Clinical trial results:
201832: A Randomised, Double-Blind, Double-Dummy,Crossover Comparison of Fluticasone Furoate/Vilanterol 100/25 mcg Once Daily Versus Fluticasone Propionate 250 mcg Twice Daily in Adolescent and Adult Subjects with Asthma and Exercise-Induced Bronchoconstriction.

Summary

EudraCT number	2017-001516-11
Trial protocol	Outside EU/EEA
Global end of trial date	03 February 2017

Results information

Result version number	v2 (current)
This version publication date	01 November 2017
First version publication date	12 August 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	201832

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the protective effect of fluticasone furoate/vilanterol (FF/VI) 100/25 mcg once-daily compared with fluticasone propionate (FP) 250 mcg twice-daily against exercise-induced bronchoconstriction in adolescent and adult subjects aged 12 to 50 with persistent asthma.

Protection of trial subjects:

Study specific stopping criteria were included in the protocol including stopping for liver events, QTc changes, severe asthma exacerbation, worsening of asthma requiring additional treatment, and pregnancy.
In relation to the exercise challenges, these could be stopped at any time and rescue medication could be given at any time if required. In addition, specific guidelines were given for when rescue medication must be provided i.e. if FEV1 dropped to >=40%. If rescue medication other than salbutamol or ipratropium was required, the patient was to be withdrawn from the study. Exercise challenges were carefully managed with a gradual warm up over 2 minutes and a gradual stop. Handrails were in place on the treadmills to aid the subject should they need them. Subjects not thought able to complete the exercise challenge were not recruited into the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 May 2016
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	Canada: 2
Country: Number of subjects enrolled	United States: 72
Worldwide total number of subjects	74
EEA total number of subjects	0

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)	17
Adults (18-64 years)	57
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multicenter, randomized, double-blind, double-dummy, crossover comparison study of fluticasone furoate (FF)/vilanterol (VI) versus fluticasone propionate (FP) in adolescent and adult participants with asthma and exercise-induced bronchoconstriction (EIB). The study was conducted in two countries–United States and Canada.

Pre-assignment

Screening details:

The study consisted of 4-week single-blind run-in, 2-week double-blind treatment period 1, 2-week single-blind wash out, 2-week double-blind treatment period 2 and 1-week Follow-up. A total of 163 participants were screened, 75 were randomized and 74 were included in Intent-To-Treat (ITT) Population who received at least 1 dose of trial medication.

Period 1

Period 1 title	Treatment period 1 (2 weeks)
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 µg followed by FP 250 µg

Arm description:

After screening, the eligible participants entered a 4-week single blind run-in period on FP 250 microgram (µg) twice daily (BID) following which the participants were randomized to receive FF/VI 100/25 µg once daily (QD) via ELLIPTA + Placebo BID via DISKUS in treatment period 1 followed by a 2-week single blind wash-out period on FP 250 µg BID. The participants then received FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA in treatment period 2. The participants were followed up for approximately 7 days after completing Treatment Period 2. Albuterol/salbutamol was issued for rescue use during the run-in, wash-out and treatment periods as needed

Arm type	Experimental
Investigational medicinal product name	FF/VI 100/25 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

100 µg of FF blended with lactose in the first strip and 25 µg of vilanterol blended with lactose and magnesium stearate in the second strip was administered via ELLIPTA inhaler QD in the evening.

Investigational medicinal product name	FP 250 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

250 µg of FP blended with lactose was administered via DISKUS/ACCUHALER inhaler BID, once in the morning and once in the evening.

Investigational medicinal product name	Placebo ELLIPTA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Placebo was administered QD in the evening via ELLIPTA inhaler containing lactose in the first strip and a blend of lactose and magnesium stearate in the second strip.

Investigational medicinal product name	Placebo DISKUS/ACCUHALER
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Lactose was administered BID, once in the morning and once in the evening via DISKUS/ACCUHALER.

Arm title	FP 250 µg followed by FF/VI 100/25 µg

Arm description:

After screening, the eligible participants entered a 4-week single blind run-in period on FP 250 µg BID following which the participants were randomized to receive FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA in treatment period 1 followed by a 2-week single blind wash-out period on FP 250 µg BID. The participants then received FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS in treatment period 2. The participants were followed up for approximately 7 days after completing Treatment Period 2. Albuterol/salbutamol was issued for rescue use during the run-in, wash-out and treatment periods as needed.

Arm type	Experimental
Investigational medicinal product name	FF/VI 100/25 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

100 µg of FF blended with lactose in the first strip and 25 µg of vilanterol blended with lactose and magnesium stearate in the second strip was administered via ELLIPTA inhaler QD in the evening.

Investigational medicinal product name	FP 250 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

250 µg of FP blended with lactose was administered via DISKUS/ACCUHALER inhaler BID, once in the morning and once in the evening.

Investigational medicinal product name	Placebo ELLIPTA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Placebo was administered QD in the evening via ELLIPTA inhaler containing lactose in the first strip and a blend of lactose and magnesium stearate in the second strip.

Investigational medicinal product name	Placebo DISKUS/ACCUHALER
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Lactose was administered BID, once in the morning and once in the evening via DISKUS/ACCUHALER.

Number of subjects in period 1	FF/VI 100/25 µg followed by FP 250 µg	FP 250 µg followed by FF/VI 100/25 µg
Started	37	37
Completed	36	37
Not completed	1	0
Adverse event, non-fatal	1	-

Period 2

Period 2 title	Wash-out period (2 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	FF/VI 100/25 µg followed by FP 250 µg

Arm description:

After screening, the eligible participants entered a 4-week single blind run-in period on FP 250 microgram (µg) twice daily (BID) following which the participants were randomized to receive FF/VI 100/25 µg once daily (QD) via ELLIPTA + Placebo BID via DISKUS in treatment period 1 followed by a 2-week single blind wash-out period on FP 250 µg BID. The participants then received FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA in treatment period 2. The participants were followed up for approximately 7 days after completing Treatment Period 2. Albuterol/salbutamol was issued for rescue use during the run-in, wash-out and treatment periods as needed

Arm type	Experimental
Investigational medicinal product name	FF/VI 100/25 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

100 µg of FF blended with lactose in the first strip and 25 µg of vilanterol blended with lactose and magnesium stearate in the second strip was administered via ELLIPTA inhaler QD in the evening.

Investigational medicinal product name	FP 250 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

250 µg of FP blended with lactose was administered via DISKUS/ACCUHALER inhaler BID, once in the morning and once in the evening.

Investigational medicinal product name	Placebo ELLIPTA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Placebo was administered QD in the evening via ELLIPTA inhaler containing lactose in the first strip and a blend of lactose and magnesium stearate in the second strip.

Investigational medicinal product name	Placebo DISKUS/ACCUHALER
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Lactose was administered BID, once in the morning and once in the evening via DISKUS/ACCUHALER.

Arm title	FP 250 µg followed by FF/VI 100/25 µg

Arm description:

After screening, the eligible participants entered a 4-week single blind run-in period on FP 250 µg BID following which the participants were randomized to receive FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA in treatment period 1 followed by a 2-week single blind wash-out period on FP 250 µg BID. The participants then received FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS in treatment period 2. The participants were followed up for approximately 7 days after completing Treatment Period 2. Albuterol/salbutamol was issued for rescue use during the run-in, wash-out and treatment periods as needed.

Arm type	Experimental
Investigational medicinal product name	FF/VI 100/25 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

100 µg of FF blended with lactose in the first strip and 25 µg of vilanterol blended with lactose and magnesium stearate in the second strip was administered via ELLIPTA inhaler QD in the evening.

Investigational medicinal product name	Placebo ELLIPTA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Placebo was administered QD in the evening via ELLIPTA inhaler containing lactose in the first strip and a blend of lactose and magnesium stearate in the second strip.

Investigational medicinal product name	FP 250 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

250 µg of FP blended with lactose was administered via DISKUS/ACCUHALER inhaler BID, once in the morning and once in the evening.

Investigational medicinal product name	Placebo DISKUS/ACCUHALER
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Lactose was administered BID, once in the morning and once in the evening via DISKUS/ACCUHALER.

Number of subjects in period 2	FF/VI 100/25 µg followed by FP 250 µg	FP 250 µg followed by FF/VI 100/25 µg
Started	36	37
Completed	35	36
Not completed	1	1
Consent withdrawn by subject	1	-
Protocol deviation	-	1

Period 3

Period 3 title	Treatment Period 2 (2 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	FF/VI 100/25 µg followed by FP 250 µg

Arm description:

After screening, the eligible participants entered a 4-week single blind run-in period on FP 250 microgram (µg) twice daily (BID) following which the participants were randomized to receive FF/VI 100/25 µg once daily (QD) via ELLIPTA + Placebo BID via DISKUS in treatment period 1 followed by a 2-week single blind wash-out period on FP 250 µg BID. The participants then received FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA in treatment period 2. The participants were followed up for approximately 7 days after completing Treatment Period 2. Albuterol/salbutamol was issued for rescue use during the run-in, wash-out and treatment periods as needed

Arm type	Experimental
Investigational medicinal product name	FF/VI 100/25 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

100 µg of FF blended with lactose in the first strip and 25 µg of vilanterol blended with lactose and magnesium stearate in the second strip was administered via ELLIPTA inhaler QD in the evening.

Investigational medicinal product name	FP 250 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

250 µg of FP blended with lactose was administered via DISKUS/ACCUHALER inhaler BID, once in the morning and once in the evening.

Investigational medicinal product name	Placebo ELLIPTA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Placebo was administered QD in the evening via ELLIPTA inhaler containing lactose in the first strip and a blend of lactose and magnesium stearate in the second strip.

Investigational medicinal product name	Placebo DISKUS/ACCUHALER
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Lactose was administered BID, once in the morning and once in the evening via DISKUS/ACCUHALER.

Arm title	FP 250 µg followed by FF/VI 100/25 µg

Arm description:

After screening, the eligible participants entered a 4-week single blind run-in period on FP 250 µg BID following which the participants were randomized to receive FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA in treatment period 1 followed by a 2-week single blind wash-out period on FP 250 µg BID. The participants then received FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS in treatment period 2. The participants were followed up for approximately 7 days after completing Treatment Period 2. Albuterol/salbutamol was issued for rescue use during the run-in, wash-out and treatment periods as needed.

Arm type	Experimental
Investigational medicinal product name	FF/VI 100/25 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

100 µg of FF blended with lactose in the first strip and 25 µg of vilanterol blended with lactose and magnesium stearate in the second strip was administered via ELLIPTA inhaler QD in the evening.

Investigational medicinal product name	FP 250 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

250 µg of FP blended with lactose was administered via DISKUS/ACCUHALER inhaler BID, once in the morning and once in the evening.

Investigational medicinal product name	Placebo ELLIPTA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Placebo was administered QD in the evening via ELLIPTA inhaler containing lactose in the first strip and a blend of lactose and magnesium stearate in the second strip.

Investigational medicinal product name	Placebo DISKUS/ACCUHALER
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Lactose was administered BID, once in the morning and once in the evening via DISKUS/ACCUHALER.

Number of subjects in period 3	FF/VI 100/25 µg followed by FP 250 µg	FP 250 µg followed by FF/VI 100/25 µg
Started	35	36
Completed	33	36
Not completed	2	0
Adverse event, non-fatal	1	-
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Treatment period 1 (2 weeks)

Reporting group description:

After screening, the eligible participants entered a 4-week single blind run-in period on FP 250 µg BID following which the participants were randomized to one of the following two treatment sequences in a ratio of 1:1: FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS in treatment period 1 followed by FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA in treatment period 2 or FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA in treatment period 1 followed by FF/VI 100/25 µg once daily (QD) via ELLIPTA + Placebo BID via DISKUS in treatment period 2. All participants entered a 2-week single blind wash-out period on FP 250 µg BID between the two treatment periods. The participants were followed up for approximately 7 days after completing Treatment Period 2. Albuterol/salbutamol was issued for rescue use during the run-in, wash-out and treatment periods as needed.

Reporting group values	Treatment period 1 (2 weeks)	Total	
Number of subjects	74	74	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 27.8 ± 10.35	 -	
Gender categorical Units: Subjects			
Female	43	43	
Male	31	31	
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	28	28	
Asian - South East Asian Heritage	3	3	
White - White/Caucasian/European Heritage	42	42	
Mixed Race	1	1	

End points

End points reporting groups

Reporting group title	FF/VI 100/25 µg followed by FP 250 µg

Reporting group description:

After screening, the eligible participants entered a 4-week single blind run-in period on FP 250 microgram (µg) twice daily (BID) following which the participants were randomized to receive FF/VI 100/25 µg once daily (QD) via ELLIPTA + Placebo BID via DISKUS in treatment period 1 followed by a 2-week single blind wash-out period on FP 250 µg BID. The participants then received FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA in treatment period 2. The participants were followed up for approximately 7 days after completing Treatment Period 2. Albuterol/salbutamol was issued for rescue use during the run-in, wash-out and treatment periods as needed

Reporting group title	FP 250 µg followed by FF/VI 100/25 µg

Reporting group description:

After screening, the eligible participants entered a 4-week single blind run-in period on FP 250 µg BID following which the participants were randomized to receive FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA in treatment period 1 followed by a 2-week single blind wash-out period on FP 250 µg BID. The participants then received FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS in treatment period 2. The participants were followed up for approximately 7 days after completing Treatment Period 2. Albuterol/salbutamol was issued for rescue use during the run-in, wash-out and treatment periods as needed.

Reporting group title	FF/VI 100/25 µg followed by FP 250 µg

Reporting group description:

After screening, the eligible participants entered a 4-week single blind run-in period on FP 250 microgram (µg) twice daily (BID) following which the participants were randomized to receive FF/VI 100/25 µg once daily (QD) via ELLIPTA + Placebo BID via DISKUS in treatment period 1 followed by a 2-week single blind wash-out period on FP 250 µg BID. The participants then received FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA in treatment period 2. The participants were followed up for approximately 7 days after completing Treatment Period 2. Albuterol/salbutamol was issued for rescue use during the run-in, wash-out and treatment periods as needed

Reporting group title	FP 250 µg followed by FF/VI 100/25 µg

Reporting group description:

After screening, the eligible participants entered a 4-week single blind run-in period on FP 250 µg BID following which the participants were randomized to receive FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA in treatment period 1 followed by a 2-week single blind wash-out period on FP 250 µg BID. The participants then received FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS in treatment period 2. The participants were followed up for approximately 7 days after completing Treatment Period 2. Albuterol/salbutamol was issued for rescue use during the run-in, wash-out and treatment periods as needed.

Reporting group title	FF/VI 100/25 µg followed by FP 250 µg

Reporting group description:

After screening, the eligible participants entered a 4-week single blind run-in period on FP 250 microgram (µg) twice daily (BID) following which the participants were randomized to receive FF/VI 100/25 µg once daily (QD) via ELLIPTA + Placebo BID via DISKUS in treatment period 1 followed by a 2-week single blind wash-out period on FP 250 µg BID. The participants then received FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA in treatment period 2. The participants were followed up for approximately 7 days after completing Treatment Period 2. Albuterol/salbutamol was issued for rescue use during the run-in, wash-out and treatment periods as needed

Reporting group title	FP 250 µg followed by FF/VI 100/25 µg

Reporting group description:

After screening, the eligible participants entered a 4-week single blind run-in period on FP 250 µg BID following which the participants were randomized to receive FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA in treatment period 1 followed by a 2-week single blind wash-out period on FP 250 µg BID. The participants then received FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS in treatment period 2. The participants were followed up for approximately 7 days after completing Treatment Period 2. Albuterol/salbutamol was issued for rescue use during the run-in, wash-out and treatment periods as needed.

Subject analysis set title	FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS
Subject analysis set type	Sub-group analysis

Subject analysis set description:

FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS

Subject analysis set title	FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA
Subject analysis set type	Sub-group analysis

Subject analysis set description:

FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA

Primary: Maximal percent decrease in forced expiratory volume in one second (FEV1) following exercise challenge at 12 hours (hrs) post evening dose from pre-exercise FEV1.

End point title	Maximal percent decrease in forced expiratory volume in one second (FEV1) following exercise challenge at 12 hours (hrs) post evening dose from pre-exercise FEV1.

End point description:

The exercise challenge test is a stepped challenge on a treadmill. It was performed at 12 hrs post evening dose at the end of the 2-week treatment period, wherein the participants exercised sufficiently to reach a heart rate between 80 to 95 percent of their predicted maximum within 4 minutes (min) and maintained the heart rate with exercise for an additional 6 min followed immediately by serial assessments of FEV1 at 5, 10, 15, 30, 45 and 60 min post-exercise. Maximal percent decrease was calculated as pre-exercise FEV1 minus minimum post exercise FEV1 (smallest FEV1 value collected within one hr following exercise challenge) divided by pre-exercise FEV1 multiplied by 100. Pre-exercise FEV1 was defined as the FEV1 collected prior to the exercise challenge test at 12 hr post dose. ITT Population comprised of all participants randomized to treatment and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

At Week 2 of treatment period 1 and 2

End point values	FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS	FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70[1]	69		
Units: Percentage of FEV1				
least squares mean (standard error)				
Percentage of FEV1	15.02 (± 1.058)	16.71 (± 1.095)		

Notes:

[1] - ITT Population. Participants with non-missing covariates and data specific to endpoint were analyzed

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS v FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.109 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.76
upper limit	0.39

Notes:

[2] - Mixed model repeated measures analysis adjusted for fixed effects of treatment, sex, age, treatment period, smoking history, period Baseline FEV1 and the mean of the two period Baseline FEV1 values. Subject is fitted as a random effect.

Secondary: Maximal percent decrease in FEV1 following exercise challenge at 23 hrs post evening dose from pre-exercise FEV1.

End point title	Maximal percent decrease in FEV1 following exercise challenge at 23 hrs post evening dose from pre-exercise FEV1.

End point description:

The exercise challenge test is a stepped challenge on a treadmill. It was performed at 23 hrs post evening dose at the end of the 2-week treatment period, wherein the participants exercised sufficiently to reach a heart rate between 80 to 95 percent of their predicted maximum within 4 min and maintained the heart rate with exercise for an additional 6 min followed immediately by serial assessments of FEV1 at 5, 10, 15, 30, 45 and 60 min post-exercise. Maximal percent decrease was calculated as pre-exercise FEV1 minus minimum post exercise FEV1 (smallest FEV1 value collected within one hr following exercise challenge) divided by pre-exercise FEV1 multiplied by 100. Pre-exercise FEV1 was defined as the FEV1 collected prior to the exercise challenge test at 23 hr post dose.

End point type	Secondary

End point timeframe:

At Week 2 of treatment period 1 and 2

End point values	FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS	FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[3]	69		
Units: Percentage of FEV1				
least squares mean (standard error)				
Percentage of FEV1	11.90 (± 1.020)	14.05 (± 1.051)		

Notes:

[3] - ITT Population. Participants with non-missing covariates and data specific to endpoint were analyzed

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS v FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.051 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.31
upper limit	0.01

Notes:

[4] - Mixed model repeated measures analysis adjusted for fixed effects of treatment, sex, age, treatment period, smoking history, period Baseline FEV1 and the mean of the two period Baseline FEV1 values. Subject is fitted as a random effect.

Secondary: Proportion of participants with a 30 min post-challenge FEV1 no more than 5 percent lower than pre-exercise FEV1 following the exercise challenge at 12 hrs and 23 hrs post evening dose.

End point title	Proportion of participants with a 30 min post-challenge FEV1 no more than 5 percent lower than pre-exercise FEV1 following the exercise challenge at 12 hrs and 23 hrs post evening dose.

End point description:

The blinded treatment exercise challenge test was performed at the end of 2-weeks of treatment period 1 and treatment period 2 on a treadmill at 12 hrs and 23 hrs after administration of the evening dose of study treatment. The challenge was followed immediately by serial assessments of FEV1 at 5, 10, 15, 30, 45 and 60 min post-exercise. Pre-exercise FEV1 was defined as the FEV1 value collected prior to the exercise challenge test at 23 hrs post-dose. Number of participants listed is the number in the ITT population. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

At Week 2 of treatment period 1 and 2

End point values	FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS	FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	73[5]	72		
Units: Participants				
FEV1 >=95% of pre-exercise FEV1, 12 hrs; n=70, 69	34	29		
FEV1 < 95% of pre-exercise FEV1, 12 hrs; n=70, 69	36	40		
FEV1 >=95% of pre-exercise FEV1, 23 hrs; n=68, 69	42	37		
FEV1 < 95% of pre-exercise FEV1, 23 hrs; n=68, 69	26	32		

Notes:

[5] - ITT Population. Participants with non-missing covariates and data specific to endpoint were analyzed

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

12 hrs: modeling the odds of having FEV1 >/=95% of pre exercise FEV1 at each of the two time points.

Comparison groups	FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS v

	FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.266 [6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	2.26

Notes:

[6] - Repeated measures logistic regression model with parameters estimated using the Generalized Estimating Equation method. Covariates of treatment, sex, age, treatment period, and period baseline FEV1 were included.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

23 hrs: modeling the odds of having FEV1 >/=95% of pre exercise FEV1 at each of the two time points.

Comparison groups	FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS v FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.322 [7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	2.58

Notes:

[7] - Repeated measures logistic regression model with parameters estimated using the Generalized Estimating Equation method

Secondary: Weighted mean 0-60 min for percentage decrease from pre-exercise FEV1 following exercise challenge at 12 hrs and 23 hrs post evening dose.

End point title	Weighted mean 0-60 min for percentage decrease from pre-exercise FEV1 following exercise challenge at 12 hrs and 23 hrs post evening dose.

End point description:

The exercise challenge testing at the end of 2 week treatment period was performed on a treadmill at 12 hrs and 23 hrs after administration of the evening dose of double-blind treatment. Following exercise challenge testing, post-exercise FEV1 values were assessed serially at 5, 10, 15, 30, 45 and 60 min. Pre-exercise FEV1 was defined as the FEV1 value collected prior to the exercise challenge test at 23 hrs post-dose. Number of participants listed is the number in the ITT population. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

At Week 2 of treatment period 1 and 2

End point values	FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS	FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	73[8]	72		
Units: Percentage of FEV1				
least squares mean (standard error)				
12 hrs post-dose; n=67, 66	5.87 (± 0.663)	6.52 (± 0.680)		
23 hrs post-dose; n=68, 67	3.98 (± 0.699)	5.73 (± 0.747)		

Notes:

[8] - ITT Population. Participants with non-missing covariates and data specific to endpoint were analyzed

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: 12 hrs post-dose	
Comparison groups	FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA v FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.342 [9]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.01
upper limit	0.71

Notes:

[9] - Mixed model repeated measures analysis adjusted for fixed effects of treatment, sex, age, treatment period, smoking history, period Baseline FEV1 and the mean of the two period Baseline FEV1 values. Subject is fitted as a random effect.

Statistical analysis title	Statistical analysis 2
Statistical analysis description: 23 hrs post-dose	
Comparison groups	FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA v FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.041 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.75

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.42
upper limit	-0.07

Notes:

[10] - Mixed model repeated measures analysis adjusted for fixed effects of treatment, sex, age, treatment period, smoking history, period Baseline FEV1 and the mean of the two period Baseline FEV1 values.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The on-treatment adverse events (AEs) and serious adverse events (SAEs) were collected from the start of study treatment until the follow-up contact (approximately up to 51 days).

Adverse event reporting additional description:

ITT Population

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS

Reporting group description:

FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS

Reporting group title	FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA

Reporting group description:

FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA

Serious adverse events	FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS	FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	FF/VI 100/25 µg QD via ELLIPTA + Placebo BID via DISKUS	FP 250 µg BID via DISKUS + Placebo QD via ELLIPTA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 73 (6.85%)	4 / 72 (5.56%)	
Infections and infestations			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 73 (6.85%) 5	4 / 72 (5.56%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 August 2015	- To include an additional exercise challenge procedure at 23 hrs after the first dose of double-blinded study medication in each Treatment Period. The purpose is to demonstrate that inhaled FF/VI 100/25 µg provides improved bronchoprotection against EIB compared with FP 250 µg after 23 hrs of treatment with blinded medication. In addition, it will allow for an evaluation of the presence and extent of tachyphylaxis. - The study title was revised to indicate the study is a 'randomized' study with a 'crossover' design.
16 December 2015	- To increase the screen failure rate to 20 percent (from 10 percent) and the run-in failure rate to 70 percent (from 55 percent). This takes into consideration the challenge of enrolling EIB participants with Symptomatic Allergic Rhinitis (SAR) at screening and also the challenge for participants to demonstrate a decrease in FEV1 of >=20 percent at one time point within 30 min of the end of the exercise challenge at Visit 2 after taking FP for approximately four weeks during the run-in period. - The amendment also allows participants with SAR at screening to be treated with intranasal corticosteroids for up to four weeks, followed by a repeat screening visit to determine eligibility prior to entry into the study. Participants with SAR during the study may be treated with intranasal corticosteroids at a constant dose for the duration of the study. - The time window for the repeat exercise challenge has been extended from 24-48 hrs to up to one week; taking into consideration the challenge for participants to return within 48 hrs for a repeat procedure. - The Asthma Control Test (ACT) questionnaire has been replaced by the Asthma Control Questionnaire-5 (ACQ-5) questionnaire given the mismatch between treatment periods of two weeks and the recall period of 4 weeks for the ACT. - Tobacco/marijuana use and pregnancy have been added as exclusion criteria. - The secondary endpoint for time to recovery has been changed to a binary endpoint defining recovery as those participants who have a 30 min post-exercise FEV1 measurement that is no more than 5 percent lower than their pre-exercise FEV1. In addition, the statistical testing hierarchy has been changed to prioritize the maximal percentage FEV1 reduction (primary endpoint) and binary recovery endpoints following the 12 hr post-dose exercise challenge.
25 May 2016	- To adjust text to better reflect the intention of the protocol with regard to visit timing: Visit 2 (currently Day 1) redefined as Day 0 and Visit 3 (currently Day 2) redefined as Day 1. Visit window around Day 29 removed and footnote added. Text regarding timing of visits clarified to ensure that the intention of the protocol is clearly reflected. - Participant number will be assigned at Pre-Screening following informed consent rather than at Visit 1. - Nucala added as an example prohibited medication. - Rescue medication supply strategy has been removed. - Confirmation that post exercise vital signs will be immediately post exercise, not after 5 min of rest.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported