



Clinical trial results:

A randomized, double-blind, repeat dose, two period crossover study to evaluate the safety and tolerability, pharmacokinetics, and pharmacodynamics of inhaled fluticasone furoate/vilanterol 100/25 mcg in children aged 5 to 11 years with persistent asthma

Summary

EudraCT number	2012-000754-55
Trial protocol	Outside EU/EEA
Global end of trial date	29 June 2012

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	07 March 2015

Trial information

Trial identification

Sponsor protocol code	HZA112777
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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)	Yes
EMA paediatric investigation plan number(s)	EMA-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	30 July 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 June 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of inhaled FF/VI 100/25mcg administered once daily in the morning for 14 days via a novel dry powder inhaler in subjects aged 5 to 11 years

Protection of trial subjects:

A parent was required to stay with the subjects for the long days in the clinic. As much as possible children in the same age group were scheduled for visits on the same day. Games and movies were provided for diversion during the long clinic days. Effort was made to have the same staff members work with the children to help reduce anxiety. Topical anesthetics were used at injection site to reduce discomfort from blood collections. An indwelling catheter was inserted for serial blood draws, to prevent the pain and distress associated with repeated needlesticks.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 October 2011
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	United States: 26
Worldwide total number of subjects	26
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)	26
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

Participants were enrolled into one of two cohorts based upon age; the younger cohort was enrolled after a review of the safety/pharmacokinetic data of at least six participants from the older cohort. Each participant was assigned to treatment randomly; assignment was not to be influenced by whether participants were in Cohort 1 or Cohort 2.

Pre-assignment

Screening details:

A Baseline assessment was carried out on Day 1 of the first treatment period. Participants were then randomized to one of the two possible treatments fluticasone furoate [FF] 100 µg/Vilanterol [VI] 25 µg or FF 100 µg, followed by a cross over after a washout period of at least 7 days.

Period 1

Period 1 title	Treatment Period (TP) 1 (Overall)
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	FF 100 µg/VI 25 µg in TP 1 and FF 100 µg in TP 2

Arm description:

Participants received fluticasone furoate (FF) 100 micrograms (µg)/Vilanterol (VI) 25 µg in Treatment Period 1 and FF 100 µg in Treatment Period 2. The first 14-day treatment period was followed by a washout period of at least 7 days. Inhaled FF 100 µg/VI 25 µg and FF 100 µg were administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler.

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

Dosage and administration details:

FF 100µg once daily x 14 days; 7 day wash out; crossover

Investigational medicinal product name	Fluticasone furoate and Vilanterol combined
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

FF/VI 100/25µg once daily x 14 days; 7 day wash out; crossover

Arm title	FF 100 µg in TP 1 and FF 100 µg/VI 25 µg in TP 2
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Arm description:

Participants received FF 100 µg in Treatment Period 1 and FF 100 µg/VI 25 µg in Treatment Period 2. The first 14-day treatment period was followed by a washout period of at least 7 days. Inhaled FF 100 µg/VI 25 µg and FF 100 µg were administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler.

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

Dosage and administration details:

FF 100µg once daily x 14 days; 7 day wash out; crossover

Investigational medicinal product name	Fluticasone furoate and Vilanterol combined
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

FF/VI 100/25µg once daily x 14 days; 7 day wash out; crossover

Number of subjects in period 1	FF 100 µg/VI 25 µg in TP 1 and FF 100 µg in TP 2	FF 100 µg in TP 1 and FF 100 µg/VI 25 µg in TP 2
Started	13	13
Completed	12	12
Not completed	1	1
Met Protocol-defined Stopping Criteria	-	1
Protocol deviation	1	-

Period 2

Period 2 title	Washout Period
Is this the baseline period?	No
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	FF 100 µg/VI 25 µg in TP 1 and FF 100 µg in TP 2

Arm description:

Participants received fluticasone furoate (FF) 100 micrograms (µg)/Vilanterol (VI) 25 µg in Treatment Period 1 and FF 100 µg in Treatment Period 2. The first 14-day treatment period was followed by a washout period of at least 7 days. Inhaled FF 100 µg/VI 25 µg and FF 100 µg were administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler.

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

Dosage and administration details:	
FF 100µg once daily x 14 days; 7 day wash out; crossover	
Investigational medicinal product name	Fluticasone furoate and Vilanterol combined
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details:	
FF/VI 100/25µg once daily x 14 days; 7 day wash out; crossover	
Arm title	FF 100 µg in TP 1 and FF 100 µg/VI 25 µg in TP 2
Arm description:	
Participants received FF 100 µg in Treatment Period 1 and FF 100 µg/VI 25 µg in Treatment Period 2. The first 14-day treatment period was followed by a washout period of at least 7 days. Inhaled FF 100 µg/VI 25 µg and FF 100 µg were administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler.	
Arm type	Experimental
Investigational medicinal product name	Fluticasone furoate singularly
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details:	
FF 100µg once daily x 14 days; 7 day wash out; crossover	
Investigational medicinal product name	Fluticasone furoate and Vilanterol combined
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details:	
FF/VI 100/25µg once daily x 14 days; 7 day wash out; crossover	

Number of subjects in period 2	FF 100 µg/VI 25 µg in TP 1 and FF 100 µg in TP 2	FF 100 µg in TP 1 and FF 100 µg/VI 25 µg in TP 2
Started	12	12
Completed	12	12

Period 3

Period 3 title	Treatment Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
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Arm title	FF 100 µg/VI 25 µg in TP 1 and FF 100 µg in TP 2
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Arm description:

Participants received fluticasone furoate (FF) 100 micrograms (µg)/Vilanterol (VI) 25 µg in Treatment Period 1 and FF 100 µg in Treatment Period 2. The first 14-day treatment period was followed by a washout period of at least 7 days. Inhaled FF 100 µg/VI 25 µg and FF 100 µg were administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler.

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

Dosage and administration details:

FF 100µg once daily x 14 days; 7 day wash out; crossover

Investigational medicinal product name	Fluticasone furoate and Vilanterol combined
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

FF/VI 100/25µg once daily x 14 days; 7 day wash out; crossover

Arm title	FF 100 µg in TP 1 and FF 100 µg/VI 25 µg in TP 2
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Arm description:

Participants received FF 100 µg in Treatment Period 1 and FF 100 µg/VI 25 µg in Treatment Period 2. The first 14-day treatment period was followed by a washout period of at least 7 days. Inhaled FF 100 µg/VI 25 µg and FF 100 µg were administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler.

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

Dosage and administration details:

FF 100µg once daily x 14 days; 7 day wash out; crossover

Investigational medicinal product name	Fluticasone furoate and Vilanterol combined
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

FF/VI 100/25µg once daily x 14 days; 7 day wash out; crossover

Number of subjects in period 3	FF 100 µg/VI 25 µg in TP 1 and FF 100 µg in TP 2	FF 100 µg in TP 1 and FF 100 µg/VI 25 µg in TP 2
Started	12	12
Completed	12	11
Not completed	0	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment Period (TP) 1 (Overall)
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Reporting group description:

All participants who received FF 100 µg/VI 25 µg in Treatment Period 1 and FF 100 µg in Treatment Period 2 or FF 100 µg in Treatment Period 1 and FF 100 µg/VI 25 µg in Treatment Period 2. The first 14-day treatment period was followed by a washout period of at least 7 days. Inhaled FF 100 µg/VI 25 µg and FF 100 µg were administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler.

Reporting group values	Treatment Period (TP) 1 (Overall)	Total	
Number of subjects	26	26	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	8.1		
standard deviation	± 1.97	-	
Gender categorical			
Units: Subjects			
Female	11	11	
Male	15	15	
Race			
Units: Subjects			
African American/African Heritage	3	3	
White - Arabic/North African Heritage	1	1	
White - White/Caucasian/European Heritage	21	21	
African American/African Heritage & White	1	1	

End points

End points reporting groups

Reporting group title	FF 100 µg/VI 25 µg in TP 1 and FF 100 µg in TP 2
Reporting group description: Participants received fluticasone furoate (FF) 100 micrograms (µg)/Vilanterol (VI) 25 µg in Treatment Period 1 and FF 100 µg in Treatment Period 2. The first 14-day treatment period was followed by a washout period of at least 7 days. Inhaled FF 100 µg/VI 25 µg and FF 100 µg were administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler.	
Reporting group title	FF 100 µg in TP 1 and FF 100 µg/VI 25 µg in TP 2
Reporting group description: Participants received FF 100 µg in Treatment Period 1 and FF 100 µg/VI 25 µg in Treatment Period 2. The first 14-day treatment period was followed by a washout period of at least 7 days. Inhaled FF 100 µg/VI 25 µg and FF 100 µg were administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler.	
Reporting group title	FF 100 µg/VI 25 µg in TP 1 and FF 100 µg in TP 2
Reporting group description: Participants received fluticasone furoate (FF) 100 micrograms (µg)/Vilanterol (VI) 25 µg in Treatment Period 1 and FF 100 µg in Treatment Period 2. The first 14-day treatment period was followed by a washout period of at least 7 days. Inhaled FF 100 µg/VI 25 µg and FF 100 µg were administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler.	
Reporting group title	FF 100 µg in TP 1 and FF 100 µg/VI 25 µg in TP 2
Reporting group description: Participants received FF 100 µg in Treatment Period 1 and FF 100 µg/VI 25 µg in Treatment Period 2. The first 14-day treatment period was followed by a washout period of at least 7 days. Inhaled FF 100 µg/VI 25 µg and FF 100 µg were administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler.	
Reporting group title	FF 100 µg/VI 25 µg in TP 1 and FF 100 µg in TP 2
Reporting group description: Participants received fluticasone furoate (FF) 100 micrograms (µg)/Vilanterol (VI) 25 µg in Treatment Period 1 and FF 100 µg in Treatment Period 2. The first 14-day treatment period was followed by a washout period of at least 7 days. Inhaled FF 100 µg/VI 25 µg and FF 100 µg were administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler.	
Reporting group title	FF 100 µg in TP 1 and FF 100 µg/VI 25 µg in TP 2
Reporting group description: Participants received FF 100 µg in Treatment Period 1 and FF 100 µg/VI 25 µg in Treatment Period 2. The first 14-day treatment period was followed by a washout period of at least 7 days. Inhaled FF 100 µg/VI 25 µg and FF 100 µg were administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler.	
Subject analysis set title	FF 100 µg/VI 25 µg
Subject analysis set type	Safety analysis
Subject analysis set description: Participants received FF 100 µg/VI 25 µg in one of the two 14-day treatment periods. FF 100 µg/VI 25 µg was administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler. The washout period between the treatment periods was at least 7 days.	
Subject analysis set title	FF 100 µg
Subject analysis set type	Safety analysis
Subject analysis set description: Participants received FF 100 µg in one of the two 14-day treatment periods. FF 100 µg was administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler. The washout period between the treatment periods was at least 7 days.	
Subject analysis set title	FF 100 µg/VI 25 µg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received FF 100 µg/VI 25 µg in one of the two 14-day treatment periods. FF 100 µg/VI 25 µg was administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler. The washout period between the treatment periods was at least 7 days.	

Subject analysis set title	FF 100 µg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received FF 100 µg in one of the two 14-day treatment periods. FF 100 µg was administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler. The washout period between the treatment periods was at least 7 days.

Primary: Number of participants with any adverse event (AE) or any serious adverse event (SAE) during the Treatment Period

End point title	Number of participants with any adverse event (AE) or any serious adverse event (SAE) during the Treatment Period ^[1]
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End point description:

An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, or is a congenital anomaly/birth defect. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations. Refer to the General Adverse AE/SAE module for a complete list of AEs and SAEs.

End point type	Primary
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End point timeframe:

From the start of study medication until Week 11 (Visit 9)/Early Withdrawal

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this primary endpoint; thus, no data are available.

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[2]	25 ^[3]		
Units: Participants				
Any AE	4	1		
Any SAE	0	0		

Notes:

[2] - All Subjects Population: all participants who received at least one dose of study medication

[3] - All Subjects Population: all participants who received at least one dose of study medication

Statistical analyses

No statistical analyses for this end point

Primary: Basophil, eosinophil, lymphocyte, monocyte, total neutrophil, platelet, and white blood cell count values at Day 14 of the respective treatment period

End point title	Basophil, eosinophil, lymphocyte, monocyte, total neutrophil, platelet, and white blood cell count values at Day 14 of the respective treatment period ^[4]
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End point description:

Blood samples were collected for the measurement of basophils, eosinophils, lymphocytes, monocytes, total neutrophils, platelets, and white blood cell (WBC) count at Day 14 of the respective treatment period.

End point type	Primary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this primary endpoint; thus, no data are available.

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[5]	25 ^[6]		
Units: 10 ⁹ cells per liter (GI/L)				
arithmetic mean (standard deviation)				
Basophils, n=21, 23	0.025 (± 0.0175)	0.025 (± 0.0153)		
Eosinophils, n=21, 23	0.296 (± 0.3395)	0.293 (± 0.3957)		
Lymphocytes, n=21, 23	2.062 (± 0.8462)	2.339 (± 0.7391)		
Monocytes, n=21, 23	0.244 (± 0.1188)	0.222 (± 0.1375)		
Total neutrophils, n=21, 23	3.805 (± 2.409)	3.106 (± 1.3526)		
Platelets, n=21, 23	270.5 (± 92.27)	299 (± 73.66)		
WBC count, n=21, 23	6.43 (± 2.889)	5.98 (± 1.897)		

Notes:

[5] - All Subjects Population: Only participants available at the specified time points were analyzed.

[6] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Hemoglobin and mean corpuscle hemoglobin concentration (MCHC) values at Day 14 of the respective treatment period

End point title	Hemoglobin and mean corpuscle hemoglobin concentration (MCHC) values at Day 14 of the respective treatment period ^[7]
End point description:	
Blood samples were collected for the measurement of hemoglobin and MCHC at Day 14 of the respective treatment period.	
End point type	Primary
End point timeframe:	
Day 14 of the respective treatment period (up to Study Day 63)	

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this primary endpoint; thus, no data are available.

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[8]	25 ^[9]		
Units: Grams per liter (g/L)				
arithmetic mean (standard deviation)				
Hemoglobin, n=21, 23	125.9 (± 13.49)	128 (± 6.52)		
MCHC, n=21, 23	330.3 (± 5.83)	330.8 (± 7.88)		

Notes:

[8] - All Subjects Population: Only participants available at the specified time points were analyzed.

[9] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Reticulocyte and Red Blood Cell (RBC) values at Day 14 of the respective treatment period

End point title	Reticulocyte and Red Blood Cell (RBC) values at Day 14 of the respective treatment period ^[10]
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End point description:

Blood samples were collected for the measurement of reticulocytes and RBCs at Day 14 of the respective treatment period.

End point type	Primary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this primary endpoint; thus, no data are available.

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[11]	25 ^[12]		
Units: 10 ¹² cells per liter (TI/L)				
arithmetic mean (standard deviation)				
Reticulocytes, n=21, 23	0.0722 (± 0.037473)	0.07323 (± 0.032203)		
RBCs, n=21, 23	4.33 (± 0.467)	4.38 (± 0.199)		

Notes:

[11] - All Subjects Population: Only participants available at the specified time points were analyzed.

[12] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Hematocrit values at Day 14 of the respective treatment period

End point title	Hematocrit values at Day 14 of the respective treatment
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End point description:

Blood samples were collected for the measurement of hematocrit at Day 14 of the respective treatment period. Hematocrit is a measure of the percentage of the volume of the whole blood that is composed of red blood cells, as determined by separation of red blood cells from the plasma (usually by centrifugation).

End point type	Primary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this primary endpoint; thus, no data are available.

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21 ^[14]	23 ^[15]		
Units: proportion of 1				
arithmetic mean (standard deviation)	0.3816 (± 0.04199)	0.3866 (± 0.0216)		

Notes:

[14] - All Subjects Population: Only participants available at the specified time points were analyzed.

[15] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Mean Corpuscle Volume (MCV) value at Day 14 of the respective treatment period

End point title	Mean Corpuscle Volume (MCV) value at Day 14 of the respective treatment period ^[16]
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End point description:

Blood samples were collected for the measurement of MCV at Day 14 of the respective treatment period.

End point type	Primary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this primary endpoint; thus, no data are available.

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21 ^[17]	23 ^[18]		
Units: 10 ¹⁵ femtoliters (fL) per cell				
arithmetic mean (standard deviation)	87.9 (± 2.61)	88.6 (± 3.37)		

Notes:

[17] - All Subjects Population: Only participants available at the specified time points were analyzed.

[18] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Mean Corpuscle Hemoglobin (MCH) values at Day 14 of the respective treatment period

End point title	Mean Corpuscle Hemoglobin (MCH) values at Day 14 of the respective treatment period ^[19]
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End point description:

Blood samples were collected for the measurement of MCH at Day 14 of the respective treatment period.

End point type	Primary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this primary endpoint; thus, no data are available.

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21 ^[20]	23 ^[21]		
Units: 10 ¹² picograms (pg) per cell				
arithmetic mean (standard deviation)	29.03 (± 0.941)	29.25 (± 1.116)		

Notes:

[20] - All Subjects Population: Only participants available at the specified time points were analyzed.

[21] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Alanine amino transferase (ALT), alkaline phosphatase (ALP), aspartate amino transferase (AST), and gamma glutamyl transferase (GGT) values at Day 14 of the respective treatment period

End point title	Alanine amino transferase (ALT), alkaline phosphatase (ALP), aspartate amino transferase (AST), and gamma glutamyl transferase (GGT) values at Day 14 of the respective treatment period ^[22]
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End point description:

Blood samples were collected for the measurement of ALT, ALP, AST, and GGT at Day 14 of the respective treatment period.

End point type	Primary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this primary endpoint; thus, no data are available.

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[23]	25 ^[24]		
Units: International units per liter (IU/L)				
arithmetic mean (standard deviation)				
ALT, n=22, 24	16.9 (± 14.63)	17.7 (± 14.88)		
ALP, n=22, 24	278.4 (± 110.01)	272.6 (± 119.48)		
AST, n=22, 24	28.2 (± 8.38)	29 (± 7.51)		
GGT, n=22, 24	14.6 (± 7.74)	16.1 (± 10.36)		

Notes:

[23] - All Subjects Population: Only participants available at the specified time points were analyzed.

[24] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Albumin and total protein values at Day 14 of the respective treatment period

End point title	Albumin and total protein values at Day 14 of the respective treatment period ^[25]
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End point description:

Blood samples were collected for the measurement of albumin and total protein at Day 14 of the respective treatment period.

End point type	Primary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this primary endpoint; thus, no data are available.

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[26]	25 ^[27]		
Units: Grams per liter				
arithmetic mean (standard deviation)				
Albumin, n=22, 24	45.5 (± 1.97)	45.6 (± 2.2)		
Total protein, n=22, 24	70.4 (± 2.99)	70.4 (± 3.12)		

Notes:

[26] - All Subjects Population: Only participants available at the specified time points were analyzed.

[27] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Calcium, chloride, carbon dioxide (CO2) content/bicarbonate, glucose, potassium, sodium, and urea/blood urea nitrogen (BUN) values at Day 14 of the respective treatment period

End point title	Calcium, chloride, carbon dioxide (CO2) content/bicarbonate, glucose, potassium, sodium, and urea/blood urea nitrogen (BUN) values at Day 14 of the respective treatment period ^[28]
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End point description:

Blood samples were collected for the measurement of calcium, chloride, carbon dioxide content/bicarbonate (CO2/BI), glucose, potassium, sodium, and urea/BUN at Day 14 of the respective treatment period.

End point type	Primary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this primary endpoint; thus, no data are available.

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[29]	25 ^[30]		
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Calcium, n=22, 24	2.416 (± 0.0591)	2.415 (± 0.0749)		
Chloride, n=22, 24	103.3 (± 1.75)	103.8 (± 1.79)		
CO2 content/bicarbonate, n=22, 24	19 (± 1.85)	19.1 (± 2.05)		
Glucose, n=22, 24	4.5 (± 0.689)	4.53 (± 0.523)		
Potassium, n=22, 24	4.24 (± 0.184)	4.27 (± 0.265)		
Sodium, n=22, 24	138.6 (± 1.84)	139 (± 1.85)		
Urea/BUN, n=22, 24	4.52 (± 1.006)	4.52 (± 1.108)		

Notes:

[29] - All Subjects Population: Only participants available at the specified time points were analyzed.

[30] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Total bilirubin, direct bilirubin, creatinine, and uric acid values at Day 14 of the respective treatment period

End point title	Total bilirubin, direct bilirubin, creatinine, and uric acid values at Day 14 of the respective treatment period ^[31]
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End point description:

Blood samples were collected for the measurement of total bilirubin, direct bilirubin, creatinine, and uric acid at Day 14 of the respective treatment period.

End point type	Primary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

Notes:

[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this primary endpoint; thus, no data are available.

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[32]	25 ^[33]		
Units: Micromoles per liter (µmol/L)				
arithmetic mean (standard deviation)				
Total bilirubin, n=22, 24	6.1 (± 1.44)	5.9 (± 1.72)		
Direct bilirubin, n=22, 24	1.7 (± 0.7)	1.9 (± 0.41)		
Creatinine, n=22, 24	36 (± 7.617)	37.09 (± 6.225)		
Uric acid, n=22, 24	231.8 (± 64.85)	233.8 (± 54.04)		

Notes:

[32] - All Subjects Population: Only participants available at the specified time points were analyzed.

[33] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Peak expiratory flow on Day 1 and Day 14 of the respective treatment period

End point title	Peak expiratory flow on Day 1 and Day 14 of the respective treatment period ^[34]
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End point description:

Peak Expiratory Flow (PEF) is defined as the maximum airflow during a forced expiration beginning with the lungs fully inflated. PEF is calculated as the maximum of three readings taken at each timepoint for each participant. Baseline is defined as the maximum pre-dose measurement at Day 1 for each period.

End point type	Primary
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End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 63)

Notes:

[34] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this primary endpoint; thus, no data are available.

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[35]	25 ^[36]		
Units: liters/minute				
arithmetic mean (standard deviation)				
Day 1, Baseline, n=25, 25	219 (± 53.27)	223.6 (± 56.91)		
Day 1, 10 minutes post-dose, n=25, 25	218.8 (± 53.02)	223 (± 55.15)		
Day 1, 20 minutes post-dose, n=25, 25	222.4 (± 53.5)	228.2 (± 56.73)		
Day 1, 1 hour post-dose, n=25, 25	223.2 (± 54.23)	227.2 (± 54.07)		
Day 1, 2 hours post-dose, n=25, 25	227 (± 55.94)	228.6 (± 54.17)		
Day 14, Pre-dose, n=23, 24	224.8 (± 52.86)	215 (± 50.71)		
Day 14, 20 minutes post-dose, n=23, 24	227.2 (± 52.18)	218.1 (± 52.12)		
Day 14, 2 hours post-dose, n=23, 24	235.7 (± 53.16)	225.8 (± 48.78)		
Day 14, 12 hours post-dose, n=23, 24	238.9 (± 55.84)	230.4 (± 52.54)		

Notes:

[35] - All Subjects Population: Only participants available at the specified time points were analyzed.

[36] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at Day 1 and Day 14 of the respective treatment period

End point title	Change from Baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at Day 1 and Day 14 of the respective treatment period ^[37]
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End point description:

SBP and DBP were measured at Day 1 and Day 14 of the respective treatment period. Baseline is

defined as the pre-dose measurement at Day 1. Change from Baseline was calculated as the Day 14 value minus the Baseline value.

End point type	Primary
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End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 63)

Notes:

[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this primary endpoint; thus, no data are available.

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[38]	25 ^[39]		
Units: Millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Day 1 SBP, Baseline, n=25, 25	97.2 (± 5.41)	99.9 (± 6.71)		
Day 1 SBP, 20 minutes, n=25, 25	-0.1 (± 2.98)	-0.1 (± 4.66)		
Day 1 SBP, 1 hour, n=25, 25	0.5 (± 2.87)	0.4 (± 3.7)		
Day 1 SBP, 2 hours, n=25, 25	0.9 (± 3.05)	1.3 (± 2.95)		
Day 14 SBP, Pre-dose, n=23, 24	1.3 (± 4.32)	-1.2 (± 6.92)		
Day 14 SBP, 20 minutes, n=23, 24	1.3 (± 4.61)	-1.2 (± 6.03)		
Day 14 SBP, 1 hour, n=23, 24	1 (± 4.42)	-0.8 (± 6.36)		
Day 14 SBP, 2 hours, n=23, 24	1.7 (± 4.17)	-0.8 (± 6.34)		
Day 14 SBP, 4 hours, n=23, 24	2.1 (± 4.22)	0.1 (± 6.47)		
Day 14 SBP, 8 hours, n=23, 24	2 (± 4.33)	-0.4 (± 7.17)		
Day 1 DBP, Baseline, n=25, 25	62.3 (± 3.54)	63.6 (± 3.86)		
Day 1 DBP, 20 minutes, n=25, 25	0.3 (± 2.81)	-0.3 (± 3.76)		
Day 1 DBP, 1 hour, n=25, 25	1 (± 3.17)	0.8 (± 3.11)		
Day 1 DBP, 2 hours, n=25, 25	0.9 (± 3.42)	1 (± 3.38)		
Day 14 DBP, Pre-dose, n=23, 24	0.6 (± 3.54)	0.2 (± 3.29)		
Day 14 DBP, 20 minutes, n=23, 24	0.1 (± 3.69)	0.1 (± 2.62)		
Day 14 DBP, 1 hour, n=23, 24	0.4 (± 4.18)	0 (± 2.3)		
Day 14 DBP, 2 hours, n=23, 24	1.3 (± 3.75)	0.4 (± 3.19)		
Day 14 DBP, 4 hours, n=23, 24	1.1 (± 4.17)	1.1 (± 3.35)		
Day 14 DBP, 8 hours, n=23, 24	1.4 (± 3.27)	-0.2 (± 3.02)		

Notes:

[38] - All Subjects Population: Only participants available at the specified time points were analyzed.

[39] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in heart rate at Day1 and Day 14 of the respective treatment period

End point title	Change from Baseline in heart rate at Day1 and Day 14 of the respective treatment period
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End point description:

Heart rate (HR) was measured at Day 1 and Day 14 of the respective treatment period. hr=hour. Baseline is defined as the pre-dose measurement at Day 1. Change from Baseline was calculated as the Day 14 value minus the Baseline value. Treatment, period, day (1 and 14), participant Baseline, period Baseline, and treatment*day interaction were fitted as fixed effects, and participant was fitted as a random effect.

End point type	Primary
End point timeframe:	
Day 1 and Day 14 of the respective treatment period (up to Study Day 63)	

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[40]	25 ^[41]		
Units: Beats per minute				
least squares mean (standard error)				
Day 1, n=25, 25	84.4 (± 1.63)	88.6 (± 1.63)		
Day 14, n=23, 24	89.4 (± 1.71)	85.7 (± 1.67)		

Notes:

[40] - All Subjects Population: Only participants available at the specified time points were analyzed.

[41] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	FF 100 µg v FF 100 µg/VI 25 µg
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other ^[42]
Parameter estimate	Mean difference (final values)
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.8
upper limit	0.4

Notes:

[42] - Day 1 HR. The estimated value represents the treatment difference: FF/VI 100/25 µg minus FF 100 µg.

Statistical analysis title	Analysis 2
Comparison groups	FF 100 µg/VI 25 µg v FF 100 µg
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other ^[43]
Parameter estimate	Mean difference (final values)
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	8.5

Notes:

[43] - Day 14 HR. The estimated value represents the treatment difference: FF/VI 100/25 µg minus FF 100 µg.

Primary: Maximum QTcF at Day 1 and Day 14 of the respective treatment period

End point title	Maximum QTcF at Day 1 and Day 14 of the respective treatment period
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End point description:

QTcF is the QT domain corrected for heart rate by Fridericia's formula. Treatment, period, day (1 and 14), participant Baseline, period Baseline, and treatment*day interaction were fitted as fixed effects, and participant was fitted as a random effect.

End point type	Primary
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End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 63)

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[44]	25 ^[45]		
Units: milliseconds				
least squares mean (standard error)				
Day 1 QTcF, n=25, 25	403.3 (± 1.98)	402.2 (± 1.98)		
Day 14 QTcF, n=23, 24	404 (± 2.06)	404.2 (± 2.02)		

Notes:

[44] - All Subjects Population: Only participants available at the specified time points were analyzed.

[45] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	FF 100 µg v FF 100 µg/VI 25 µg
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other ^[46]
Parameter estimate	Mean difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	6.7

Notes:

[46] - Day 1 QTcF. The estimated value represents the treatment difference: FF/VI 100/25 µg minus FF 100 µg.

Statistical analysis title	Analysis 2
Comparison groups	FF 100 µg/VI 25 µg v FF 100 µg
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other ^[47]
Parameter estimate	Mean difference (final values)
Point estimate	-0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	5.5

Notes:

[47] - Day 14 QTcF. The estimated value represents the treatment difference: FF/VI 100/25 µg minus FF 100 µg.

Secondary: AUC(0-t) and AUC(0-4) of FF on Day 14 of the respective treatment period

End point title	AUC(0-t) and AUC(0-4) of FF on Day 14 of the respective treatment period
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End point description:

Area under the concentration-time (AUC) curve from time zero (pre-dose) to the last time AUC(0-t) and from time zero to 4 hours AUC(0-4) of quantifiable concentration of FF on Day 14 of the respective treatment period was measured. Samples were collected at the following times: pre-dose; 10 minutes (min) and 30 min post-dose; and 1, 2, and 4 hours post-dose. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the PK Population.

End point type	Secondary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24 ^[48]	24 ^[49]		
Units: picograms*hour per milliliter (pg*hr/mL)				
geometric mean (confidence interval 95%)				
AUC(0-t), n=23, 24	38.895 (21.63 to 69.941)	32.88 (18.268 to 59.179)		
AUC(0-4), n=17, 15	86.14 (70.03 to 105.96)	83.83 (71.49 to 98.3)		

Notes:

[48] - FF PK Population:all participants in the All Subjects Pop for whom a FF PK sample was analyzed

[49] - FF PK Population:all participants in the All Subjects Pop for whom a FF PK sample was analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of FF on Day 14 of the respective treatment period

End point title	Cmax of FF on Day 14 of the respective treatment period
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End point description:

Cmax is defined as the maximum observed concentration of FF on Day 14 of the respective treatment period. Samples were collected at the following times: pre-dose; 10 minutes (min) and 30 min post-dose; and 1, 2, and 4 hours post-dose.

End point type	Secondary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23 ^[50]	24 ^[51]		
Units: picograms per milliliter (pg/mL)				
geometric mean (confidence interval 95%)	20.73 (15.16 to 28.36)	21.16 (14.91 to 30.02)		

Notes:

[50] - FF PK Population: Only participants available at the specified time points were analyzed.

[51] - FF PK Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: tmax and tlast of FF on Day 14 of the respective treatment period

End point title	tmax and tlast of FF on Day 14 of the respective treatment period
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End point description:

tmax is defined as the time to reach the observed maximum concentration, and tlast is defined as the time of the last observed quantifiable concentration on Day 14 of the respective treatment period. Samples were collected at the following times: pre-dose; 10 minutes (min) and 30 min post-dose; and 1, 2, and 4 hours post-dose.

End point type	Secondary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24 ^[52]	24 ^[53]		
Units: hours				
median (full range (min-max))				
tmax, n=20, 19	0.965 (0 to 2.07)	0.5 (0 to 3.95)		
tlast, n=20, 19	4.03 (0.52 to 4.13)	4.02 (1.03 to 4.05)		

Notes:

[52] - FF PK Population: Only participants available at the specified time points were analyzed.

[53] - FF PK Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-t) and AUC(0-4) of VI on Day 14 of the respective treatment period

End point title	AUC(0-t) and AUC(0-4) of VI on Day 14 of the respective treatment period
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End point description:

Area under the concentration-time (AUC) curve from time zero (pre-dose) to the last time AUC(0-t) and from time zero to 4 hours AUC(0-4) of quantifiable concentration of VI on Day 14 of the respective treatment period was measured. Samples were collected at the following times: pre-dose; 10 minutes (min) and 30 min post-dose; and 1, 2, and 4 hours post-dose. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the VI PK Population.

End point type	Secondary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

End point values	FF 100 µg/VI 25 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	23 ^[54]			
Units: picograms*hour per milliliter (pg*hr/mL)				
geometric mean (confidence interval 95%)				
AUC(0-t), n=23	44.297 (26.996 to 72.688)			
AUC(0-4), n=11	119.19 (102.41 to 138.73)			

Notes:

[54] - VI PK Population: all participants in the All Subjects Pop for whom a VI PK sample was analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of VI on Day 14 of the respective treatment period

End point title	Cmax of VI on Day 14 of the respective treatment period
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End point description:

Cmax is defined as the maximum observed concentration of VI on Day 14 of the respective treatment period. Samples were collected at the following times: pre-dose; 10 minutes (min) and 30 min post-dose; and 1, 2, and 4 hours post-dose.

End point type	Secondary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

End point values	FF 100 µg/VI 25 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	23 ^[55]			
Units: picograms per milliliter (pg/mL)				
geometric mean (confidence interval 95%)	44.21 (27.65 to 70.7)			

Notes:

[55] - VI PK Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: tmax and tlast of VI on Day 1 of the respective treatment period

End point title	tmax and tlast of VI on Day 1 of the respective treatment period
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End point description:

tmax is defined as the time to reach the observed maximum VI concentration, and tlast is defined as the time of the last observed quantifiable VI concentration on Day 14 of the respective treatment period. Samples were collected at the following times: pre-dose; 10 minutes (min) and 30 min post-dose; and 1, 2, and 4 hours post-dose.

End point type	Secondary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

End point values	FF 100 µg/VI 25 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	23 ^[56]			
Units: hours				
median (full range (min-max))				
tmax, n=21	0.17 (0 to 2.08)			
tlast, n=21	3.87 (0.5 to 4.13)			

Notes:

[56] - VI PK Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Blood glucose and potassium values on Day 14 of the respective treatment period

End point title	Blood glucose and potassium values on Day 14 of the respective treatment period
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End point description:

Blood glucose and potassium values were measured on Day 14 of the respective treatment period. Samples were collected at the following times: pre-dose; 10 minutes (min) and 30 min post-dose; and 1, 2, and 4 hours post-dose. Weighted means were derived using the linear trapezoidal rule. Actual relative times were used for the calculation except where actual times were missing. If any actual times were missing, planned relative time were used for these observations. Treatment and period were fitted as fixed effects and participant was fitted as a random effect.

End point type	Secondary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[57]	25 ^[58]		
Units: Millimoles per liter (mmol/L)				
least squares mean (confidence interval 95%)				
Glucose, n=22, 24	5.578 (5.275 to 5.881)	5.074 (4.781 to 5.367)		
Potassium, n=21, 23	4.059 (3.969 to 4.15)	4.148 (4.062 to 4.234)		

Notes:

[57] - All Subjects Population: Only participants available at the specified time points were analyzed.

[58] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum cortisol (SC) weighted mean (0–12 hours) on Day 14 of the respective treatment period

End point title	Serum cortisol (SC) weighted mean (0–12 hours) on Day 14 of the respective treatment period
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End point description:

SC weighted mean was determined for each participant over the time period of 0–12 hours on Day 14 of the respective treatment period. SC weighted mean was derived by dividing the area under the concentration-time curve (AUC; defined as the area under the concentration-time curve from time zero up to 24 hours) by the sample collection time interval. The sample collection time interval is defined as the difference between the time of the last cortisol sample and the time of the first cortisol sample. Samples were collected at the following time points: 0 (first blood draw/pre-dose); 2, 4, 8, and 12 hours (relative to the "0" time point). Weighted means were derived using the linear trapezoidal rule. Actual relative times were used for the calculation except where actual times were missing. If any actual times were missing, planned relative time were used for these observations. Treatment and period were fitted as fixed effects and participant was fitted as a random effect.

End point type	Secondary
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 63)

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23 ^[59]	23 ^[60]		
Units: nanomoles per Liter				
geometric mean (confidence interval 95%)	193.77 (168.42 to 222.93)	192.5 (167.32 to 221.48)		

Notes:

[59] - All Subjects Population: Only participants available at the specified time points were analyzed.

[60] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Average oropharyngeal cross-sectional area on Day 1 and Day 14 of the respective treatment period

End point title	Average oropharyngeal cross-sectional area on Day 1 and Day 14 of the respective treatment period
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End point description:

During the pharyngometry assessment, participants inhaled through a wavetube, which had a mouthpiece with the same dimensions as the mouthpiece on the dry powder inhaler used for the study. This technique was used to measure the size of the throat and mouth (oropharynx) in the form of pharyngograms. Pharyngometry data were recorded for each day (Day 1 and Day 14 of the respective treatment period) using the mean of four measurements (pharyngograms), and the average oropharyngeal cross-sectional area was calculated.

End point type	Secondary
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End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 63)

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[61]	25 ^[62]		
Units: centimeters squared (cm ²)				
arithmetic mean (standard deviation)				
Day 1, n=23, 23	4.13 (± 2.01)	3.85 (± 2.043)		
Day 14, n=23, 23	3.76 (± 2.195)	3.7 (± 2.279)		

Notes:

[61] - All Subjects Population: Only participants available at the specified time points were analyzed.

[62] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Distance of assessment on Day 1 and Day 14 of the respective treatment period

End point title	Distance of assessment on Day 1 and Day 14 of the respective treatment period
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End point description:

During the pharyngometry assessment, participants inhaled through a wavetube, which had a mouthpiece with the same dimensions as the mouthpiece on the dry powder inhaler used for this study. This technique was used to measure the size of the throat and mouth (oropharynx) in the form of pharyngograms. Distance of assessment is defined as the distance (length measured in centimeters [cm]) estimated to be from the lips to the larynx. Pharyngometry data were recorded for each day (Days 1 and 14 of the respective treatment period) using the mean of four measurements (pharyngograms), and the average oropharyngeal cross-sectional area was calculated.

End point type	Secondary
End point timeframe:	
Day 1 and Day 14 of the respective treatment period (up to Study Day 63)	

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[63]	25 ^[64]		
Units: centimeters (cm)				
arithmetic mean (standard deviation)				
Day 1, n=23, 23	19.2 (± 1.097)	19.24 (± 0.959)		
Day 14, n=23, 23	19.26 (± 0.717)	19.1 (± 1.003)		

Notes:

[63] - All Subjects Population: Only participants available at the specified time points were analyzed.

[64] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Oropharyngeal volume on Day 1 and Day 14 of the respective treatment period

End point title	Oropharyngeal volume on Day 1 and Day 14 of the respective treatment period
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End point description:

During the pharyngometry assessment, participants inhaled through a wavetube, which had a mouthpiece with the same dimensions as the mouthpiece on the dry powder inhaler used for this study. This technique was used to measure the size of the throat and mouth (oropharynx) in the form of pharyngograms. Oropharyngeal volume is defined as the volume (cm³) of the mouth and throat estimated to be from the lips to the larynx. Pharyngometry data were recorded for each day (Days 1 and 14 of the respective treatment period) using the mean of four measurements (pharyngograms), and the average oropharyngeal cross-sectional area was calculated.

End point type	Secondary
End point timeframe:	
Day 1 and Day 14 of the respective treatment period (up to Study Day 63)	

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[65]	25 ^[66]		
Units: Liters per minute (L/min)				
arithmetic mean (standard deviation)				
Day 1, n=23, 23	79.49 (± 43.398)	75.54 (± 44.195)		
Day 14, n=23, 23	72.35 (± 42.437)	71.47 (± 45.841)		

Notes:

[65] - All Subjects Population: Only participants available at the specified time points were analyzed.

[66] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Average flow rate and Peak Inspiratory Flow Rate (PIFR) on Day 1 and Day 14 of the respective treatment period

End point title	Average flow rate and Peak Inspiratory Flow Rate (PIFR) on Day 1 and Day 14 of the respective treatment period
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End point description:

During the inhalation profile assessment, participants inhaled through a mouthpiece from a device with a similar resistance to the dry powder inhaler used for this study. Average flow rate is defined as the average inspiratory flow rate (Liters [L]/min) across the inhalation profile when inhaling across the resistance of the inhaler. PIFR is defined as the Peak Inspiratory Flow Rate (L/min) of the inhalation profile when inhaling across the resistance of the inhaler. The pressure drop during the inhalation was measured, and the inhalation profiles (pressure drop versus time profile) of the participants were obtained. The mean of the two inhalation profile measurements was used for each day (Days 1 and 14 of the respective treatment period), and the average flow rate and PIFR were determined.

End point type	Secondary
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End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 63)

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[67]	25 ^[68]		
Units: Liters per minute (L/min)				
arithmetic mean (standard deviation)				
Day 1, Average flow rate, n=23, 23	41.11 (± 11.294)	42.72 (± 11.593)		
Day 14, Average flow rate, n=23, 23	42.29 (± 10.895)	41.36 (± 10.354)		
Day 1, PIFR, n=23, 23	65.85 (± 16.649)	67.6 (± 16.097)		
Day 14, PIFR, n=23, 23	67.36 (± 16.432)	64.79 (± 15.886)		

Notes:

[67] - All Subjects Population: Only participants available at the specified time points were analyzed.

[68] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Inhalation time on Days 1 and 14 of of the respective treatment period

End point title	Inhalation time on Days 1 and 14 of of the respective treatment period
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End point description:

During the inhalation profile assessment, participants inhaled through a mouthpiece from a device with a similar resistance to the dry powder inhaler used for this study. Inhalation time is defined as the duration of the inhalation(s) when inhaling across the resistance of the inhaler. The pressure drop during the inhalation was measured, and the inhalation profiles (pressure drop versus time profile) of the participants were obtained. The mean of the two inhalation profile measurements was used for each day (Days 1 and 14 of the respective treatment period), and the inhalation time was determined.

End point type	Secondary
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End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 63)

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[69]	25 ^[70]		
Units: Seconds (sec)				
arithmetic mean (standard deviation)				
Day 1, n=23, 23	0.97 (± 0.35)	0.83 (± 0.385)		
Day 14, n=23, 23	0.96 (± 0.314)	0.91 (± 0.347)		

Notes:

[69] - All Subjects Population: Only participants available at the specified time points were analyzed.

[70] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Inhaled volume on Days 1 and 14 of the respective treatment period

End point title	Inhaled volume on Days 1 and 14 of the respective treatment period
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End point description:

During the inhalation profile assessment, participants inhaled through a mouthpiece from a device with a similar resistance to the dry powder inhaler used for this study. Inhaled volume is defined as the volume of air (Liters) inhaled during the inhalation across the resistance of the inhaler. The pressure drop during the inhalation was measured, and the inhalation profiles (pressure drop versus time profile) of the participants were obtained. The mean of the two inhalation profile measurements was used for each day (Days 1 and 14 of the respective treatment period), and the inhaled volume was determined.

End point type	Secondary
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End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 63)

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[71]	25 ^[72]		
Units: Liters				
arithmetic mean (standard deviation)				
Day 1, n=23, 23	0.69 (± 0.337)	0.58 (± 0.285)		
Day 14, n=23, 23	0.68 (± 0.308)	0.65 (± 0.352)		

Notes:

[71] - All Subjects Population: Only participants available at the specified time points were analyzed.

[72] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Peak pressure drop on Days 1 and 14 of the respective treatment period

End point title	Peak pressure drop on Days 1 and 14 of the respective treatment period
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End point description:

During the inhalation profile assessment, participants inhaled through a mouthpiece from a device with a similar resistance to the dry powder inhaler used for this study. Peak pressure drop is defined as the maximum pressure drop (kilopascal [kPa]) achieved during inhalation across the resistance of the inhaler. The pressure drop during the inhalation was measured, and the inhalation profiles (pressure drop versus time profile) of the participants were obtained. The mean of the two inhalation profile measurements was calculated for each day (Days 1 and 14 of the respective treatment period), and used for subsequent modeling and prediction of dose emission attributes.

End point type	Secondary
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End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 63)

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[73]	25 ^[74]		
Units: Kilopascal (kpa)				
arithmetic mean (standard deviation)				
Day 1, n=23, 23	3.79 (± 1.706)	3.97 (± 1.787)		
Day 14, n=23, 23	3.93 (± 1.877)	3.67 (± 1.611)		

Notes:

[73] - All Subjects Population: Only participants available at the specified time points were analyzed.

[74] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Total emitted dose (TED) on Day 14 of the respective treatment period

End point title	Total emitted dose (TED) on Day 14 of the respective treatment period
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End point description:

The total emitted dose (TED) is defined as the mass (micrograms) of the nominal dose that passes beyond the throat. The recorded inhalation profiles of the participants and the mouth-throat (oropharyngeal) models of the sizes that approximated to pharyngometry measurements of the participants were used in conjunction with the electronic Lung (eLung) for in vitro assessment. The eLung is a breathing simulator that replicates the selected inhalation profile with an active inhaler placed at the lips end of the selected oropharyngeal model. After the dose is emitted from the inhaler, the analysis and assay of throat deposition and material passing beyond the throat was used to derive the nominal, minimum, and maximum predicted total emitted dose. The TED of VI was not assessed in

participants receiving only FF; therefore, the values are reported as 0.

End point type	Secondary
End point timeframe:	
Day 14 of the respective treatment period (up to Study Day 63)	

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[75]	25 ^[76]		
Units: micrograms				
arithmetic mean (standard deviation)				
Nominal TED FF, n=23, 23	87.58 (± 0.305)	86.33 (± 1.505)		
Minimum TED FF, n=23, 23	87.64 (± 0.33)	86.72 (± 1.589)		
Maximum TED FF, n=23, 23	87.51 (± 0.289)	85.93 (± 1.534)		
Nominal TED VI, n=23, 0	20.26 (± 0.162)	0 (± 0)		
Minimum TED VI, n=23, 0	20.22 (± 0.153)	0 (± 0)		
Maximum TED VI, n=23, 0	20.29 (± 0.175)	0 (± 0)		

Notes:

[75] - All Subjects Population: Only participants available at the specified time points were analyzed.

[76] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Ex-throat dose (ETD) and ETD <2 microns on Day 14 of the respective treatment period

End point title	Ex-throat dose (ETD) and ETD <2 microns on Day 14 of the respective treatment period
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End point description:

The ex-throat dose (ETD) and the "nominal ETD" is the mass (micrograms) of active investigational material that passes beyond the throat, nominal being the mean. The recorded inhalation profiles of the participants and the mouth-throat (oropharyngeal) models of the sizes that approximated to pharyngometry measurements of the participants were used in conjunction with the electronic Lung (eLung) for in vitro assessment. The eLung is a breathing simulator that replicates the selected inhalation profile with an active inhaler placed at the lips end of the selected oropharyngeal model. After the dose is emitted from the inhaler, the analysis and assay of throat deposition and material passing beyond the throat was used to derive the nominal, minimum, and maximum predicted ETD and ETD <2 microns. The ETD of VI was not assessed in participants receiving only FF; therefore, the values were entered as 0.

End point type	Secondary
End point timeframe:	
Day 14 of the respective treatment period (up to Study Day 63)	

End point values	FF 100 µg/VI 25 µg	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 ^[77]	25 ^[78]		
Units: micrograms				
arithmetic mean (standard deviation)				
Nominal ETD FF, n=23, 23	24.96 (± 5.801)	24.34 (± 8.574)		
Minimum ETD FF, n=23, 23	23.38 (± 7.023)	22.99 (± 9.12)		
Maximum ETD FF, n=23, 23	26.24 (± 4.825)	25.48 (± 8.197)		
ETD <2 microns FF, n=23, 23	6.66 (± 0.948)	5.97 (± 1.382)		
Minimum ETD <2 microns FF, n=23, 23	6.45 (± 0.788)	5.77 (± 1.319)		
Maximum ETD <2 microns FF, n=23, 23	6.92 (± 1.147)	6.21 (± 1.476)		
Nominal ETD VI, n=23, 0	8.54 (± 0.953)	0 (± 0)		
Minimum ETD VI, n=23, 0	8.33 (± 0.793)	0 (± 0)		
Maximum ETD VI, n=23, 0	8.8 (± 1.154)	0 (± 0)		
ETD <2 microns VI, n=23, 0	4.86 (± 1.162)	0 (± 0)		
Minimum ETD <2 microns VI, n=23, 0	4.6 (± 0.965)	0 (± 0)		
Maximum ETD <2 microns VI, n=23, 0	5.18 (± 1.409)	0 (± 0)		

Notes:

[77] - All Subjects Population: Only participants available at the specified time points were analyzed.

[78] - All Subjects Population: Only participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment AEs

Adverse event reporting additional description:

Serious adverse events (SAEs) and non-serious AEs were collected in members of the All Subjects Population, comprised of all participants who received at least one dose of study medication.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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Reporting groups

Reporting group title	FF 100 µg/VI 25 µg
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Reporting group description:

Participants received FF 100 µg/VI 25 µg in one of the two 14-day treatment periods. FF 100 µg/VI 25 µg was administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler. The washout period between the treatment periods was at least 7 days.

Reporting group title	FF 100 µg
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Reporting group description:

Participants received FF 100 µg in one of the two 14-day treatment periods. FF 100 µg was administered once daily in the morning (Day 1 to Day 14) via the Dry Powder Inhaler. The washout period between the treatment periods was at least 7 days.

Serious adverse events	FF 100 µg/VI 25 µg	FF 100 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	FF 100 µg/VI 25 µg	FF 100 µg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 25 (16.00%)	1 / 25 (4.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Eye disorders			

Conjunctivitis subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 25 (0.00%) 0	
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 25 (0.00%) 0	
Conjunctivitis, Viral subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 25 (4.00%) 1	
Pharyngitis, Streptococcal subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	1 / 25 (4.00%) 1	
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 25 (4.00%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported