Clinical trial results:
A randomized, double-blind, double-dummy, parallel group, multicenter study of once daily Fluticasone Furoate/Vilanterol 100/25 mcg Inhalation Powder, twice daily Fluticasone Propionate/Salmeterol 250/50 mcg Inhalation Powder, and twice daily Fluticasone Propionate 250 mcg Inhalation Powder in the treatment of persistent asthma in adults and adolescents already adequately controlled on twice-daily inhaled corticosteroid and long-acting beta2 agonist.

Summary

EudraCT number	2014-002253-19
Trial protocol	ES NL CZ DE
Global end of trial date	25 November 2016

Results information

Result version number	v1 (current)
This version publication date	24 May 2017
First version publication date	24 May 2017

Trial information

Trial identification

Sponsor protocol code	201378

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 November 2016
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 demonstrate non-inferiority of RELVAR ELLIPTA 100/25 once-daily to SERETIDE ACCUHALER/DISKUS 250/50 twice-daily in adult and adolescent subjects 12 years of age and older with persistent bronchial asthma, adequately controlled on twice-daily ICS/LABA.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 597
Country: Number of subjects enrolled	United States: 491
Country: Number of subjects enrolled	Argentina: 439
Country: Number of subjects enrolled	Germany: 425
Country: Number of subjects enrolled	Mexico: 326
Country: Number of subjects enrolled	Romania: 306
Country: Number of subjects enrolled	Czech Republic: 151
Country: Number of subjects enrolled	Chile: 109
Country: Number of subjects enrolled	Spain: 100
Country: Number of subjects enrolled	Netherlands: 98
Country: Number of subjects enrolled	Brazil: 71
Country: Number of subjects enrolled	Korea, Republic of: 49
Worldwide total number of subjects	3162
EEA total number of subjects	1080

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)	7
Adolescents (12-17 years)	167
Adults (18-64 years)	2620
From 65 to 84 years	368
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible participants at screening and run-in visits entered a 24 Week treatment period and were randomized to receive either Fluticasone furoate/Vilanterol (FF/VI) 100/25 micrograms (mcg) or Fluticasone propionate/salmeterol (FP/S) 250/50mcg or only FP 250mcg followed by a follow-up phase. The total duration for study participation was 30 weeks.

Pre-assignment

Screening details:

A total of 3162 adult and adolescent participants with asthma were screened, out of which 516 were screen-failures, 1124 were run-in failures, 1522 participants were randomized, and 1504 subjects received at least one dose of study medication to be included in the Intent-to-Treat (ITT) Population.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	FF/VI 100/25 mcg once daily

Arm description:

Participants received FF/VI 100/25 mcg via ELLIPTA® inhaler once daily (at evening) along with placebo via ACCUHALER/DISKUS® twice daily for 24 weeks. Albuterol/Salbutamol inhalation aerosol was also provided to treat acute asthma symptoms.

Arm type	Experimental
Investigational medicinal product name	Fluticasone Furoate/Vilanterol (FF/VI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

FF/VI 100/25 mcg was administered via inhalation route using ELLIPTA inhaler once daily in the evening.

Arm title	FP/S 250/50 mcg twice daily

Arm description:

Participants received FP/S 250/50 mcg via ACCUHALER/DISKUS inhaler twice daily along with placebo via ELLIPTA inhaler once daily (at evening) for 24 weeks. Albuterol/Salbutamol inhalation aerosol was also provided to treat acute asthma symptoms.

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

Dosage and administration details:

FP/S 250/50 mcg was administered via inhalation route using DISKUS/ACCUHALER twice daily; once in the morning and once in the evening.

Arm title	FP 250 mcg twice daily

Arm description:

Participants received FP 250 mcg via ACCUHALER/DISKUS inhaler twice daily along with placebo via ELLIPTA inhaler once daily (at evening) for 24 weeks. Albuterol/Salbutamol inhalation aerosol was also provided to treat acute asthma symptoms.

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

Dosage and administration details:

FP 250 mcg was administered via inhalation route using DISKUS/ACCUHALER twice daily; once in the morning and once in the evening.

Number of subjects in period 1[1]	FF/VI 100/25 mcg once daily	FP/S 250/50 mcg twice daily	FP 250 mcg twice daily
Started	504	501	499
Completed	473	476	477
Not completed	31	25	22
Physician decision	4	2	3
Consent withdrawn by subject	15	12	11
Adverse event, non-fatal	8	3	2
Lost to follow-up	-	2	2
Lack of efficacy	1	1	1
Protocol deviation	3	5	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 3162 adult and adolescent participants with asthma were screened, out of which 516 were screen-failures, 1124 were run-in failures, 1522 participants were randomized, and 1504 subjects received at least one dose of study medication to be included in the Intent-to-Treat (ITT) Population.

Baseline characteristics

Reporting groups	
Reporting group title	FF/VI 100/25 mcg once daily
Reporting group description:	
Participants received FF/VI 100/25 mcg via ELLIPTA® inhaler once daily (at evening) along with placebo via ACCUHALER/DISKUS® twice daily for 24 weeks. Albuterol/Salbutamol inhalation aerosol was also provided to treat acute asthma symptoms.	
Reporting group title	FP/S 250/50 mcg twice daily
Reporting group description:	
Participants received FP/S 250/50 mcg via ACCUHALER/DISKUS inhaler twice daily along with placebo via ELLIPTA inhaler once daily (at evening) for 24 weeks. Albuterol/Salbutamol inhalation aerosol was also provided to treat acute asthma symptoms.	
Reporting group title	FP 250 mcg twice daily
Reporting group description:	
Participants received FP 250 mcg via ACCUHALER/DISKUS inhaler twice daily along with placebo via ELLIPTA inhaler once daily (at evening) for 24 weeks. Albuterol/Salbutamol inhalation aerosol was also provided to treat acute asthma symptoms.	

Reporting group values	FF/VI 100/25 mcg once daily	FP/S 250/50 mcg twice daily	FP 250 mcg twice daily
Number of subjects	504	501	499
Age categorical Units: Subjects			
Age continuous Units: years			
log mean	44.4	43	43
standard deviation	± 16.3	± 15.2	± 16.58
Gender categorical Units: Subjects			
Female	314	336	314
Male	190	165	185
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska native	0	0	1
Asian - East Asian Heritage	8	11	4
Asian- Japanese Heritage	1	0	0
Asian- South East Asian Heritage	1	0	1
Black/African American Heritage	12	14	17
White- Arabic/ North African Heritage	0	1	2
White- White/Caucasian/European Heritage	415	407	410
White- Mixed White Race	1	0	0
African American/ African and White Heritage	0	5	0
American Indian/Alaskan Native and White Heritage	66	62	64
Asian - East Asian and White Heritage	0	1	0

Reporting group values	Total		
Number of subjects	1504		
Age categorical Units: Subjects			

Age continuous Units: years log mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	964		
Male	540		
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska native	1		
Asian - East Asian Heritage	23		
Asian- Japanese Heritage	1		
Asian- South East Asian Heritage	2		
Black/African American Heritage	43		
White- Arabic/ North African Heritage	3		
White- White/Caucasian/European Heritage	1232		
White- Mixed White Race	1		
African American/ African and White Heritage	5		
American Indian/Alaskan Native and White Heritage	192		
Asian - East Asian and White Heritage	1		

End points

End points reporting groups

Reporting group title	FF/VI 100/25 mcg once daily
Reporting group description:	
Participants received FF/VI 100/25 mcg via ELLIPTA® inhaler once daily (at evening) along with placebo via ACCUHALER/DISKUS® twice daily for 24 weeks. Albuterol/Salbutamol inhalation aerosol was also provided to treat acute asthma symptoms.	
Reporting group title	FP/S 250/50 mcg twice daily
Reporting group description:	
Participants received FP/S 250/50 mcg via ACCUHALER/DISKUS inhaler twice daily along with placebo via ELLIPTA inhaler once daily (at evening) for 24 weeks. Albuterol/Salbutamol inhalation aerosol was also provided to treat acute asthma symptoms.	
Reporting group title	FP 250 mcg twice daily
Reporting group description:	
Participants received FP 250 mcg via ACCUHALER/DISKUS inhaler twice daily along with placebo via ELLIPTA inhaler once daily (at evening) for 24 weeks. Albuterol/Salbutamol inhalation aerosol was also provided to treat acute asthma symptoms.	

Primary: Change from Baseline in evening (post meridiem [PM]) Forced Expiratory Volume in one second (FEV1) using Intent-to-Treat (ITT) Population

End point title	Change from Baseline in evening (post meridiem [PM]) Forced Expiratory Volume in one second (FEV1) using Intent-to-Treat (ITT) Population
End point description:	
FEV1 was defined as the volume of air that can be forced out in one second after taking a deep breath. FEV1 (pre-bronchodilator and pre-dose) was measured at Baseline up to Week 24 at evening using spirometry. Repeated Measures analysis was adjusted for Baseline, region, sex, age, treatment, visit, visit by Baseline interaction and visit by treatment interaction. Visit 3 values were taken as Baseline value and change from Baseline was defined as the difference between the value of the endpoint at the time point of interest and the Baseline value. Statistical analysis was performed using the mixed model repeated measures (MMRM) model and least square mean and standard error were calculated. The analysis was performed on ITT Population which comprised of all participants randomized to treatment and who received at least one dose of study medication.	
End point type	Primary
End point timeframe:	
Baseline and Week 24	

End point values	FF/VI 100/25 mcg once daily	FP/S 250/50 mcg twice daily	FP 250 mcg twice daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	487[1]	487[2]	479[3]	
Units: Liter (L)				
least squares mean (standard error)				
Liter (L)	0.019 (± 0.0107)	0 (± 0.0108)	-0.104 (± 0.0109)	

Notes:

[1] - ITT Population

[2] - ITT Population

[3] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/VI 100/25 mcg once daily v FP/S 250/50 mcg twice daily
Number of subjects included in analysis	974
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Least square mean change difference
Point estimate	0.019
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.011
upper limit	0.049

Notes:

[4] - Non-inferiority was defined if the lower bound of the 95% CI for the difference between mean change from Baseline in clinic visit PM FEV1 for FF/VI and FP/S was more than -100 milliliter (mL)

Statistical analysis title	Statistical analysis 2
Comparison groups	FF/VI 100/25 mcg once daily v FP 250 mcg twice daily
Number of subjects included in analysis	966
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least square mean change difference
Point estimate	0.123
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.093
upper limit	0.153

Notes:

[5] - Inequality

Statistical analysis title	Statistical analysis 3
Comparison groups	FP/S 250/50 mcg twice daily v FP 250 mcg twice daily
Number of subjects included in analysis	966
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least square mean change difference
Point estimate	0.104
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.074
upper limit	0.134

Notes:

[6] - Inequality

Primary: Change from Baseline in PM FEV1 using Per Protocol (PP) Population

End point title	Change from Baseline in PM FEV1 using Per Protocol (PP) Population

End point description:

FEV1 was defined as the volume of air that can be forced out in one second after taking a deep breath. FEV1 (pre-bronchodilator and pre-dose) was measured at Baseline up to Week 24 at evening using spirometry. Repeated Measures analysis was adjusted for Baseline, region, sex, age, treatment, visit, visit by Baseline interaction and visit by treatment interaction. Visit 3 values were taken as Baseline value and change from Baseline was defined as the difference between the value of the endpoint at the time point of interest and the Baseline value. Statistical analysis was performed using the MMRM models and least square mean and standard error were calculated. The analysis was performed on PP Population which comprised of all participants in the ITT Population who did not had any full protocol deviations.

End point type	Primary

End point timeframe:

Baseline and Week 24

End point values	FF/VI 100/25 mcg once daily	FP/S 250/50 mcg twice daily	FP 250 mcg twice daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	425[7]	426[8]	419[9]	
Units: Liter (L)				
least squares mean (standard error)				
Liter (L)	0.02 (± 0.012)	0.014 (± 0.012)	-0.099 (± 0.0121)	

Notes:

[7] - PP Population

[8] - PP Population

[9] - PP Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/VI 100/25 mcg once daily v FP/S 250/50 mcg twice daily
Number of subjects included in analysis	851
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	Least square mean change difference
Point estimate	0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.027
upper limit	0.04

Notes:

[10] - Non-inferiority was defined if the lower bound of the 95% CI for the difference between mean change from Baseline in clinic visit for FF/VI and FP/S was more than -100 mL

Statistical analysis title	Statistical analysis 2

Comparison groups	FF/VI 100/25 mcg once daily v FP 250 mcg twice daily
Number of subjects included in analysis	844
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least square mean change difference
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.086
upper limit	0.153

Notes:

[11] - Inequality

Statistical analysis title	Statistical analysis 1
Comparison groups	FP/S 250/50 mcg twice daily v FP 250 mcg twice daily
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least square mean change difference
Point estimate	0.113
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.147

Notes:

[12] - Inequality

Secondary: Change from Baseline in the percentage of rescue-free 24-hour periods

End point title	Change from Baseline in the percentage of rescue-free 24-hour periods

End point description:

The number of inhalations of rescue medication used during the day and night were recorded by participants using an electronic diary (e-diary). 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 24-week treatment period minus the Baseline value. Statistical analysis was performed using an Analysis of Covariance (ANCOVA) model with covariates of Baseline, region, sex, age and treatment and least square mean and standard error were calculated.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1-24

End point values	FF/VI 100/25 mcg once daily	FP/S 250/50 mcg twice daily	FP 250 mcg twice daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	500[13]	498[14]	496[15]	
Units: Percentage of rescue-free 24-hr periods				
least squares mean (standard error)				
Percentage of rescue-free 24-hr periods	-3 (± 0.62)	-4.2 (± 0.62)	-5.7 (± 0.62)	

Notes:

[13] - ITT Population

[14] - ITT Population

[15] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/VI 100/25 mcg once daily v FP/S 250/50 mcg twice daily
Number of subjects included in analysis	998
Analysis specification	Pre-specified
Analysis type	other[16]
Parameter estimate	Least square mean change difference
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	3

Notes:

[16] - Descriptive

Statistical analysis title	Statistical analysis 2
Comparison groups	FF/VI 100/25 mcg once daily v FP 250 mcg twice daily
Number of subjects included in analysis	996
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Least square mean change difference
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	4.4

Notes:

[17] - Inequality

Statistical analysis title	Statistical analysis 3
Comparison groups	FP/S 250/50 mcg twice daily v FP 250 mcg twice daily

Number of subjects included in analysis	994
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.106
Method	ANCOVA
Parameter estimate	Least square mean change difference
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	3.2

Notes:

[18] - Inequality

Secondary: Change from Baseline in the percentage of symptom-free 24-hour periods

End point title	Change from Baseline in the percentage of symptom-free 24-hour periods

End point description:

Change from Baseline in the percentage of symptom-free 24 hour period was evaluated. 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 24-week treatment period minus the Baseline value.Statistical analysis was performed using an ANCOVA model with covariates of Baseline, region, sex, age and treatment and least square mean and standard error were calculated.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1-24

End point values	FF/VI 100/25 mcg once daily	FP/S 250/50 mcg twice daily	FP 250 mcg twice daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	500[19]	498[20]	496[21]	
Units: Percentage of symptom-free 24 hour perio				
least squares mean (standard error)				
Percentage of symptom-free 24 hour perio	-3.5 (± 0.67)	-4.7 (± 0.67)	-6.2 (± 0.67)	

Notes:

[19] - ITT Population

[20] - ITT Population

[21] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/VI 100/25 mcg once daily v FP/S 250/50 mcg twice daily

Number of subjects included in analysis	998
Analysis specification	Pre-specified
Analysis type	other[22]
Parameter estimate	Least square mean change difference
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	3.1

Notes:

[22] - Descriptive

Statistical analysis title	Statistical analysis 2
Comparison groups	FF/VI 100/25 mcg once daily v FP 250 mcg twice daily
Number of subjects included in analysis	996
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Least square mean change difference
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	4.5

Notes:

[23] - Inequality

Statistical analysis title	Statistical analysis 3
Comparison groups	FP/S 250/50 mcg twice daily v FP 250 mcg twice daily
Number of subjects included in analysis	994
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	= 0.115
Method	ANCOVA
Parameter estimate	Least square mean change difference
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	3.3

Notes:

[24] - Inequality

Secondary: Change from Baseline in morning (ante meridiem [AM]) peak expiratory flow (PEF)

End point title	Change from Baseline in morning (ante meridiem [AM]) peak

	expiratory flow (PEF)

End point description:

PEF was measured using an electric flow meter each morning. Change from Baseline (defined as the last 7 days prior to randomization of the participants) was calculated as the value of the averaged daily AM PEF over the 24-week treatment period minus the Baseline value. Statistical analysis was performed using an ANCOVA model with covariates of Baseline, region, sex, age and treatment and least square mean and standard error were calculated.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1-24

End point values	FF/VI 100/25 mcg once daily	FP/S 250/50 mcg twice daily	FP 250 mcg twice daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	501[25]	499[26]	497[27]	
Units: Liter per minute (L/min)				
least squares mean (standard error)				
Liter per minute (L/min)	8.9 (± 1.48)	3.7 (± 1.49)	-12.6 (± 1.49)	

Notes:

[25] - ITT Population

[26] - ITT Population

[27] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/VI 100/25 mcg once daily v FP/S 250/50 mcg twice daily
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	other[28]
Parameter estimate	Least square mean change difference
Point estimate	5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	9.4

Notes:

[28] - Descriptive

Statistical analysis title	Statistical analysis 2
Comparison groups	FF/VI 100/25 mcg once daily v FP 250 mcg twice daily
Number of subjects included in analysis	998
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean change difference
Point estimate	21.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	17.4
upper limit	25.6

Notes:

[29] - Inequality

Statistical analysis title	Statistical analysis 3
Comparison groups	FP/S 250/50 mcg twice daily v FP 250 mcg twice daily
Number of subjects included in analysis	996
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean change difference
Point estimate	16.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.2
upper limit	20.4

Notes:

[30] - Inequality

Secondary: Percentage of participants with Asthma Control Test (ACT) Score greater than or equal to 20

End point title	Percentage of participants with Asthma Control Test (ACT) Score greater than or equal to 20

End point description:

The ACT was a five-item questionnaire developed as a measure of participant's asthma control. The percentage of participants controlled, defined as having ACT score greater than or equal to 20 at the end of Week 24 were analyzed using logistic regression model with covariates of Baseline ACT score, region, sex, age and treatment group.

End point type	Secondary

End point timeframe:

Week 24

End point values	FF/VI 100/25 mcg once daily	FP/S 250/50 mcg twice daily	FP 250 mcg twice daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	471[31]	467[32]	461[33]	
Units: Percentage of participants				
Percentage of participants	92	93	91	

Notes:

[31] - ITT Population

[32] - ITT Population

[33] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/VI 100/25 mcg once daily v FP/S 250/50 mcg twice daily
Number of subjects included in analysis	938
Analysis specification	Pre-specified
Analysis type	other[34]
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.54

Notes:

[34] - Descriptive

Statistical analysis title	Statistical analysis 2
Comparison groups	FF/VI 100/25 mcg once daily v FP 250 mcg twice daily
Number of subjects included in analysis	932
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.595
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.9

Notes:

[35] - Inequality

Statistical analysis title	Statistical analysis 3
Comparison groups	FP/S 250/50 mcg twice daily v FP 250 mcg twice daily
Number of subjects included in analysis	928
Analysis specification	Pre-specified
Analysis type	other[36]
P-value	= 0.372
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	2.12

Notes:

[36] - Inequality

Secondary: Change from Baseline in PM PEF

End point title	Change from Baseline in PM PEF

End point description:

PEF was measured using an electric flow meter each evening. 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 24-week treatment period minus the Baseline value. Statistical analysis was performed using an ANCOVA model with covariates of Baseline, region, sex, age and treatment and least square mean and standard error were calculated.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1-24

End point values	FF/VI 100/25 mcg once daily	FP/S 250/50 mcg twice daily	FP 250 mcg twice daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	501[37]	498[38]	496[39]	
Units: L/min				
least squares mean (standard error)				
L/min	5.5 (± 1.55)	0.5 (± 1.55)	-13.7 (± 1.55)	

Notes:

[37] - ITT Population

[38] - ITT Population

[39] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/VI 100/25 mcg once daily v FP/S 250/50 mcg twice daily
Number of subjects included in analysis	999
Analysis specification	Pre-specified
Analysis type	other[40]
Parameter estimate	Least square mean change difference
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	9.3

Notes:

[40] - Descriptive

Statistical analysis title	Statistical analysis 2
Comparison groups	FF/VI 100/25 mcg once daily v FP 250 mcg twice daily

Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean change difference
Point estimate	19.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.9
upper limit	23.5

Statistical analysis title	Statistical analysis 3
Comparison groups	FP/S 250/50 mcg twice daily v FP 250 mcg twice daily
Number of subjects included in analysis	994
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean change difference
Point estimate	14.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.9
upper limit	18.5

Notes:

[41] - Inequality

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of the study treatment until the follow up contact one week after completion of study medication (Up to Week 25).

Adverse event reporting additional description:

AEs and SAEs were collected in ITT Population

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	FF/VI 100/25 mcg once daily

Reporting group description:

Participants received FF/VI 100/25 mcg via ELLIPTA® inhaler once daily (at evening) along with placebo via ACCUHALER/DISKUS® twice daily for 24 weeks. Albuterol/Salbutamol inhalation aerosol was also provided to treat acute asthma symptoms.

Reporting group title	FP 250 mcg twice daily

Reporting group description:

Participants received FP 250 mcg via ACCUHALER/DISKUS inhaler twice daily along with placebo via ELLIPTA inhaler once daily (at evening) for 24 weeks. Albuterol/Salbutamol inhalation aerosol was also provided to treat acute asthma symptoms.

Reporting group title	FP/S 250/50 mcg twice daily

Reporting group description:

Participants received FP/S 250/50 mcg via ACCUHALER/DISKUS inhaler twice daily along with placebo via ELLIPTA inhaler once daily (at evening) for 24 weeks. Albuterol/Salbutamol inhalation aerosol was also provided to treat acute asthma symptoms.

Serious adverse events	FF/VI 100/25 mcg once daily	FP 250 mcg twice daily	FP/S 250/50 mcg twice daily
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 504 (1.19%)	5 / 499 (1.00%)	4 / 501 (0.80%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive lobular breast carcinoma			
subjects affected / exposed	1 / 504 (0.20%)	0 / 499 (0.00%)	0 / 501 (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
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	1 / 504 (0.20%)	0 / 499 (0.00%)	0 / 501 (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
Foot fracture			
subjects affected / exposed	0 / 504 (0.00%)	1 / 499 (0.20%)	0 / 501 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 504 (0.00%)	1 / 499 (0.20%)	0 / 501 (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
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 504 (0.00%)	0 / 499 (0.00%)	1 / 501 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Large intestine perforation			
subjects affected / exposed	0 / 504 (0.00%)	0 / 499 (0.00%)	1 / 501 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 504 (0.00%)	1 / 499 (0.20%)	0 / 501 (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			
Vocal cord leukoplakia			
subjects affected / exposed	0 / 504 (0.00%)	0 / 499 (0.00%)	1 / 501 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychotic disorder			

subjects affected / exposed	0 / 504 (0.00%)	0 / 499 (0.00%)	1 / 501 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 504 (0.20%)	0 / 499 (0.00%)	0 / 501 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 504 (0.20%)	0 / 499 (0.00%)	0 / 501 (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
Joint instability			
subjects affected / exposed	0 / 504 (0.00%)	1 / 499 (0.20%)	0 / 501 (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
Osteoarthritis			
subjects affected / exposed	0 / 504 (0.00%)	1 / 499 (0.20%)	0 / 501 (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
Synovial cyst			
subjects affected / exposed	1 / 504 (0.20%)	0 / 499 (0.00%)	0 / 501 (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
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 504 (0.00%)	1 / 499 (0.20%)	0 / 501 (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
Pneumonia			
subjects affected / exposed	1 / 504 (0.20%)	0 / 499 (0.00%)	0 / 501 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	FF/VI 100/25 mcg once daily	FP 250 mcg twice daily	FP/S 250/50 mcg twice daily
Total subjects affected by non-serious adverse events			
subjects affected / exposed	126 / 504 (25.00%)	124 / 499 (24.85%)	123 / 501 (24.55%)
Nervous system disorders			
Headache			
subjects affected / exposed	41 / 504 (8.13%)	40 / 499 (8.02%)	37 / 501 (7.39%)
occurrences (all)	70	59	67
Infections and infestations			
Bronchitis			
subjects affected / exposed	20 / 504 (3.97%)	13 / 499 (2.61%)	10 / 501 (2.00%)
occurrences (all)	24	13	10
Influenza			
subjects affected / exposed	9 / 504 (1.79%)	19 / 499 (3.81%)	12 / 501 (2.40%)
occurrences (all)	9	21	13
Nasopharyngitis			
subjects affected / exposed	61 / 504 (12.10%)	57 / 499 (11.42%)	67 / 501 (13.37%)
occurrences (all)	69	72	85
Pharyngitis			
subjects affected / exposed	15 / 504 (2.98%)	18 / 499 (3.61%)	13 / 501 (2.59%)
occurrences (all)	18	20	14

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 November 2014	To increase the minimum age requirement for the participants in the Czech Republic from 12 years and older to 18 years and older
29 January 2015	To prescribe appropriate asthma treatment to participants who discontinue investigational product (IP) early but elect to continue in the study; In addition, a withdrawal criterion was added to require Investigators to withdraw participants from IP if the participant needs alternative asthma treatment; Additional edits were made to clarify placebo inhaler details, to address rescue medication taken before exercise, and to describe how unblinded participants should be discontinued from IP prior to continuing in the study; Edits were also made to clarify that rescue medication use would be evaluated over a seven day rolling period, that countries will conduct a complete physical exam at Visit 1, that an Interactive Web Response System will be used, and that vital signs will only be databased at Visit 1. Further, edits were made to clarify that daytime symptoms will be evaluated as randomization criteria, that prohibited asthma medications are applicable up until the permanent discontinuation of IP and to remove 'pre-bronchodilator' from Inclusion Criteria 4.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported