Clinical trial results:
HZA106853: A dose-ranging study of vilanterol (VI) inhalation powder in children aged 5-11 years with asthma on a background of inhaled corticosteroid therapy.

Summary

EudraCT number	2011-003337-34
Trial protocol	DE Outside EU/EEA PL SK
Global end of trial date	28 April 2014

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	28 March 2015

Trial information

Trial identification

Sponsor protocol code	HZA106853

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 8664357343,
Scientific contact	GSK Response Center, GlaxoSmithKline, +1 8664357343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000431-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the dose response, efficacy and safety of three doses of VI inhalation powder administered once daily in the evening in children aged 5-11 years with persistent uncontrolled asthma over a 4 week treatment period.

Protection of trial subjects:

The following steps were taken to protect trial participants:
1). Only participants meeting all of the inclusion criteria and none of the exclusion criteria were randomized to investigational medication.
2). All participants enrolled into the study were provided rescue medication for use as necessary.
3). Subject lung function, as measured by morning (AM) and evening (PM) peak expiratory flow (PEF), was monitored for stability through the use of a daily electronic diary.
4). The investigator or treating physician could have unblinded a participant's treatment assignment in the case of an emergency, when knowledge of the study treatment was essential for the appropriate clinical management or welfare of the participant.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 51
Country: Number of subjects enrolled	Slovakia: 32
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	South Africa: 12
Country: Number of subjects enrolled	Ukraine: 39
Country: Number of subjects enrolled	Peru: 150
Country: Number of subjects enrolled	Puerto Rico: 6
Country: Number of subjects enrolled	Argentina: 225
Country: Number of subjects enrolled	United States: 239
Country: Number of subjects enrolled	Philippines: 82
Country: Number of subjects enrolled	Georgia: 18
Country: Number of subjects enrolled	Chile: 114
Country: Number of subjects enrolled	Mexico: 153
Country: Number of subjects enrolled	Japan: 49

Worldwide total number of subjects	1208
EEA total number of subjects	121

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)	1208
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

1208 participants (par.) were screened; 760 were enrolled/entered the Run-in Phase, 463 were randomized, and 2 received study medication (SM) but weren't randomized/included in the Intent-to-Treat (ITT) Population (randomized to treatment and receiving >=1 SM dose). 7 randomized par. didn't receive SM; hence, 456 par. comprised the ITT Population.

Pre-assignment

Screening details:

Participants who met the eligibility criteria at screening (Visit 1) entered the Run-in Phase for completion of Baseline safety evaluations and measures of asthma status. Participants meeting all randomization criteria at Visit 3 were randomized to 1 of 4 treatment arms. The total duration of study participation was up to a maximum of 9 weeks.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo once daily (OD) in the evening from a dry powder inhaler for 4 weeks in addition to open-label fluticasone propionate (FP) 100 micrograms (µg) twice daily (BID). Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication.

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

Dosage and administration details:

Placebo once daily via a dry powder inhaler

Investigational medicinal product name	Fluticasone propionate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

100 µg twice daily via a dry powder inhaler

Arm title	VI 6.25 µg OD

Arm description:

Participants received vilanterol (VI) 6.25 µg OD in the evening from a dry powder inhaler for 4 weeks in addition to open-label FP 100 µg BID. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication.

Arm type	Experimental

Investigational medicinal product name	Vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

6.25 µg once daily via a dry powder inhaler

Investigational medicinal product name	Fluticasone propionate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

100 µg twice daily via a dry powder inhaler

Arm title	VI 12.5 µg OD

Arm description:

Participants received VI 12.5 µg OD in the evening from a dry powder inhaler for 4 weeks in addition to open-label FP 100 µg BID. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication.

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

Dosage and administration details:

12.5 µg once daily via a dry powder inhaler

Investigational medicinal product name	Fluticasone propionate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

100 µg twice daily via a dry powder inhaler

Arm title	VI 25 µg OD

Arm description:

Participants received VI 25 µg OD in the evening from a dry powder inhaler for 4 weeks in addition to open-label FP 100 µg BID. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication.

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

Dosage and administration details:

25 µg (micrograms) once daily via a dry powder inhaler

Investigational medicinal product name	Fluticasone propionate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

100 µg twice daily via a dry powder inhaler

Number of subjects in period 1[1]	Placebo	VI 6.25 µg OD	VI 12.5 µg OD
Started	115	114	113
Completed	93	93	99
Not completed	22	21	14
Physician decision	1	2	-
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	1	-
Lost to follow-up	-	1	1
Lack of efficacy	18	15	12
Protocol deviation	3	1	1

Number of subjects in period 1[1]	VI 25 µg OD
Started	114
Completed	90
Not completed	24
Physician decision	2
Consent withdrawn by subject	-
Adverse event, non-fatal	1
Lost to follow-up	1
Lack of efficacy	17
Protocol deviation	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: 1208 participants (par.) were screened; 760 were enrolled/entered the Run-in Phase, 463 were randomized, and 2 received study medication (SM) but weren't randomized/included in the Intent-to-Treat (ITT) Population (randomized to treatment and receiving >=1 SM dose). 7 randomized par. didn't receive SM; hence, 456 par. comprised the ITT Population.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo once daily (OD) in the evening from a dry powder inhaler for 4 weeks in addition to open-label fluticasone propionate (FP) 100 micrograms (µg) twice daily (BID). Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication.	
Reporting group title	VI 6.25 µg OD
Reporting group description:	
Participants received vilanterol (VI) 6.25 µg OD in the evening from a dry powder inhaler for 4 weeks in addition to open-label FP 100 µg BID. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication.	
Reporting group title	VI 12.5 µg OD
Reporting group description:	
Participants received VI 12.5 µg OD in the evening from a dry powder inhaler for 4 weeks in addition to open-label FP 100 µg BID. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication.	
Reporting group title	VI 25 µg OD
Reporting group description:	
Participants received VI 25 µg OD in the evening from a dry powder inhaler for 4 weeks in addition to open-label FP 100 µg BID. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication.	

Reporting group values	Placebo	VI 6.25 µg OD	VI 12.5 µg OD
Number of subjects	115	114	113
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	8	8	7.9
standard deviation	± 1.81	± 1.95	± 1.74
Gender categorical Units: Subjects			
Female	50	43	42
Male	65	71	71
Race, customized Units: Subjects			
African American/African Heritage	5	5	5
American Indian or Alaska Native	16	21	17
Asian - Japanese Heritage	5	5	5
Asian - South East Asian Heritage	1	1	2
White - Arabic/North African Heritage	1	1	0
White - White/Caucasian/European Heritage	67	62	55
Mixed Race	20	19	29

Reporting group values	VI 25 µg OD	Total	
Number of subjects	114	456	

Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	7.9		
standard deviation	± 1.72	-	
Gender categorical Units: Subjects			
Female	45	180	
Male	69	276	
Race, customized Units: Subjects			
African American/African Heritage	3	18	
American Indian or Alaska Native	18	72	
Asian - Japanese Heritage	5	20	
Asian - South East Asian Heritage	1	5	
White - Arabic/North African Heritage	1	3	
White - White/Caucasian/European Heritage	61	245	
Mixed Race	25	93	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo once daily (OD) in the evening from a dry powder inhaler for 4 weeks in addition to open-label fluticasone propionate (FP) 100 micrograms (µg) twice daily (BID). Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication.	
Reporting group title	VI 6.25 µg OD
Reporting group description:	
Participants received vilanterol (VI) 6.25 µg OD in the evening from a dry powder inhaler for 4 weeks in addition to open-label FP 100 µg BID. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication.	
Reporting group title	VI 12.5 µg OD
Reporting group description:	
Participants received VI 12.5 µg OD in the evening from a dry powder inhaler for 4 weeks in addition to open-label FP 100 µg BID. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication.	
Reporting group title	VI 25 µg OD
Reporting group description:	
Participants received VI 25 µg OD in the evening from a dry powder inhaler for 4 weeks in addition to open-label FP 100 µg BID. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication.	

Primary: Change from Baseline in daily pre-dose evening (PM) peak expiratory flow (PEF) from participant electronic daily diary averaged over the 4-week Treatment Period

End point title	Change from Baseline in daily pre-dose evening (PM) peak expiratory flow (PEF) from participant electronic daily diary averaged over the 4-week Treatment Period
End point description:	
PEF is defined as the maximum airflow during a forced expiration beginning with the lungs fully inflated. PEF was measured by the participants using a hand-held electronic peak flow meter each evening prior to the dose of study medication and any rescue albuterol/salbutamol inhalation aerosol use each morning. The best of three measurements was recorded. Change from Baseline was calculated as the value of the averaged daily PM PEF over the 4-week Treatment Period minus the Baseline value. The Baseline PEF value is defined as the average of the last 7 days of the Run-in Phase. The analysis was performed using an analysis of covariance (ANCOVA) model with covariates of Baseline, region, sex, age, and treatment. Only those participants contributing data per the daily eDiary were analyzed.	
End point type	Primary
End point timeframe:	
Baseline; Week 1 up to Week 4	

End point values	Placebo	VI 6.25 µg OD	VI 12.5 µg OD	VI 25 µg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	113[1]	113[2]	112[3]	110[4]
Units: Liters per minute (L/min)				
least squares mean (standard error)	215.9 (± 2.53)	221.4 (± 2.53)	222.4 (± 2.54)	220.3 (± 2.56)

Notes:

[1] - ITT Population: participants randomized to treatment who received >=1 dose of study medication

[2] - ITT Population: participants randomized to treatment who received >=1 dose of study medication

[3] - ITT Population: participants randomized to treatment who received >=1 dose of study medication

[4] - ITT Population: participants randomized to treatment who received >=1 dose of study medication

Statistical analyses

Statistical analysis title	Statistical Analysis #1
Comparison groups	Placebo v VI 25 µg OD
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.227 [5]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	11.4

Notes:

[5] - Inference for VI 12.5 µg versus (vs) placebo was dependent upon statistical significance (SS) having first been achieved for VI 25 µg vs placebo; inference for VI 6.25 µg vs placebo was dependent on SS having been achieved for VI 12.5 µg vs placebo.

Statistical analysis title	Statistical Analysis #2
Comparison groups	Placebo v VI 12.5 µg OD
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.073
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	13.5

Statistical analysis title	Statistical Analysis #3
Comparison groups	Placebo v VI 6.25 µg OD

Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.127
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	12.5

Secondary: Change from Baseline in evening clinic visit trough (pre-bronchodilator and pre-dose) forced expiratory volume in one second (FEV1) at the end of the 4-week Treatment Period in children who could perform the maneuver

End point title	Change from Baseline in evening clinic visit trough (pre-bronchodilator and pre-dose) forced expiratory volume in one second (FEV1) at the end of the 4-week Treatment Period in children who could perform the maneuver

End point description:

Pulmonary function was measured by FEV1, defined as the maximal amount of air that can be forcefully exhaled in one second. Trough FEV1 is defined as a pre-dose FEV1 measurement taken at a clinic visit while still on treatment. Change from Baseline in trough FEV1 at the end of the 4-week Treatment Period was defined using the pre-dose FEV1 measurement taken at the Week 4 clinic visit. Change from Baseline was calculated as the Week 4 trough FEV1 value minus the Baseline value. The Baseline FEV1 value is defined as the value at Visit 3 (randomization). The analysis was performed using an ANCOVA model with covariates of Baseline trough FEV1, region, sex, age, and treatment. The last observation carried forward (LOCF) method was used to impute missing data, in which the last non-missing post-Baseline on-treatment measurement at scheduled clinic visits was used to impute the missing measurements.

End point type	Secondary

End point timeframe:

Baseline; Week 4

End point values	Placebo	VI 6.25 µg OD	VI 12.5 µg OD	VI 25 µg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	85[6]	83[7]	86[8]	86[9]
Units: Liters				
least squares mean (standard error)	0.223 (± 0.0287)	0.166 (± 0.0292)	0.24 (± 0.0285)	0.193 (± 0.0288)

Notes:

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

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

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

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

Statistical analyses

Statistical analysis title	Statistical Analysis #1
Comparison groups	Placebo v VI 6.25 µg OD
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.138
upper limit	0.024

Statistical analysis title	Statistical Analysis #2
Comparison groups	Placebo v VI 12.5 µg OD
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.063
upper limit	0.096

Statistical analysis title	Statistical Analysis #3
Comparison groups	Placebo v VI 25 µg OD
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.051

Secondary: Change from Baseline in the percentage of rescue-free 24-hour periods during the 4-week Treatment Period

End point title	Change from Baseline in the percentage of rescue-free 24-hour periods during the 4-week Treatment Period

End point description:

The number of inhalations of rescue albuterol/salbutamol inhalation aerosol (medication used to relieve symptoms immediately) used during the day and night) was recorded by the participants in a daily diary. A 24-hour period in which a participant's responses to both the morning and evening assessments indicated no use of rescue medication was considered as rescue free. Participants who were rescue free for 24-hour periods during the 4-week Treatment Period were assessed. The Baseline value was derived from the last 7 days of the daily diary prior to the randomization of the participant. Change from Baseline is calculated as the average value during the 4-week Treatment Period minus the value at Baseline. The Baseline value is defined as the value at Visit 3 (randomization). Analysis was performed using ANCOVA with covariates of Baseline, region, sex, age, and treatment.

End point type	Secondary

End point timeframe:

Baseline; Week 1 up to Week 4

End point values	Placebo	VI 6.25 µg OD	VI 12.5 µg OD	VI 25 µg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	113[10]	113[11]	112[12]	110[13]
Units: Percentage of rescue-free 24-hr periods				
least squares mean (standard error)	14.4 (± 2.97)	12.2 (± 2.97)	15.8 (± 2.98)	23.1 (± 3.01)

Notes:

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

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

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

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

Statistical analyses

Statistical analysis title	Statistical Analysis #1
Comparison groups	Placebo v VI 6.25 µg OD
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	6

Statistical analysis title	Statistical Analysis #2
Comparison groups	Placebo v VI 12.5 µg OD

Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	9.6

Statistical analysis title	Statistical Analysis #3
Comparison groups	Placebo v VI 25 µg OD
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	8.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	17

Secondary: Change from Baseline in daily morning (AM) PEF averaged over the 4-week Treatment Period

End point title	Change from Baseline in daily morning (AM) PEF averaged over the 4-week Treatment Period

End point description:

PEF is defined as the maximum airflow during a forced expiration beginning with the lungs fully inflated. PEF was measured by the participants using a hand-held electronic peak flow meter each morning prior to the dose of study medication and any rescue albuterol/salbutamol inhalation aerosol use. Change from Baseline was calculated as the value of the averaged daily AM PEF over the 4-week Treatment Period (at Week 4) minus the Baseline value. The Baseline value is defined as the value at Visit 3 (randomization). The analysis was performed using an ANCOVA model with covariates of Baseline, region, sex, age, and treatment group.

End point type	Secondary

End point timeframe:

Baseline; Week 1 up to Week 4

End point values	Placebo	VI 6.25 µg OD	VI 12.5 µg OD	VI 25 µg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	114[14]	113[15]	112[16]	110[17]
Units: L/min				
least squares mean (standard error)	6.4 (± 2.42)	12 (± 2.43)	13.9 (± 2.44)	13.7 (± 2.46)

Notes:

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

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

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

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

Statistical analyses

Statistical analysis title	Statistical Analysis #1
Comparison groups	VI 6.25 µg OD v Placebo
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	12.3

Statistical analysis title	Statistical Analysis #2
Comparison groups	Placebo v VI 12.5 µg OD
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	14.2

Statistical analysis title	Statistical Analysis #3
Comparison groups	Placebo v VI 25 µg OD

Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	7.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	14

Secondary: Change from Baseline in evening (PM) PEF over the last 7 days of the Treatment Period (Week 4)

End point title	Change from Baseline in evening (PM) PEF over the last 7 days of the Treatment Period (Week 4)

End point description:

PEF is defined as the maximum airflow during a forced expiration beginning with the lungs fully inflated. PEF was measured by the participants using a hand-held electronic peak flow meter each evening prior to the dose of study medication and any rescue albuterol/salbutamol inhalation aerosol use. Change from Baseline is calculated as the value over the last 7 days of the Treatment Period minus the Baseline value. The Baseline value is defined as the value at Visit 3 (randomization). The analysis was performed using an ANCOVA model with covariates of Baseline, region, sex, age, and treatment group. The LOCF method was used to impute missing data, in which the last non-missing post-Baseline on-treatment measurement at scheduled clinic visits was used to impute the missing measurements.

End point type	Secondary

End point timeframe:

Baseline; Week 4

End point values	Placebo	VI 6.25 µg OD	VI 12.5 µg OD	VI 25 µg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	113[18]	113[19]	112[20]	110[21]
Units: L/min				
least squares mean (standard error)	5.9 (± 3.44)	9.4 (± 3.44)	13.7 (± 3.45)	11.1 (± 3.48)

Notes:

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

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

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

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

Statistical analyses

Statistical analysis title	Statistical Analysis #1
Comparison groups	Placebo v VI 6.25 µg OD

Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1
upper limit	13.1

Statistical analysis title	Statistical Analysis #2
Comparison groups	Placebo v VI 12.5 µg OD
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	7.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	17.4

Statistical analysis title	Statistical Analysis #3
Comparison groups	Placebo v VI 25 µg OD
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	14.9

Secondary: Change from Baseline in AM PEF over the last 7 days of the Treatment Period (Week 4)

End point title	Change from Baseline in AM PEF over the last 7 days of the Treatment Period (Week 4)

End point description:

PEF is defined as the maximum airflow during a forced expiration beginning with the lungs fully inflated. PEF was measured by the participants using a hand-held electronic peak flow meter each morning prior to the dose of study medication and any rescue albuterol/salbutamol inhalation aerosol use. Change

from Baseline is calculated as the value of the averaged daily AM PEF over the 4-week Treatment Period (at Week 4) minus the Baseline value. The Baseline value is defined as the value at Visit 3 (randomization). The analysis was performed using an ANCOVA model with covariates of Baseline, region, sex, age, and treatment group.

End point type	Secondary

End point timeframe:

Baseline; Week 4

End point values	Placebo	VI 6.25 µg OD	VI 12.5 µg OD	VI 25 µg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	114[22]	113[23]	112[24]	110[25]
Units: L/min				
least squares mean (standard error)	7.4 (± 3.45)	13.3 (± 3.47)	17 (± 3.48)	14.4 (± 3.51)

Notes:

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

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

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

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

Statistical analyses

Statistical analysis title	Statistical Analysis #1
Comparison groups	Placebo v VI 6.25 µg OD
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	15.6

Statistical analysis title	Statistical Analysis #2
Comparison groups	Placebo v VI 12.5 µg OD
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	9.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	19.3

Statistical analysis title	Statistical Analysis #3
Comparison groups	Placebo v VI 25 µg OD
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	16.7

Secondary: Change from Baseline in the percentage of symptom-free 24-hour periods during the 4-week Treatment Period

End point title	Change from Baseline in the percentage of symptom-free 24-hour periods during the 4-week Treatment Period

End point description:

Asthma symptoms were recorded in a daily eDairy by the participants every day in the morning and evening before taking any rescue or study medication and before the PEF measurement. A 24-hour (hr) period in which a participant's responses to both the morning and evening assessments indicated no symptoms was considered to be symptom free. The Baseline symptom-free value is defined as the value at Visit 3 (randomization). Change from Baseline was calculated as the averaged value during the 4-week Treatment Period minus the Baseline value. The analysis was performed using an ANCOVA model with covariates of Baseline, region, sex, age, and treatment group.

End point type	Secondary

End point timeframe:

Baseline; Week 1 up to Week 4

End point values	Placebo	VI 6.25 µg OD	VI 12.5 µg OD	VI 25 µg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	113[26]	113[27]	112[28]	110[29]
Units: Percentage of symptom-free 24-hr periods				
least squares mean (standard error)	9.9 (± 2.65)	10.1 (± 2.65)	18.3 (± 2.66)	19.7 (± 2.69)

Notes:

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

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

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

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

Statistical analyses

Statistical analysis title	Statistical Analysis #1
Comparison groups	Placebo v VI 6.25 µg OD

Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	7.5

Statistical analysis title	Statistical Analysis #2
Comparison groups	Placebo v VI 12.5 µg OD
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	15.7

Statistical analysis title	Statistical Analysis #3
Comparison groups	Placebo v VI 25 µg OD
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	9.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.3
upper limit	17.2

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 study medication until the follow-up visit (up to 9 weeks).

Adverse event reporting additional description:

On-treatment SAEs and non-serious AEs are reported for members of the ITT Population, comprised of all participants who were randomized to treatment and received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo once daily (OD) in the evening from a dry powder inhaler for 4 weeks in addition to open-label fluticasone propionate (FP) 100 micrograms (µg) twice daily (BID). Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication.

Reporting group title	VI 6.25 OD

Reporting group description:

Participants received vilanterol (VI) 6.25 µg OD in the evening from a dry powder inhaler for 4 weeks in addition to open-label FP 100 µg BID. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication.

Reporting group title	VI 12.5 OD

Reporting group description:

Participants received VI 12.5 µg OD in the evening from a dry powder inhaler for 4 weeks in addition to open-label FP 100 µg BID. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication.

Reporting group title	VI 25 OD

Reporting group description:

Participants received VI 25 µg OD in the evening from a dry powder inhaler for 4 weeks in addition to open-label FP 100 µg BID. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication.

Serious adverse events	Placebo	VI 6.25 OD	VI 12.5 OD
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 115 (0.00%)	0 / 114 (0.00%)	0 / 113 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 114 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	VI 25 OD		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 114 (0.88%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 114 (0.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	VI 6.25 OD	VI 12.5 OD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 115 (8.70%)	17 / 114 (14.91%)	12 / 113 (10.62%)
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 115 (3.48%)	6 / 114 (5.26%)	2 / 113 (1.77%)
occurrences (all)	4	8	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 115 (6.96%)	8 / 114 (7.02%)	10 / 113 (8.85%)
occurrences (all)	8	8	11
Influenza			
subjects affected / exposed	0 / 115 (0.00%)	4 / 114 (3.51%)	0 / 113 (0.00%)
occurrences (all)	0	4	0

Non-serious adverse events	VI 25 OD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 114 (9.65%)		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 114 (1.75%)		
occurrences (all)	2		
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	9 / 114 (7.89%)		
occurrences (all)	9		
Influenza			
subjects affected / exposed	0 / 114 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2012	This amendment was implemented to remove the requirement that participants must achieve a reversibility of 12% at Visit 1. This amendment also includes changes to the inhaled corticosteroid (ICS) doses allowed prior to Visit 1 and addresses the re-screening of participants found to be ineligible prior to this amendment. Additional edits were made to the statistical sections to the effect that the primary analysis will be the pairwise comparison of each dose regimen of vilanterol with placebo.
14 December 2012	The purpose of this amendment was to allow for the-re-screening of participants who failed Visit 1 criteria. Additional edits were made to the statistical sections to the effect that the primary analysis will be the comparison of each dose regimen of vilanterol with placebo.
19 September 2013	The purpose of this amendment was to implement a change to the time point for the primary endpoint (from an endpoint assessment to the average over the treatment period) and to the analysis for the primary endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported