Clinical trial results:
A randomised, double-blind, parallel group, multicentre, stratified, study evaluating the efficacy and safety of once daily fluticasone furoate/vilanterol inhalation powder compared to once daily fluticasone furoate inhalation powder in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids

Summary

EudraCT number	2016-004086-87
Trial protocol	DE ES IT PL Outside EU/EEA LT HU BG RO
Global end of trial date	25 April 2022

Results information

Result version number	v1 (current)
This version publication date	28 September 2022
First version publication date	28 September 2022

Trial information

Trial identification

Sponsor protocol code	HZA107116

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03248128
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom, TW8 9GS
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 May 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and efficacy study of fluticasone furoate/vilanterol (FF/VI) fixed dose combination (FDC) compared to FF alone in subjects with asthma

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 307
Country: Number of subjects enrolled	Bulgaria: 53
Country: Number of subjects enrolled	Canada: 132
Country: Number of subjects enrolled	Japan: 117
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Italy: 62
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Romania: 48
Country: Number of subjects enrolled	Lithuania: 14
Country: Number of subjects enrolled	Poland: 311
Country: Number of subjects enrolled	Mexico: 190
Country: Number of subjects enrolled	Russian Federation: 330
Country: Number of subjects enrolled	South Africa: 331
Country: Number of subjects enrolled	United States: 452
Country: Number of subjects enrolled	China: 3
Worldwide total number of subjects	2402
EEA total number of subjects	540

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)	1778
Adolescents (12-17 years)	624
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

2402 participants screened, 906 participants were randomised, of which 4 participants did not receive study treatment. 902 participants received at least 1 dose of study medication creating 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	Participants who received FF/ VI FDC

Arm description:

5-11 years old pediatric population were administered FF/VI as a FDC of 50/25 micrograms (mcg) and the 12-17 years old adolescent population received 100/25 mcg once daily via ELLIPTA dry powder inhaler (DPI). Each participant, in addition used albuterol/salbutamol (inhalation aerosol or nebuliser) as required throughout the entire study period as rescue medication for symptomatic relief of asthma symptoms.

Arm type	Experimental
Investigational medicinal product name	Participants aged 5-17 years who received FF/ VI FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants aged 5 to 11 years received FDC of 50 mcg/ 25 mcg and 12 to 17 years received FDC of 100 mcg/ 25 mcg of FF/VI. Both age groups received dose once daily in the morning via ELLIPTA DPI.

Arm title	Participants who received FF

Arm description:

5-11 years old pediatric population were administered FF/VI as a monotherapy of 50 mcg and the 12-17 years old adolescent population received 100 mcg once daily via ELLIPTA DPI. Each participant, in addition used albuterol/salbutamol (inhalation aerosol or nebuliser) as required throughout the entire study period as rescue medication for symptomatic relief of asthma symptoms.

Arm type	Experimental
Investigational medicinal product name	Participants aged 5-17 years who received FF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants aged 5 to 11 years received 50 mcg and aged 12 to 17 years received 100 mcg of FF. Both age groups received dose once daily in the morning via ELLIPTA DPI.

Number of subjects in period 1[1]	Participants who received FF/ VI FDC	Participants who received FF
Started	454	448
Completed	433	431
Not completed	21	17
Consent withdrawn by subject	16	14
Site Closed	4	3
Lost to follow-up	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 2402 participants were screened, 906 patients were randomized of which 4 participants did not receive study treatment. 902 participants received at least 1 dose of
study medication creating the ITT Population for which baseline characteristics are reported.

Baseline characteristics

Reporting groups

Reporting group title	Participants who received FF/ VI FDC

Reporting group description:

5-11 years old pediatric population were administered FF/VI as a FDC of 50/25 micrograms (mcg) and the 12-17 years old adolescent population received 100/25 mcg once daily via ELLIPTA dry powder inhaler (DPI). Each participant, in addition used albuterol/salbutamol (inhalation aerosol or nebuliser) as required throughout the entire study period as rescue medication for symptomatic relief of asthma symptoms.

Reporting group title	Participants who received FF

Reporting group description:

5-11 years old pediatric population were administered FF/VI as a monotherapy of 50 mcg and the 12-17 years old adolescent population received 100 mcg once daily via ELLIPTA DPI. Each participant, in addition used albuterol/salbutamol (inhalation aerosol or nebuliser) as required throughout the entire study period as rescue medication for symptomatic relief of asthma symptoms.

Reporting group values	Participants who received FF/ VI FDC	Participants who received FF	Total
Number of subjects	454	448	902
Age categorical Units: Subjects			
>=5 years to <=7 years	102	100	202
>=8 years to <=11 years	235	236	471
>=12 years to <=17 years	117	112	229
Sex: Female, Male Units: Participants			
Female	165	191	356
Male	289	257	546
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	34	40	74
American Indian or Alaska Native	22	29	51
Asian	32	26	58
Multiple	31	33	64
White	335	320	655
Age, Continuous Units: Years			
arithmetic mean	9.9	10.0	
standard deviation	± 3.02	± 2.97	-

End points reporting groups

Reporting group title	Participants who received FF/ VI FDC

Reporting group description:

5-11 years old pediatric population were administered FF/VI as a FDC of 50/25 micrograms (mcg) and the 12-17 years old adolescent population received 100/25 mcg once daily via ELLIPTA dry powder inhaler (DPI). Each participant, in addition used albuterol/salbutamol (inhalation aerosol or nebuliser) as required throughout the entire study period as rescue medication for symptomatic relief of asthma symptoms.

Reporting group title	Participants who received FF

Reporting group description:

5-11 years old pediatric population were administered FF/VI as a monotherapy of 50 mcg and the 12-17 years old adolescent population received 100 mcg once daily via ELLIPTA DPI. Each participant, in addition used albuterol/salbutamol (inhalation aerosol or nebuliser) as required throughout the entire study period as rescue medication for symptomatic relief of asthma symptoms.

Subject analysis set title	Participants receiving FF/ VI FDC (5-11 year old population)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subset of the ITT Population for pediatric participants of age 11 years and younger at Screening who were administered FF/VI as a FDC of 50/25 mcg.

Subject analysis set title	Participants receiving FF (5-11 year old population)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subset of the ITT Population for pediatric participants of age 11 years and younger at Screening who were administered FF as a monotherapy of 50 mcg.

Primary: Absolute weighted mean of forced expiratory volume in 1 second (FEV1) (0-4 hours) at week 12 in 5-17 years old population

End point title	Absolute weighted mean of forced expiratory volume in 1 second (FEV1) (0-4 hours) at week 12 in 5-17 years old population

End point description:

Pulmonary function was measured by FEV1, defined as the maximal amount of air that can be forcefully exhaled in one second using a standardized calibrated spirometer. Weighted mean FEV1 was derived using the post-dose assessments (after 30 minutes and 1, 2, 3, 4 hours) with their actual times and using the pre-dose assessment as the 0 hour measurement. ITT (5-17 years old) included all randomized participants who received at least one dose of study treatment. Only those participants with data available at specified time points have been analyzed.

End point type	Primary

End point timeframe:

Week 12

End point values	Participants who received FF/ VI FDC	Participants who received FF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	397	399		
Units: Litres				
arithmetic mean (standard deviation)	2.082 (± 0.7598)	1.994 (± 0.6998)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using analysis of covariance (ANCOVA) with covariates of baseline, region, sex, age and treatment.	
Comparison groups	Participants who received FF/ VI FDC v Participants who received FF
Number of subjects included in analysis	796
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	0.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.129

Primary: Change from baseline in mean pre-dose morning peak expiratory flow (AM PEF) in 5-11 years old population

End point title	Change from baseline in mean pre-dose morning peak expiratory flow (AM PEF) in 5-11 years old population
End point description:	
PEF was defined as the maximum speed of expiration of a participant. PEF was measured 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. The best of three measurements were recorded in the electronic patient diary. The mean morning PEF was calculated for each participant as an averaged mean over weeks 1-12 of the treatment period. Baseline was defined as the average of measurements with a non-missing value from Day -6 to Day 1 of pre-dose. Intent-to treat (ITT) (5- 11 years old) was a subset of the ITT (5-17 Years Old) population for participants 11 years old and younger at screening (Visit 1). Only those participants with data available at specified time points have been analyzed.	
End point type	Primary
End point timeframe:	
Baseline and Week 1-12	

End point values	Participants receiving FF/ VI FDC (5-11 year old population)	Participants receiving FF (5-11 year old population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	336	335		
Units: Litres per minute (L/min)				
arithmetic mean (standard deviation)	11.9 (± 37.63)	8.9 (± 35.62)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using ANCOVA with covariates of baseline, region, sex, age and treatment.	
Comparison groups	Participants receiving FF/ VI FDC (5-11 year old population) v Participants receiving FF (5-11 year old population)
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.228
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	8.4

Secondary: Change from baseline in mean pre-dose AM PEF in 5-17 years old population

End point title	Change from baseline in mean pre-dose AM PEF in 5-17 years old population

End point description:

PEF was defined as the maximum speed of expiration of a participant. PEF was measured 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. The best of three measurements were recorded in the daily diary. The mean morning PEF was calculated for each participant as an averaged mean over weeks 1-12 of the treatment period. Baseline was defined as the average of measurements with a non-missing value from Day -6 to Day 1 of pre-dose. Analysed population was ITT (5-17 years old). Only those participants with data available at specified time points has been analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 1-12

End point values	Participants who received FF/ VI FDC	Participants who received FF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	453	447		
Units: L/min				
arithmetic mean (standard deviation)	14.9 (± 39.94)	9.3 (± 38.95)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using ANCOVA with covariates of baseline, region, sex, age and treatment.	
Comparison groups	Participants who received FF/ VI FDC v Participants who received FF
Number of subjects included in analysis	900
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	10.9

Secondary: Absolute weighted mean of FEV1 (0-4 hours) at week 12 in 5-11 years old population

End point title	Absolute weighted mean of FEV1 (0-4 hours) at week 12 in 5-11 years old population
End point description:	
Pulmonary function was measured by FEV1, defined as the maximal amount of air that can be forcefully exhaled in one second using a standardized calibrated spirometer. Weighted mean FEV1 was derived using the post-dose assessments (after 30 minutes and 1, 2, 3, 4 hours) with their actual times and using the pre-dose assessment as the 0 hour measurement. ITT (5- 11 years old). Only those participants with data available at specified time points has been analyzed.	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Participants receiving FF/ VI FDC (5-11 year old population)	Participants receiving FF (5-11 year old population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	286	289		
Units: Litres				
arithmetic mean (standard deviation)	1.772 (± 0.0161)	1.700 (± 0.0160)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using ANCOVA with covariates of baseline, region, sex, age and treatment.	
Comparison groups	Participants receiving FF/ VI FDC (5-11 year old population) v Participants receiving FF (5-11 year old population)
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	0.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.028
upper limit	0.118

Secondary: Change from baseline in the percentage of rescue-free 24-hour periods over weeks 1-12 of the treatment period in 5-17 years old population

End point title	Change from baseline in the percentage of rescue-free 24-hour periods over weeks 1-12 of the treatment period in 5-17 years old population

End point description:

The number of inhalations of rescue albuterol/salbutamol aerosol used during the day and night were recorded in a daily electronic diary. Percentages of rescue-free 24-hour periods was calculated based on the number of 24-hour periods on which a participant recorded no use of albuterol/salbutamol divided by the length of the time period being assessed (with non-missing values of rescue medication recorded, respectively). A 24-hour period in which the response of participants to both the morning and evening assessments indicated no use of rescue medication was considered as rescue free. Baseline was calculated from the evening (Day -7 to Day -1) and morning (Day -6 to Day 1) measurements. Change from Baseline was calculated as the averaged value during the 12-week treatment period minus the Baseline value. Analysed population was ITT (5-17 years old). Only those participants with data available at specified time points has been analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 1-12

End point values	Participants who received FF/ VI FDC	Participants who received FF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	453	447		
Units: Percentage				
arithmetic mean (standard deviation)	25.9 (± 33.78)	25.8 (± 36.55)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using ANCOVA with covariates of baseline, region, sex, age and treatment.	
Comparison groups	Participants who received FF/ VI FDC v Participants who received FF
Number of subjects included in analysis	900
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	3.8

Secondary: Change from baseline in the percentage of symptom-free 24-hour periods over weeks 1-12 of the treatment period in 5-17 years old population

End point title	Change from baseline in the percentage of symptom-free 24-hour periods over weeks 1-12 of the treatment period in 5-17 years old population

End point description:

The symptom-free days were recorded in a daily electronic diary every day in the morning and evening before taking any rescue or study medication and before the PEF measurement. Percentages of symptom-free 24-hour periods was calculated based on the number of 24-hour periods on which a participant recorded no symptoms divided by the length of the time period being assessed (with non-missing values of rescue medication recorded, respectively). A 24-hour period in which the response of participants to both the morning and evening assessments indicated no symptoms was considered as symptom free. Baseline was calculated from evening (Day -7 to Day -1) and morning (Day -6 to Day 1) measurements. Change from Baseline was calculated as the averaged value during the 12-week treatment period minus the Baseline value. Analysed population was ITT (5-17 years old). Only those participants with data available at specified time points has been analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 1-12

End point values	Participants who received FF/ VI FDC	Participants who received FF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	453	447		
Units: Percentage				
arithmetic mean (standard deviation)	25.7 (± 32.77)	24.6 (± 34.62)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using ANCOVA with covariates of baseline, region, sex, age and treatment.	
Comparison groups	Participants who received FF/ VI FDC v Participants who received FF
Number of subjects included in analysis	900
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.988
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	4.1

Secondary: Change from baseline in morning (AM) FEV1 at week 12 in 5-17 years old population

End point title	Change from baseline in morning (AM) FEV1 at week 12 in 5-17 years old population
End point description:	
Pulmonary function was measured by FEV1, defined as the maximal amount of air that can be forcefully exhaled in one second. Morning FEV1 was measured using the pre-dose serial spirometry assessment at the Week 12. Baseline was defined as the pre-dose assessment with a non missing value on Visit 2 (Day -5). Analysed population was ITT (5-17 years old). Only those participants with data available at specified time points have been analyzed.	
End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Participants who received FF/ VI FDC	Participants who received FF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	417	413		
Units: Litres				
arithmetic mean (standard deviation)	0.312 (± 0.3865)	0.275 (± 0.3512)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using a repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit by baseline interaction and visit by treatment group interaction

Comparison groups	Participants who received FF v Participants who received FF/ VI FDC
Number of subjects included in analysis	830
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.124
Method	Repeated measures analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.035
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	-0.01
upper limit	0.08

Secondary: Change from Baseline in asthma control questionnaire (ACQ-5) Score at week 24 in 5-17 years old population

End point title	Change from Baseline in asthma control questionnaire (ACQ-5) Score at week 24 in 5-17 years old population

End point description:

Asthma control as measured by improvements in ACQ-5, a five-item questionnaire with response options for each question rated from 0 to 6 scale. A score of 0 indicates well controlled asthma and a score of 6 indicates extremely poorly controlled asthma. Individual questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath and wheeze) are equally weighted and the ACQ-5 score is calculated as the mean of these 5 item responses. A lower mean score indicates greater asthma control and higher mean score indicates lesser asthma control. Baseline was defined as the pre-dose assessment with a non missing value on Visit 3 (Day 1). Analysed population was ITT (5-17 years old). Only those participants with data available at specified time points has been analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Participants who received FF/ VI FDC	Participants who received FF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	385	378		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-1.21 (± 0.935)	-1.09 (± 0.976)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using a repeated measures ANCOVA adjusted for baseline, region, sex, age, treatment, visit, visit by baseline interaction and visit by treatment group interaction.

Comparison groups	Participants who received FF/ VI FDC v Participants who received FF
Number of subjects included in analysis	763
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.91
Method	Repeated measures analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.09

Secondary: Change from baseline in the percentage of rescue-free 24-hour periods over weeks 1-12 of the treatment period in 5-11 years old population

End point title	Change from baseline in the percentage of rescue-free 24-hour periods over weeks 1-12 of the treatment period in 5-11 years old population

End point description:

The number of inhalations of rescue albuterol/salbutamol aerosol used during the day and night were recorded in a daily electronic diary. Percentages of rescue-free 24-hour periods was calculated based on the number of 24-hour periods on which a participant recorded no use of albuterol/salbutamol divided by the length of the time period being assessed (with non-missing values of rescue medication recorded, respectively). A 24-hour period in which the response of participants to both the morning and evening assessments indicated no use of rescue medication was considered as rescue free. Baseline was calculated from the evening (Day -7 to Day -1) and morning (Day -6 to Day 1) measurements. Change from Baseline was calculated as the averaged value during the 12-week treatment period minus the Baseline value. Analysed population was ITT (5- 11 years old). Only those participants with data available at specified time points has been analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 1-12

End point values	Participants receiving FF/ VI FDC (5-11 year old population)	Participants receiving FF (5-11 year old population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	336	335		
Units: Percentage				
arithmetic mean (standard deviation)	27.3 (± 34.4)	25.6 (± 37.03)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using ANCOVA with covariates of baseline, region, sex, age and treatment.	
Comparison groups	Participants receiving FF/ VI FDC (5-11 year old population) v Participants receiving FF (5-11 year old population)
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.614
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	6.2

Secondary: Change from baseline in the percentage of symptom-free 24-hour periods over weeks 1-12 of the treatment period in 5-11 years old population

End point title	Change from baseline in the percentage of symptom-free 24-hour periods over weeks 1-12 of the treatment period in 5-11 years old population

End point description:

The symptom-free days were recorded in a daily electronic diary every day in the morning and evening before taking any rescue or study medication and before the PEF measurement. Percentages of symptom-free 24-hour periods was calculated based on the number of 24-hour periods on which a participant recorded no symptoms divided by the length of the time period being assessed (with non-missing values of rescue medication recorded, respectively). A 24-hour period in which the response of participants to both the morning and evening assessments indicated no symptoms was considered as symptom free. Baseline was calculated from evening (Day -7 to Day -1) and morning (Day -6 to Day 1) measurements. Change from Baseline was calculated as the averaged value during the 12-week treatment period minus the Baseline value. Analysed population was ITT (5- 11 years old). Only those participants with data available at specified time points has been analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 1-12

End point values	Participants receiving FF/ VI FDC (5-11 year old population)	Participants receiving FF (5-11 year old population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	336	335		
Units: Percentage				
arithmetic mean (standard deviation)	27.2 (± 833.16)	25.8 (± 34.94)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using ANCOVA with covariates of baseline, region, sex, age and treatment.	
Comparison groups	Participants receiving FF/ VI FDC (5-11 year old population) v Participants receiving FF (5-11 year old population)
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.594
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	6.3

Secondary: Change from baseline in morning (AM) FEV1 at week 12 in 5-11 years old population

End point title	Change from baseline in morning (AM) FEV1 at week 12 in 5-11 years old population

End point description:

Pulmonary function was measured by FEV1, defined as the maximal amount of air that can be forcefully exhaled in one second. Morning FEV1 was measured using the pre-dose serial spirometry assessment at the Week 12. Baseline was defined as the pre-dose assessment with a non missing value on Visit 2 (Day -5). Analysed population was ITT (5- 11 years old). Only those participants with data available at specified time points have been analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Participants receiving FF/ VI FDC (5-11 year old population)	Participants receiving FF (5-11 year old population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	307	304		
Units: Litres				
arithmetic mean (standard deviation)	0.263 (± 0.3029)	0.245 (± 0.3192)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using a repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit by baseline interaction and visit by treatment group interaction.

Comparison groups	Participants receiving FF/ VI FDC (5-11 year old population) v Participants receiving FF (5-11 year old population)
Number of subjects included in analysis	611
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.226
Method	Repeated measures analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.017
upper limit	0.073

Secondary: Change from baseline in ACQ-5 Score at week 24 in 5-11 years old population

End point title	Change from baseline in ACQ-5 Score at week 24 in 5-11 years old population

End point description:

Asthma control as measured by improvements in ACQ-5, a five-item questionnaire with response options for each question rated from 0 to 6 scale. A score of 0 indicates well controlled asthma and a score of 6 indicates extremely poorly controlled asthma. Individual questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath and wheeze) are equally weighted and the ACQ-5 score is calculated as the mean of these 5 item responses. A lower mean score indicates greater asthma control and higher mean score indicates lesser asthma control. Baseline was defined as the pre-dose assessment with a non missing value on Visit 3 (Day 1). Analysed population was ITT (5- 11 years old). Only those participants with data available at specified time points has been analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Participants receiving FF/ VI FDC (5-11 year old population)	Participants receiving FF (5-11 year old population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	291	286		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-1.25 (± 0.944)	-1.13 (± 0.975)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using a repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit by baseline interaction and visit by treatment group interaction.

Comparison groups	Participants receiving FF/ VI FDC (5-11 year old population) v Participants receiving FF (5-11 year old population)
Number of subjects included in analysis	577
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.663
Method	Repeated measures analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.09

Secondary: Number of participants with adverse events (AEs) and serious adverse events (SAEs) in 5-17 years old population

End point title	Number of participants with adverse events (AEs) and serious adverse events (SAEs) in 5-17 years old population

End point description:

An AE is any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. SAE is defined as any untoward medical occurrence that, at any dose: results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent disability/incapacity; is a congenital anomaly/birth defect and important medical events may jeopardize the participant or may require medical or surgical intervention/SOC to prevent one of the other outcomes mentioned before. Analysed population was ITT (5-17 years old).

End point type	Secondary

End point timeframe:

Up to week 25

End point values	Participants who received FF/ VI FDC	Participants who received FF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	454	448		
Units: Participants				
AEs	183	164		
SAEs	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal electrocardiogram (ECG) findings in 5-17 years old population

End point title	Number of participants with abnormal electrocardiogram (ECG) findings in 5-17 years old population

End point description:

A single 12-lead ECG was obtained using an ECG machine that automatically calculates the heartrate and measures PR, QRS, QT, and QT interval corrected (QTc). Analysed population was ITT (5-17 years old). Only those participants with data available at specified time points has been analyzed.

End point type	Secondary

End point timeframe:

Week 24

End point values	Participants who received FF/ VI FDC	Participants who received FF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	402	398		
Units: Participants	64	49		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in fasting glucose in 5-17 years old population

End point title	Change from baseline in fasting glucose in 5-17 years old population

End point description:

Blood samples were collected for evaluation of fasting blood glucose pre and post-treatment. Baseline was defined as Visit 1 (Screening). Analysed population was ITT (5- 11 years old). Only those participants with data available at specified time point have been analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Participants who received FF/ VI FDC	Participants who received FF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	370	388		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.12 (± 0.587)	-0.15 (± 0.626)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with incidence of an asthma exacerbation over the 24-week treatment period in 5-17 years old population

End point title	Number of participants with incidence of an asthma exacerbation over the 24-week treatment period in 5-17 years old population

End point description:

Asthma exacerbation was defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension or injection) for at least three days or a single depot corticosteroid injection or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. Analysed population was ITT (5-17 years old)

End point type	Secondary

End point timeframe:

Up to week 24

End point values	Participants who received FF/ VI FDC	Participants who received FF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	454	448		
Units: Participants	33	38		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with AEs and SAEs in 5-11 years old population

End point title	Number of participants with AEs and SAEs in 5-11 years old population

End point description:

An AE is any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. SAE is defined as any untoward medical occurrence that, at any dose: results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent disability/incapacity; is a congenital anomaly/birth defect and important medical events may jeopardize the participant or may require medical or surgical intervention/Standard of care (SOC) to prevent one of the other outcomes mentioned before. Analysed population was ITT (5-11 years old).

End point type	Secondary

End point timeframe:

Up to week 25

End point values	Participants receiving FF/ VI FDC (5-11 year old population)	Participants receiving FF (5-11 year old population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	337	336		
Units: Participants				
AEs	133	122		
SAEs	4	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal ECG findings in 5-11 years old population

End point title	Number of participants with abnormal ECG findings in 5-11 years old population

End point description:

A single 12-lead ECG was obtained using an ECG machine that automatically calculates the heartrate and measures PR, QRS, QT, and QTc. Analysed population was ITT (5-11 years old). Only those participants with data available at specified time points has been analyzed.

End point type	Secondary

End point timeframe:

Week 24

End point values	Participants receiving FF/ VI FDC (5-11 year old population)	Participants receiving FF (5-11 year old population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	303	298		
Units: Participants	53	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in fasting glucose in 5-11 years old population

End point title	Change from baseline in fasting glucose in 5-11 years old population

End point description:

Blood samples were collected for evaluation of fasting blood glucose pre and post-treatment. Baseline was defined as Visit 1 (screening). Analysed population was ITT (5- 11 years old). Only those participants with data available at specified time point have been analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Participants receiving FF/ VI FDC (5-11 year old population)	Participants receiving FF (5-11 year old population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	274	288		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.13 (± 0.563)	-0.17 (± 0.638)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any incidence of asthma exacerbation over the 24-week treatment period in 5-11 years old population

End point title	Number of participants with any incidence of asthma exacerbation over the 24-week treatment period in 5-11 years old population

End point description:

Asthma exacerbation was defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension or injection) for at least three days or a single depot corticosteroid injection or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. Analysis was performed on the ITT (5-11 years old) population.

End point type	Secondary

End point timeframe:

Up to week 24

End point values	Participants receiving FF/ VI FDC (5-11 year old population)	Participants receiving FF (5-11 year old population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	337	336		
Units: Participants	27	32		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All cause mortality, Non-serious adverse events (Non-SAEs) and serious adverse events (SAEs) were collected up to 25 weeks (which included one week of follow up contact after completion of the treatment period).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Participants aged 5-17 years who received FF/ VI FDC

Reporting group description:

Participants aged 5 to 11 years received FDC of 50 mcg/ 25 mcg and 12 to 17 years received FDC of 100 mcg/ 25 mcg of FF/VI. Both age groups received dose once daily in the morning via ELLIPTA dry powder inhaler (DPI).

Reporting group title	Participants aged 5-17 years who received FF

Reporting group description:

Participants aged 5 to 11 years received 50 mcg and aged 12 to 17 years received 100 mcg of FF. Both age groups received dose once daily in the morning via ELLIPTA DPI.

Serious adverse events	Participants aged 5-17 years who received FF/ VI FDC	Participants aged 5-17 years who received FF	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 454 (1.10%)	5 / 448 (1.12%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	1 / 454 (0.22%)	0 / 448 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 454 (0.44%)	3 / 448 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			

subjects affected / exposed	1 / 454 (0.22%)	0 / 448 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 454 (0.22%)	0 / 448 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis			
subjects affected / exposed	0 / 454 (0.00%)	1 / 448 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 454 (0.00%)	1 / 448 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Participants aged 5-17 years who received FF/ VI FDC	Participants aged 5-17 years who received FF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 454 (23.57%)	71 / 448 (15.85%)	
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 454 (3.08%)	9 / 448 (2.01%)	
occurrences (all)	23	13	
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	19 / 454 (4.19%)	6 / 448 (1.34%)	
occurrences (all)	22	8	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	47 / 454 (10.35%)	34 / 448 (7.59%)	
occurrences (all)	60	42	
Rhinitis			

subjects affected / exposed	15 / 454 (3.30%)	6 / 448 (1.34%)	
occurrences (all)	16	6	
Upper respiratory tract infection			
subjects affected / exposed	32 / 454 (7.05%)	25 / 448 (5.58%)	
occurrences (all)	42	27	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 June 2019	Amendment 01: The aim of this amendment was to aid in the recruitment of participants in this study. The changes will allow flexibility to perform spirometry maneuvers during screening especially in the younger participants.
10 December 2019	Amendment 02: The changes in this amendment took into account the variability in asthma by allowing re-screening, and also by increasing the maximum permitted FEV1 at screening and randomisation to 100% predicted normal. These changes were made to help with recruitment of this population.
13 January 2020	Amendment 03: The aim of this amendment was to specify that Visit 4 to no longer be considered optional parent only visit. As Visit 4 is the first visit after randomization to study treatment, it is considered an important visit at which to collect clinical data.
24 August 2020	Amendment 04: The aim was to allow the option for certain visits to either be conducted at home by a qualified nurse or replaced by video-calls with the site, when appropriate and if permitted by local regulations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported