-missing covariates and post-BL data were

analyzed.

[3] - ITT Population. Only those participants with non-missing covariates and post-BL data were analyzed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v FF 100 µg OD
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.136
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.051
upper limit	0.222

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v FF/VI 100/25 µg OD
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.172
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.087
upper limit	0.258

Statistical analysis title	Statistical Analysis 3
Comparison groups	FF 100 µg OD v FF/VI 100/25 µg OD

Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.405
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.048
upper limit	0.12

Primary: Weighted mean serial FEV1 over 0-24 hours post-dose at Week 12

End point title	Weighted mean serial FEV1 over 0-24 hours post-dose at Week 12

End point description:

Pulmonary function was measured by FEV1, 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 Week 12 clinic visit. Weighted mean was calculated using the 24-hour serial FEV1 measurements that included the pre-dose assessment (within 5 minutes prior to dosing at Week 12) and 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. The analysis was performed using an ANCOVA model with covariates of Baseline FEV1, region, sex, age, and treatment group.

End point type	Primary

End point timeframe:

Week 12

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95[4]	106[5]	108[6]	
Units: Liters				
least squares mean (standard error)	2.542 (± 0.0456)	2.728 (± 0.0432)	2.843 (± 0.043)	

Notes:

[4] - ITT Population. Data were calculated for participants for whom Week 12 serial FEV1 was performed.
[5] - ITT Population. Data were calculated for participants for whom Week 12 serial FEV1 was performed.
[6] - ITT Population. Data were calculated for participants for whom Week 12 serial FEV1 was performed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v FF 100 µg OD

Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.186
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.062
upper limit	0.31

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v FF/VI 100/25 µg OD
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.302
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.178
upper limit	0.426

Statistical analysis title	Statistical Analysis 3
Comparison groups	FF 100 µg OD v FF/VI 100/25 µg OD
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.236

Secondary: Change from Baseline in the percentage of rescue-free 24-hour (hr)

periods during the 12-week Treatment Period

End point title	Change from Baseline in the percentage of rescue-free 24-hour (hr) periods during the 12-week Treatment Period

End point description:

The number of inhalations of rescue albuterol/salbutamol inhalation aerosol used during the day and night was recorded by the participants in a daily electronic diary (eDiary). A 24-hour (hr) 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. 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 12-week Treatment Period minus the Baseline value. The analysis was performed using an ANCOVA model with covariates of Baseline, region, sex, age, and treatment group.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202[7]	204[8]	201[9]	
Units: Percentage of rescue-free 24-hr periods				
least squares mean (standard error)	17.8 (± 2.26)	26.5 (± 2.25)	37.1 (± 2.26)	

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 the percentage of symptom-free 24-hour (hr) periods during the 12-week Treatment Period

End point title	Change from Baseline in the percentage of symptom-free 24-hour (hr) periods during the 12-week Treatment Period

End point description:

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 (hr) period in which a participant's responses to both the morning and evening assessments indicated no symptoms was considered to be 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 12-week Treatment Period minus the Baseline value. The analysis was performed using an ANCOVA model with covariates of Baseline, region, sex, age, and treatment group.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202[10]	204[11]	201[12]	
Units: Percentage of symptom-free 24-hr periods				
least squares mean (standard error)	14.6 (± 2.15)	20.4 (± 2.13)	32.5 (± 2.14)	

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 total Asthma Quality of Life Questionnaire (AQLQ) (+12) score at Week 12/Early Withdrawal

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

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 Week 12 minus the total score at Baseline.

End point type	Secondary

End point timeframe:

Baseline and Week 12/Early Withdrawal

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149[13]	184[14]	180[15]	
Units: Scores on a scale				
least squares mean (standard error)	0.61 (± 0.061)	0.76 (± 0.055)	0.91 (± 0.055)	

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 12-week treatment period

End point title	Number of participants who withdrew due to lack of efficacy

	during the 12-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 12/Early Withdrawal

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	203[16]	205[17]	201[18]	
Units: participants	32	6	7	

Notes:

[16] - ITT Population

[17] - ITT Population

[18] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Serial FEV1 over 0-1 hour post-dose at Randomization

End point title	Serial FEV1 over 0-1 hour post-dose at Randomization

End point description:

Pulmonary function was measured by FEV1, defined as the maximal amount of air that can be forcefully exhaled in one second. Serial FEV1 measurements were taken electronically by spirometry at Randomization. Serial FEV1 measurements after 5, 15, and 30 minutes and 1 hour post-dose were assessed. At each time point, the highest of 3 technically acceptable measurements was recorded. The analysis was performed using a repeated measures model adjusted for baseline, region, sex, age, treatment group, and planned time points.

End point type	Secondary

End point timeframe:

Randomization

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	203[19]	205[20]	201[21]	
Units: Liters				
least squares mean (standard error)				
5 Minutes, n=117, 112, 117	2.489 (± 0.0308)	2.493 (± 0.0314)	2.484 (± 0.0308)	
15 Minutes, n=118, 115, 117	2.491 (± 0.0336)	2.529 (± 0.0342)	2.566 (± 0.0336)	
30 Minutes, n=118, 116, 118	2.532 (± 0.0354)	2.552 (± 0.0359)	2.596 (± 0.0354)	
1 Hour, n=119, 116, 119	2.552 (± 0.0344)	2.571 (± 0.035)	2.674 (± 0.0344)	

Notes:

[19] - ITT Population. Serial FEV1 was calculated for the participants for whom serial FEV1 was performed.
[20] - ITT Population. Serial FEV1 was calculated for the participants for whom serial FEV1 was performed.
[21] - ITT Population. Serial FEV1 was calculated for the participants for whom serial FEV1 was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinic visit 12-hour post-dose FEV1 at Week 12

End point title	Clinic visit 12-hour post-dose FEV1 at Week 12

End point description:

Pulmonary function was measured by FEV1, 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 12 clinic visit. The highest of 3 technically acceptable measurements was recorded. The analysis was performed using an ANCOVA model with covariates of Baseline FEV1, region, sex, age, and treatment group.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93[22]	104[23]	108[24]	
Units: Liters				
least squares mean (standard error)	2.462 (± 0.0502)	2.674 (± 0.0475)	2.83 (± 0.0468)	

Notes:

[22] - ITT Population. Data were analyzed in the participants for whom serial FEV1 at Week 12 was performed
[23] - ITT Population. Data were analyzed in the participants for whom serial FEV1 at Week 12 was performed
[24] - ITT Population. Data were analyzed in the participants for whom serial FEV1 at Week 12 was performed

Statistical analyses

No statistical analyses for this end point

Secondary: Weighted mean serial FEV1 over 0-24 hours post-dose on Day 0

End point title	Weighted mean serial FEV1 over 0-24 hours post-dose on Day 0

End point description:

Pulmonary function was measured by FEV1, defined as the maximal amount of air that can be forcefully exhaled in one second. Serial FEV1 measurements were taken electronically by spirometry on Day 0. Weighted mean was calculated using the 24-hour serial FEV1 measurements that included the pre-dose assessment (within 30 minutes prior to dosing) and 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 were recorded.

End point type	Secondary

End point timeframe:
Day 0

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119[25]	116[26]	119[27]	
Units: Liters				
arithmetic mean (standard deviation)	2.543 (± 0.8494)	2.552 (± 0.7527)	2.709 (± 0.8153)	

Notes:

[25] - ITT Population. Data were calculated in the participants for whom serial FEV1 was performed.

[26] - ITT Population. Data were calculated in the participants for whom serial FEV1 was performed.

[27] - ITT Population. Data were calculated in the participants for whom serial FEV1 was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Weighted mean serial FEV1 over 0-4 hours post-dose at Day 0 and Week 12

End point title	Weighted mean serial FEV1 over 0-4 hours post-dose at Day 0 and Week 12

End point description:

Pulmonary function was measured by FEV1, defined as the maximal amount of air that can be forcefully exhaled in one second. Serial FEV1 measurements were taken electronically by spirometry at Day 0 and Week 12 clinic visits. Weighted mean serial FEV1 over 0-4 hours was calculated using the serial FEV1 measurements that included the pre-dose assessment (within 30 minutes prior to dosing at Baseline and within 5 minutes prior to dosing at Week 12) 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 were recorded.

End point type	Secondary

End point timeframe:
Day 0 and Week 12

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120[28]	115[29]	119[30]	
Units: Liters				
arithmetic mean (standard deviation)				
Day 0, n=120, 115, 119	2.563 (± 0.8194)	2.522 (± 0.7479)	2.693 (± 0.7626)	
Week 12, n=96, 105, 109	2.636 (± 0.8519)	2.657 (± 0.7912)	2.894 (± 0.8383)	

Notes:

[28] - ITT Population. Data were calculated in the participants for whom Week 12 serial FEV1 was performed.

[29] - ITT Population. Data were calculated in the participants for whom Week 12 serial FEV1 was performed.

[30] - ITT Population. Data were calculated in the participants for whom Week 12 serial FEV1 was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with bronchodilator effect

End point title	Number of participants with bronchodilator effect

End point description:

Bronchodilator effect is defined as an increase of FEV1 (defined as the maximal amount of air that can be forcefully exhaled in one second) from Baseline of both 12% and 200 milliliters (mL) during 24 hours, which was evaluated using the serial FEV1 measurements at Baseline (Visit 3).

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120[31]	116[32]	120[33]	
Units: participants	73	77	97	

Notes:

[31] - ITT Population. Only the subset of participants performing serial measurements were analyzed.

[32] - ITT Population. Only the subset of participants performing serial measurements were analyzed.

[33] - ITT Population. Only the subset of participants performing serial measurements were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in daily morning (AM) peak expiratory flow (PEF) averaged over the 12-week Treatment Period

End point title	Mean change from Baseline in daily morning (AM) peak expiratory flow (PEF) averaged over the 12-week Treatment Period

End point description:

Peak Expiratory Flow (PEF) 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 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 12-week treatment period (at Week 12) minus the Baseline value. The analysis was performed using an ANCOVA model with covariates of Baseline, region, sex, age, and treatment group.

End point type	Secondary

End point timeframe:

From Baseline up to Week 12

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	203[34]	204[35]	201[36]	
Units: Liters per minute				
least squares mean (standard error)	-0.4 (± 2.42)	18.3 (± 2.41)	32.9 (± 2.42)	

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in daily evening (PM) PEF averaged over the 12-week Treatment Period

End point title	Mean change from Baseline in daily evening (PM) PEF averaged over the 12-week Treatment Period

End point description:

PEF 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 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 PM PEF over the 12-week treatment period (at Week 12) minus the Baseline value. The analysis was performed using an ANCOVA model with covariates of Baseline, region, sex, age, and treatment group.

End point type	Secondary

End point timeframe:

From Baseline up to Week 12

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202[37]	204[38]	201[39]	
Units: Liters per minute				
least squares mean (standard error)	-1.8 (± 2.36)	14.1 (± 2.34)	26.4 (± 2.35)	

Notes:

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

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

[39] - 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 Asthma Control Test (ACT) score at Week 12

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

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/Early Withdrawal minus the total score at Baseline.

End point type	Secondary

End point timeframe:

Baseline and Week 12/Early Withdrawal

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[40]	189[41]	185[42]	
Units: Scores on a scale				
least squares mean (standard error)	2.5 (± 0.26)	3.8 (± 0.23)	4.4 (± 0.23)	

Notes:

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

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

[42] - 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 with the indicated Global Assessment of Change responses at Week 4, Week 8, and Week 12/Early Withdrawal

End point title	Number of participants with the indicated Global Assessment of Change responses at Week 4, Week 8, and Week 12/Early Withdrawal

End point description:

At the end of Week 4, Week 8, and Week 12/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 symptom); 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).

End point type	Secondary

End point timeframe:

Week 4, Week 8, and Week 12/Early Withdrawal

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174[43]	198[44]	191[45]	
Units: participants				
Week 4, AS - Much better, n=174, 198, 191	34	47	65	
Week 4, AS - Somewhat better, n=174, 198, 191	45	65	61	
Week 4, AS - A little better, n=174, 198, 191	42	47	37	
Week 4, AS - The same, n=174, 198, 191	33	29	23	
Week 4, AS - A little worse, n=174, 198, 191	6	10	3	
Week 4, AS - Somewhat worse, n=174, 198, 191	8	0	2	
Week 4, AS - Much worse, n=174, 198, 191	6	0	0	
Week 4, RMU - Much less often, n=174, 198, 191	39	59	75	
Week 4, RMU - Somewhat less often, n=174, 198, 191	40	48	51	
Week 4, RMU - A little less often, n=174, 198, 191	35	49	32	
Week 4, RMU - The same, n=174, 198, 191	31	33	28	
Week 4, RMU - A little more often, n=174, 198, 191	13	6	4	
Week 4, RMU - Somewhat more often, n=174, 198, 191	11	3	1	
Week 4, RMU - Much more often, n=174, 198, 191	5	0	0	
Week 8, AS - Much better, n=159, 192, 184	36	54	69	
Week 8, AS - Somewhat better, n=159, 192, 184	44	60	63	
Week 8, AS - A little better, n=159, 192, 184	38	40	22	
Week 8, AS - The same, n=159, 192, 184	29	33	24	
Week 8, AS - A little worse, n=159, 192, 184	7	5	3	
Week 8, AS - Somewhat worse, n=159, 192, 184	4	0	2	
Week 8, AS - Much worse, n=159, 192, 184	1	0	1	
Week 8, RMU - Much less often, n=159, 191, 184	37	65	86	
Week 8, RMU - Somewhat less often, n=159, 191, 184	32	48	43	
Week 8, RMU - A little less often, n=159, 191, 184	37	34	25	
Week 8, RMU - The same, n=159, 191, 184	36	39	23	
Week 8, RMU - A little more often, n=159, 191, 184	12	1	5	
Week 8, RMU - Somewhat more often, n=159, 191, 184	4	4	0	
Week 8, RMU - Much more often, n=159, 191, 184	1	0	2	

Week 12, AS - Much better, n=152, 187, 182	38	66	86	
Week 12, AS - Somewhat better, n=152, 187, 182	37	49	52	
Week 12, AS - A little better, n=152, 187, 182	29	35	13	
Week 12, AS - The same, n=152, 187, 182	29	30	23	
Week 12, AS - A little worse, n=152, 187, 182	9	7	7	
Week 12, AS - Somewhat worse, n=152, 187, 182	6	0	1	
Week 12, AS - Much worse, n=152, 187, 182	4	0	0	
Week 12, RMU - Much less often, n=150, 187, 182	42	76	89	
Week 12, RMU - Somewhat less often,n=150, 187, 182	32	46	43	
Week 12, RMU - A little less often,n=150, 187, 182	24	25	21	
Week 12, RMU - The same, n=150, 187, 182	34	32	23	
Week 12, RMU - A little more often,n=150, 187, 182	12	6	5	
Week 12, RMU - Somewhat more often,n=150, 187, 182	3	1	1	
Week 12, RMU - Much more often, n=150, 187, 182	3	1	0	

Notes:

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

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

[45] - 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 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 were recorded.

End point type	Secondary

End point timeframe:

From Baseline up to Week 12/Early Withdrawal

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	203[46]	205[47]	201[48]	
Units: visits				
arithmetic mean (standard deviation)				
Number of Home Visits (Day)	0 (± 0)	0 (± 0)	0 (± 0)	
Number of Home Visits (Night)	0 (± 0)	0 (± 0)	0 (± 0)	
Number of Physician Office/Practice Visits	0 (± 0.24)	0 (± 0.39)	0 (± 0.1)	
Number of Urgent Care/Outpatient Clinic Visits	0 (± 0.07)	0 (± 0.07)	0 (± 0)	
Number of Emergency Room Visits	0 (± 0)	0 (± 0)	0 (± 0)	
Number of Inpatient Hospitalization Days (ICU)	0 (± 0)	0 (± 0)	0 (± 0)	
Number of Inpatient Hospitalization (GW) Days	0 (± 0)	0 (± 0)	0 (± 0)	

Notes:

[46] - ITT Population

[47] - ITT Population

[48] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who used the inhaler correctly or incorrectly at Baseline, Week 2, and Week 4

End point title	Number of participants who used the inhaler correctly or incorrectly at Baseline, Week 2, and Week 4

End point description:

Participants were given a demonstration of correct inhaler use (using placebo inhalers), and the participants' competence to correctly use the demonstration inhaler was then assessed.

End point type	Secondary

End point timeframe:

Baseline (BL), Week 2 (W2), and Week 4 (W4)

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	203[49]	205[50]	201[51]	
Units: participants				
BL: Used Inhaler Correctly, n=203, 205, 201	194	196	188	
BL: Used Inhaler Incorrectly, n=203, 205, 201	9	9	13	
W2: Used Inhaler Correctly, n=190, 203, 200	190	203	200	
W2: Used Inhaler Incorrectly, n=190, 203, 200	0	0	0	
W4: Used Inhaler Correctly, n=175, 199, 195	175	199	195	
W4: Used Inhaler Incorrectly, n=175, 199, 195	0	9	0	

Notes:

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

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

[51] - 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 with the indicated reason for incorrect inhaler use and who required additional instruction the indicated number of times at Baseline, Week 2, and Week 4

End point title	Number of participants with the indicated reason for incorrect inhaler use and who required additional instruction the indicated number of times at Baseline, Week 2, and Week 4

End point description:

Participants were given a demonstration of correct inhaler use (using placebo inhalers), and the participants' competence to correctly use the demonstration inhaler was then assessed based on 3 steps: open the device, inhale the dose, and close the device. If the participants did not perform the maneuvers correctly, the step of the inhaler use that was performed incorrectly by the participants was recorded. The entire procedure was demonstrated once again, and the number of times that the participants required additional instruction (RAI) was recorded. "99999" is used to indicate that data are not available (no participants used the inhaler incorrectly; thus, no data can be reported at the specified time point).

End point type	Secondary

End point timeframe:

Baseline, Week 2, and Week 4

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9[52]	9[53]	13[54]	
Units: participants				
BL: Opened the Device Incorrectly, n= 9, 9, 13	8	4	6	
BL: Inhaled the Dose Incorrectly, n= 9, 9, 13	1	5	6	
BL: Closed the Device Incorrectly, n= 9, 9, 13	1	0	1	
BL: RAI once, n= 9, 9, 13	9	5	8	
BL: RAI 2 Times, n= 9, 9, 13	0	4	4	
BL: RAI 3 Times, n= 9, 9, 13	0	0	1	
BL: RAI >3 Times, n= 9, 9, 13	0	0	0	
W2: Opened the Device Incorrectly, n= 0, 0, 0	99999	99999	99999	
W2: Inhaled the Dose Incorrectly, n= 0, 0, 0	99999	99999	99999	
W2: Closed the Device Incorrectly, n= 0, 0, 0	99999	99999	99999	
W2: RAI once, n= 0, 0, 0	99999	99999	99999	
W2: RAI 2 Times, n= 0, 0, 0,	99999	99999	99999	
W2: RAI 3 Times, n= 0, 0, 0	99999	99999	99999	

W2: RAI >3 Times, n= 0, 0, 0	99999	99999	99999	
W4: Opened the Device Incorrectly, n= 0, 0, 0	99999	99999	99999	
W4: Inhaled the Dose Incorrectly, n= 0, 0, 0	99999	99999	99999	
W4: Closed the Device Incorrectly, n= 0, 0, 0	99999	99999	99999	
W4: RAI once, n= 0, 0, 0	99999	99999	99999	
W4: RAI 2 Times, n= 0, 0, 0	99999	99999	99999	
W4: RAI 3 Times, n= 0, 0, 0	99999	99999	99999	
W4: RAI >3 Times, n= 0, 0, 0	99999	99999	99999	

Notes:

[52] - ITT Population. Only those participants who used the inhaler incorrectly were analyzed.

[53] - ITT Population. Only those participants who used the inhaler incorrectly were analyzed.

[54] - ITT Population. Only those participants who used the inhaler incorrectly were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated responses to the ease of use questions regarding the inhaler at Week 4

End point title	Number of participants with the indicated responses to the ease of use questions regarding the inhaler at Week 4

End point description:

Participants were asked to rate the inhaler (INH) by answering the following 2 questions: How do you rate the ease of use of the inhaler?; How easily are you able to tell how many doses of medication are left in the inhaler? For each of the questions, answers were made on a five-point scale: 1, very easy; 2, easy; 3, neutral; 4, difficult; 5, very difficult.

End point type	Secondary

End point timeframe:

Week 4

End point values	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176[55]	199[56]	195[57]	
Units: participants				
Use of the INH: Very easy	107	126	129	
Use of the INH: Easy	53	50	54	
Use of the INH: Neutral	13	19	11	
Use of the INH: Difficult	2	4	1	
Use of the INH: Very difficult	1	0	0	
Identifying doses left in the INH: Very easy	126	146	147	
Identifying doses left in the INH: Easy	41	46	39	
Identifying doses left in the INH: Neutral	8	6	8	
Identifying doses left in the INH: Difficult	1	1	1	
Identifying doses left in the INH: Very difficult	0	0	0	

Notes:
[55] - ITT Population. Only those participants available at the specified time point were analyzed.
[56] - ITT Population. Only those participants available at the specified time point were analyzed.
[57] - ITT Population. Only those participants available at the specified time point were analyzed.

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 first dose of study medication up to Week 12/Early Withdrawal.

Adverse event reporting additional description:

SAEs and AEs were collected in members of Intent-to-Treat (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	Placebo

Reporting group description:

Participants (par.) received placebo once daily (OD) in the evening from the dry powder inhaler (DPI) for 12 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

Reporting group title	FF 100 µg OD

Reporting group description:

Participants received Fluticasone Furoate (FF) 100 microgram (µg) inhalation powder OD in the evening from the DPI for 12 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

Reporting group title	FF/VI 100/25 µg OD

Reporting group description:

Participants received FF/Vilanterol (VI) 100/25 µg inhalation powder OD in the evening from the DPI for 12 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

Serious adverse events	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 203 (0.00%)	1 / 205 (0.49%)	0 / 201 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 205 (0.49%)	0 / 201 (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	Placebo	FF 100 µg OD	FF/VI 100/25 µg OD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 203 (10.84%)	20 / 205 (9.76%)	29 / 201 (14.43%)
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 203 (3.94%)	9 / 205 (4.39%)	10 / 201 (4.98%)
occurrences (all)	8	18	12
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 203 (7.39%)	14 / 205 (6.83%)	20 / 201 (9.95%)
occurrences (all)	16	14	24

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 August 2010	The original protocol, dated 22 June 2010, was amended twice. Amendment 1, dated 31 August 2010, applied to all investigational sites and was in place after the initiation of subject enrolment but prior to the unblinding of the trial data. Protocol changes specified in Amendment No. 01 were required to add a new European Union and International Medical Monitor and to extend the pre-dose FEV1 timeline, as follows: • Sites in another study had been having difficulty in meeting the timeline of 5 minutes between pre-dose FEV1 and dosing at randomisation for the serial FEV1 procedure. Therefore, in this current study, the pre-dose timeline was extended to within 30 minutes of dosing to provide the sites with more time after the pre-dose assessment to randomise the subject and retrieve the appropriate clinical supplies medication for the subjects' first dose.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported