Clinical trial results:
A Randomized, Double blind, Placebo controlled, Two-Way Crossover 7-day study to Investigate the Safety, Tolerability, Pharmacodynamics and Pharmacokinetics of Repeat Dose Inhaled GW642444 25g in Children aged 5-11 years with Persistent Asthma

Summary

EudraCT number	2012-000741-12
Trial protocol	Outside EU/EEA
Global end of trial date	12 April 2011

Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	14 May 2015

Trial information

Trial identification

Sponsor protocol code	HZA112776

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01453296
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)	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	27 May 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 April 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the safety and tolerability following administration of GW642444 25 µg, via a novel dry powder inhaler, once-daily for 7 days in subjects aged 5–11 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 cannula was inserted for serial blood draws, to prevent the pain and distress associated with repeated needle sticks.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 March 2010
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: 28
Worldwide total number of subjects	28
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)	28
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:

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 treatment sequences (Vilanterol [VI] 25 micrograms [µg] followed by matching Placebo; matching placebo followed by VI 25 µg) in a 1:1 ratio in an AB or BA sequence.

Period 1

Period 1 title	Treatment Period 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	Sequence 1: VI 25 µg followed by Placebo

Arm description:

Participants received vilanterol (VI) 25 micrograms (µg) and matching placebo in Treatment Periods 1 and 2, respectively. Inhaled VI 25 µg and matching placebo were administered once daily in the morning (Day 1 to Day 14) via a Dry Powder Inhaler. The washout period between the 14-day treatment periods was at least 7 days.

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

Dosage and administration details:

Vilanterol 25mg or Placebo once daily x 14 days; 7 day wash out (w/o); crossover

Arm title	Sequence 2: Placebo followed by VI 25 µg

Arm description:

Participants received placebo and VI 25 µg in Treatment Periods 1 and 2, respectively. Inhaled VI 25 µg and matching placebo were administered once daily in the morning (Day 1 to Day 14) via a Dry Powder Inhaler. The washout period between the 14-day treatment periods was at least 7 days.

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

Dosage and administration details:

Vilanterol 25mg or Placebo once daily x 14 days; 7 day w/o; crossover

Number of subjects in period 1	Sequence 1: VI 25 µg followed by Placebo	Sequence 2: Placebo followed by VI 25 µg
Started	14	14
Completed	13	13
Not completed	1	1
Met protocol-Defined Stopping Criteria	1	-
Adverse event, non-fatal	-	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	Sequence 1: VI 25 µg followed by Placebo

Arm description:

Participants received vilanterol (VI) 25 micrograms (µg) and matching placebo in Treatment Periods 1 and 2, respectively. Inhaled VI 25 µg and matching placebo were administered once daily in the morning (Day 1 to Day 14) via a Dry Powder Inhaler. The washout period between the 14-day treatment periods was at least 7 days.

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

Dosage and administration details:

Vilanterol 25mg or Placebo once daily x 14 days; 7 day w/o; crossover

Arm title	Sequence 2: Placebo followed by VI 25 µg

Arm description:

Participants received placebo and VI 25 µg in Treatment Periods 1 and 2, respectively. Inhaled VI 25 µg and matching placebo were administered once daily in the morning (Day 1 to Day 14) via a Dry Powder Inhaler. The washout period between the 14-day treatment periods was at least 7 days.

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

Dosage and administration details:

Vilanterol 25mg or Placebo once daily x 14 days; 7 day w/o; crossover

Number of subjects in period 2	Sequence 1: VI 25 µg followed by Placebo	Sequence 2: Placebo followed by VI 25 µg
Started	13	13
Completed	13	13

Period 3	
Period 3 title	Treatment Period 2
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	Sequence 1: VI 25 µg followed by Placebo

Arm description:

Participants received vilanterol (VI) 25 micrograms (µg) and matching placebo in Treatment Periods 1 and 2, respectively. Inhaled VI 25 µg and matching placebo were administered once daily in the morning (Day 1 to Day 14) via a Dry Powder Inhaler. The washout period between the 14-day treatment periods was at least 7 days.

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

Dosage and administration details:

Vilanterol 25mg or Placebo once daily x 14 days; 7 day w/o; crossover

Arm title	Sequence 2: Placebo followed by VI 25 µg

Arm description:

Participants received placebo and VI 25 µg in Treatment Periods 1 and 2, respectively. Inhaled VI 25 µg and matching placebo were administered once daily in the morning (Day 1 to Day 14) via a Dry Powder Inhaler. The washout period between the 14-day treatment periods was at least 7 days.

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

Dosage and administration details:

Vilanterol 25mg or Placebo once daily x 14 days; 7 day w/o; crossover

Number of subjects in period 3	Sequence 1: VI 25 µg followed by Placebo	Sequence 2: Placebo followed by VI 25 µg
Started	13	13
Completed	11	13
Not completed	2	0
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Period 1 (Overall)

Reporting group description:

Participants received either vilanterol (VI) 25 micrograms (µg) or matching placebo in the first of two 14-day treatment periods, followed by a repeat dose of the other therapy (the therapy not received in the first treatment period) in the second 14-day treatment period. Inhaled VI 25 µg or matching placebo 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 values	Treatment Period 1 (Overall)	Total	
Number of subjects	28	28	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	28	28	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	8		
standard deviation	± 1.9	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	18	18	
Race, Customized Units: Subjects			
African American/African Heritage	5	5	
White - White/Caucasian/European Heritage	22	22	
Mixed Race	1	1	

End points

End points reporting groups

Reporting group title	Sequence 1: VI 25 µg followed by Placebo

Reporting group description:

Participants received vilanterol (VI) 25 micrograms (µg) and matching placebo in Treatment Periods 1 and 2, respectively. Inhaled VI 25 µg and matching placebo were administered once daily in the morning (Day 1 to Day 14) via a Dry Powder Inhaler. The washout period between the 14-day treatment periods was at least 7 days.

Reporting group title	Sequence 2: Placebo followed by VI 25 µg

Reporting group description:

Participants received placebo and VI 25 µg in Treatment Periods 1 and 2, respectively. Inhaled VI 25 µg and matching placebo were administered once daily in the morning (Day 1 to Day 14) via a Dry Powder Inhaler. The washout period between the 14-day treatment periods was at least 7 days.

Reporting group title	Sequence 1: VI 25 µg followed by Placebo

Reporting group description:

Participants received vilanterol (VI) 25 micrograms (µg) and matching placebo in Treatment Periods 1 and 2, respectively. Inhaled VI 25 µg and matching placebo were administered once daily in the morning (Day 1 to Day 14) via a Dry Powder Inhaler. The washout period between the 14-day treatment periods was at least 7 days.

Reporting group title	Sequence 2: Placebo followed by VI 25 µg

Reporting group description:

Participants received placebo and VI 25 µg in Treatment Periods 1 and 2, respectively. Inhaled VI 25 µg and matching placebo were administered once daily in the morning (Day 1 to Day 14) via a Dry Powder Inhaler. The washout period between the 14-day treatment periods was at least 7 days.

Reporting group title	Sequence 1: VI 25 µg followed by Placebo

Reporting group description:

Participants received vilanterol (VI) 25 micrograms (µg) and matching placebo in Treatment Periods 1 and 2, respectively. Inhaled VI 25 µg and matching placebo were administered once daily in the morning (Day 1 to Day 14) via a Dry Powder Inhaler. The washout period between the 14-day treatment periods was at least 7 days.

Reporting group title	Sequence 2: Placebo followed by VI 25 µg

Reporting group description:

Participants received placebo and VI 25 µg in Treatment Periods 1 and 2, respectively. Inhaled VI 25 µg and matching placebo were administered once daily in the morning (Day 1 to Day 14) via a Dry Powder Inhaler. The washout period between the 14-day treatment periods was at least 7 days.

Subject analysis set title	Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants who received matching placebo in one or both of the two 14-day treatment periods. Matching placebo 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	VI 25 µg
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants who received VI 25 µg in one or both of the 14-day treatment periods. Inhaled 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	VI 25 µg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All participants who received VI 25 µg in one or both of the 14-day treatment periods. Inhaled 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.

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]

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 AE/SAE module for a complete list of AEs and SAEs.

End point type	Primary

End point timeframe:

From the start of study medication until Week 11 (Visit 8)/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	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[2]	27[3]		
Units: Participants				
Any AE	6	9		
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]

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. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg.

End point type	Primary

End point timeframe:

Day 14 of the respective treatment period (up to Study Day 49)

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	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[5]	27[6]		
Units: 10^9 cells per liter (GI/L)				
arithmetic mean (standard deviation)				
Basophils, n=24, 25	0.021 (± 0.0145)	0.034 (± 0.0185)		
Eosinophils, n=24, 25	0.276 (± 0.3002)	0.348 (± 0.3458)		
Lymphocytes, n=24, 25	2.404 (± 0.8652)	2.419 (± 0.8729)		
Monocytes, n=24, 25	0.268 (± 0.131)	0.376 (± 0.1419)		
Total neutrophils, n=24, 25	3.354 (± 1.3054)	3.127 (± 0.9625)		
Platelets, n=23, 25	280.7 (± 54.11)	279.4 (± 54.71)		
WBCs, n=24, 25	6.32 (± 1.808)	6.3 (± 1.64)		

Notes:

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

[6] - All Subjects Population,Only those 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. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg.

End point type	Primary

End point timeframe:

Day 14 of the respective treatment period (up to Study Day 49)

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	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[8]	27[9]		
Units: Grams per liter (g/L)				
arithmetic mean (standard deviation)				
Hemoglobin, n=24, 25	133 (± 11.3)	130.7 (± 11.22)		
MCHC, n=24, 25	337.1 (± 5.5)	338.3 (± 11.6)		

Notes:

[8] - All Subjects Population, only those participants available at the specified time points were analyed

[9] - All Subjects Population, only those participants available at the specified time points were analyed

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]

End point description:

Blood samples were collected for the measurement of reticulocytes and RBCs at Day 14 of the respective treatment period. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg.

End point type	Primary

End point timeframe:

Day 14 of the respective treatment period (up to Study Day 49)

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	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[11]	27[12]		
Units: 10^12 cells per liter (TI/L)				
arithmetic mean (standard deviation)				
Reticulocytes, n=24, 25	0.0501 (± 0.020696)	0.05275 (± 0.024571)		
RBCs, n=24, 25	4.6 (± 0.374)	4.47 (± 0.339)		

Notes:

[11] - All Subjects Population,only those participants available at the specified time points were analyzed
[12] - All Subjects Population,only those participants available at the specified time points were analyzed

Statistical analyses

No statistical analyses for this end point

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

End point title	Hematocrit value at Day 14 of the respective treatment

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). Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg.

End point type	Primary

End point timeframe:

Day 14 of the respective treatment period (up to Study Day 49)

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	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24[14]	25[15]		
Units: proportion of 1				
arithmetic mean (standard deviation)				
proportion of 1	0.3948 (± 0.0343)	0.3863 (± 0.02617)		

Notes:

[14] - All Subjects Population,only those participants available at the specified time points were analyzed
[15] - All Subjects Population,only those 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]

End point description:

Blood samples were collected for the measurement of MCV at Day 14 of the respective treatment period. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg.

End point type	Primary

End point timeframe:

Day 14 of the respective treatment period (up to Study Day 49)

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	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24[17]	25[18]		
Units: 10^15 femtoliters (fL) per cell				
arithmetic mean (standard deviation)				
10^15 femtoliters (fL) per cell	86 (± 4.08)	86.6 (± 3.59)		

Notes:

[17] - All Subjects Population,only those participants available at the specified time points were analyzed
[18] - All Subjects Population,only those participants available at the specified time points were analyzed

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Blood samples were collected for the measurement of MCH at Day 14 of the respective treatment period . Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI

25 µg.

End point type	Primary

End point timeframe:

Day 14 of the respective treatment period (up to Study Day 49)

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	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24[20]	25[21]		
Units: 10^12 picograms (pg) per cell				
arithmetic mean (standard deviation)				
10^12 picograms (pg) per cell	28.97 (± 1.337)	29.29 (± 1.464)		

Notes:

[20] - All Subjects Population,only those participants available at the specified time points were analyzed
[21] - All Subjects Population,only those 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]

End point description:

Blood samples were collected for the measurement of ALT, ALP, AST, and GGT at Day 14 of the respective treatment period. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg.

End point type	Primary

End point timeframe:

Day 14 of the respective treatment period (up to Study Day 49)

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	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[23]	27[24]		
Units: International units per liter (IU/L)				
arithmetic mean (standard deviation)				
ALT, n=22, 25	13.9 (± 4.21)	13.5 (± 3.56)		
ALP, n=22, 25	260.5 (± 109.65)	273.4 (± 103.51)		
AST, n=22, 24	27.7 (± 6.11)	25.5 (± 4.52)		
GGT, n=22, 25	14.1 (± 4.12)	13.6 (± 3.51)		

Notes:

[23] - All Subjects Population,only those participants available at the specified time points were analyzed
[24] - All Subjects Population,only those 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]

End point description:

Blood samples were collected for the measurement of albumin and total protein at Day 14 of the respective treatment period. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg.

End point type	Primary

End point timeframe:

Day 14 of the respective treatment period (up to Study Day 49)

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	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[26]	27[27]		
Units: Grams per liter				
arithmetic mean (standard deviation)				
Albumin, n=22, 25	42.8 (± 2.95)	43.2 (± 1.96)		
Total protein, n=22, 25	67.9 (± 4.82)	68.6 (± 3.16)		

Notes:

[26] - All Subjects Population,only those participants available at the specified time points were analyzed
[27] - All Subjects Population,only those 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]

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. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg.

End point type	Primary

End point timeframe:

Day 14 of the respective treatment period (up to Study Day 49)

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	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[29]	27[30]		
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Calcium, n=22, 24	2.327 (± 0.1357)	2.359 (± 0.0666)		
Chloride, n=22, 25	105.5 (± 3.9)	105.1 (± 2.01)		
CO2 content/bicarbonate, n=22, 24	17.6 (± 2.3)	18.1 (± 1.98)		
Glucose, n=22, 25	4.95 (± 0.51)	5.04 (± 0.513)		
Potassium, n=22, 24	4.3 (± 0.408)	4.33 (± 0.242)		
Sodium, n=22, 25	137.7 (± 2.43)	137.8 (± 2.12)		
Urea/BUN, n=22, 25	4.91 (± 1.368)	4.48 (± 1.15)		

Notes:

[29] - All Subjects Population,only those participants available at the specified time points were analyzed
[30] - All Subjects Population,only those 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]

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. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg.

End point type	Primary

End point timeframe:

Day 14 of the respective treatment period (up to Study Day 49)

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	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[32]	27[33]		
Units: Micromoles per liter (µmol/L)				
arithmetic mean (standard deviation)				
Total bilirubin, n=22, 25	6.2 (± 2.22)	5.8 (± 1.99)		
Direct bilirubin, n=22, 25	1.7 (± 0.94)	1.2 (± 1)		
Creatinine, n=22, 25	39.45 (± 7.653)	39.35 (± 6.731)		

Uric acid, n=22, 25	241.4 (± 69.51)	245.6 (± 47.27)		

Notes:

[32] - All Subjects Population,only those participants available at the specified time points were analyzed
[33] - All Subjects Population,only those 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, Day 8, and Day 14 of the respective treatment period

End point title	Peak expiratory flow on Day 1, Day 8, and Day 14 of the respective treatment period[34]

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 pre-dose measurement at Day 1 for the respective period. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg (n=28).

End point type	Primary

End point timeframe:

Day 1, Day 8, and Day 14 of the respective treatment period (up to Study Day 49)

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	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[35]	28[36]		
Units: liters/minute				
arithmetic mean (standard deviation)				
Day 1, Baseline, n=26, 28	230.6 (± 72.55)	233 (± 68.55)		
Day 1, 20 minutes post-dose, n=26, 28	237.5 (± 69.65)	245.6 (± 73.47)		
Day 8, Pre-dose, n=26, 28	232.1 (± 64.76)	228.8 (± 64.42)		
Day 8, 20 minutes post-dose, n=25, 28	233.8 (± 220)	240.7 (± 65.66)		
Day 14, Pre-dose, n=24, 26	240.3 (± 75.9)	239 (± 72.02)		
Day 14, 20 minutes post-dose, n=24, 26	243.3 (± 75.18)	248.1 (± 76.2)		

Notes:

[35] - All Subjects Population,only those participants available at the specified time points were analyzed
[36] - All Subjects Population,only those participants available at the specified time points were analyzed

Statistical analyses

No statistical analyses for this end point

Primary: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) at Day 1, Day 8, and Day 14 of the respective treatment period

End point title	Systolic blood pressure (SBP) and diastolic blood pressure (DBP) at Day 1, Day 8, and Day 14 of the respective treatment period[37]

End point description:

SBP and DBP were measured at Day 1, Day 8, and Day 14 of the respective treatment period. PD=post-dose. Baseline is defined as the pre-dose measurement at Day 1 for the respective period. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg (n=28).

End point type	Primary

End point timeframe:

Day 1, Day 8, and Day 14 of the respective treatment period (up to Study Day 49)

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	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[38]	28[39]		
Units: Millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Day 1 SBP, Baseline, n=26, 28	101.8 (± 6.59)	102.9 (± 9.21)		
Day 1 SBP, 10 minutes PD, n=26, 28	100.7 (± 7.59)	102.4 (± 7.69)		
Day 1 SBP, 30 minutes PD, n=26, 28	100.9 (± 9.35)	103.5 (± 6.89)		
Day 1 SBP, 45 minutes PD, n=26, 28	100.9 (± 7.41)	103.5 (± 7.05)		
Day 1 SBP, 74 minutes PD, n=26, 28	102.7 (± 7.95)	104.4 (± 6.81)		
Day 1 SBP, 2 hours PD, n=26, 28	103.3 (± 8.16)	104.8 (± 7.82)		
Day 8 SBP, Pre-dose, n=25, 28	99.6 (± 6.92)	103.7 (± 8.64)		
Day 8 SBP, 30 minutes PD, n=25, 28	101.7 (± 7.29)	102.9 (± 7.31)		
Day 8 SBP, 1 hour PD, n=25, 28	101.8 (± 8.38)	103.6 (± 7.17)		
Day 14 SBP, Pre-dose, n=24, 26	101.5 (± 9.18)	103.9 (± 6.15)		
Day 14 SBP, 10 minutes PD, n=24, 26	101.3 (± 9.98)	103.7 (± 6.7)		
Day 14 SBP, 30 minutes PD, n=24, 26	103.9 (± 8.72)	102.9 (± 8.91)		
Day 14 SBP, 45 minutes PD, n=24, 26	103.6 (± 7.95)	103.4 (± 7.03)		
Day 14 SBP, 75 minues PD, n=24, 26	104.9 (± 8.33)	103.9 (± 6.36)		
Day 14 SBP, 2 hours PD, n=24, 26	103 (± 6.68)	102.9 (± 6.42)		
Day 14 SBP, 4 hours PD, n=24, 26	102.2 (± 7.8)	106 (± 5.2)		
Day 14 SBP, 8 hours PD, n=24, 26	104.7 (± 8.92)	104.7 (± 7.76)		
Day 1 DBP, Baseline, n=26, 28	62 (± 5.12)	62.1 (± 6.38)		
Day 1 DBP, 10 minutes PD, n=26, 28	62.4 (± 7.16)	63.5 (± 4.08)		
Day 1 DBP, 30 minutes PD, n=26, 28	62.4 (± 6.55)	62.6 (± 4.29)		
Day 1 DBP, 45 minutes PD, n=26, 28	63 (± 7.93)	63.3 (± 5.99)		
Day 1 DBP, 75 minutes PD, n=26, 28	63.3 (± 5.74)	64.4 (± 7.91)		
Day 1 DBP, 2 hours PD, n=26, 28	63 (± 4.81)	63.4 (± 5.49)		
Day 8 DBP, Pre-dose, n=25, 28	63.7 (± 8.17)	62.8 (± 5.58)		
Day 8 DBP, 30 minutes PD, n=25, 28	62.3 (± 9.19)	62.4 (± 7.26)		
Day 8 DBP, 1 hour PD, n=25, 28	63.2 (± 6.68)	62.2 (± 7.9)		
Day 14 DBP, Pre-dose, n=24, 26	60.8 (± 5.7)	63.8 (± 8.14)		
Day 14 DBP, 10 minutes PD, n=24, 26	60.9 (± 6.55)	62.7 (± 7.07)		
Day 14 DBP, 30 minutes PD, n=24, 26	62.8 (± 3.83)	63.7 (± 7.88)		
Day 14 DBP, 45 minutes PD, n=24, 26	61.9 (± 4.05)	64.5 (± 4.68)		
Day 14 DBP, 75 minutes PD, n=23, 26	63 (± 5.12)	63.6 (± 6.34)		
Day 14 DBP, 2 hours PD, n=23, 26	64.1 (± 7.33)	63.3 (± 5.5)		
Day 14 DBP, 4 hours PD, n=23, 26	62.3 (± 8.56)	63.9 (± 6.59)		

Day 14 DBP, 8 hours PD, n=23, 26	63.2 (± 4.78)	63.3 (± 7.29)		

Notes:

[38] - All Subjects Population,only those participants available at the specified time points were analyzed

[39] - All Subjects Population,only those participants available at the specified time points were analyzed

Statistical analyses

No statistical analyses for this end point

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

End point title	Maximum heart rate at Day 1 and Day 14 of the respective treatment period

End point description:

Heart rate (HR) was measured at Day 1 and Day 14 of the respective treatment period. hr=hour. For 0-8 hr parameters, treatment, period, participant Baseline, and period Baseline were fitted as fixed effects, and participant was fitted as a random effect. For 0-2 hr parameters, 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. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg (n=28).

End point type	Primary

End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 49)

End point values	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[40]	28[41]		
Units: Beats per minute				
least squares mean (standard error)				
Day 1 maximum HR (0-2 hr), n=26, 28	83.6 (± 1.44)	86.1 (± 1.4)		
Day 14 maximum HR (0-2 hr), n=24, 26	84.3 (± 1.38)	85 (± 1.35)		
Day 14 maximum HR (0-8 hr), n=24, 26	88.1 (± 1.45)	88.6 (± 1.41)		

Notes:

[40] - All Subjects Population,only those participants available at the specified time points were analyzed

[41] - All Subjects Population,only those participants available at the specified time points were analyzed

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo v VI 25 µg
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[42]
Parameter estimate	Mean difference (final values)
Point estimate	2.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	5.7

Notes:

[42] - Estimation based analysis. Day 1 maximum HR (0-2 hr). The estimated value represents the treatment difference: VI 25 µg minus placebo.

Statistical analysis title	Analysis 2
Comparison groups	Placebo v VI 25 µg
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[43]
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	3.7

Notes:

[43] - Estimation based analysis. Day 14 maximum HR (0-2 hr). The estimated value represents the treatment difference: VI 25 µg minus placebo.

Statistical analysis title	Analysis 3
Comparison groups	Placebo v VI 25 µg
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[44]
Parameter estimate	Median difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	3.6

Notes:

[44] - Estimation based analysis. Day 14 maximum HR (0-8 hr). The estimated value represents the treatment difference: VI 25 µg minus placebo.

Primary: Weighted mean heart rate at Day 1 and Day 14 of the respective treatment period

End point title	Weighted mean heart rate at Day 1 and Day 14 of the respective treatment period

End point description:

Heart rate (HR) was measured at Day 1 and Day 14 of the respective treatment period. hr=hour. 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 times were used for these observations. For 0-8 hr parameters, treatment, period, participant Baseline, and period Baseline were fitted as fixed effects, and participant was fitted as a random effect. For 0-2 hr parameters, 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. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg (n=28).

End point type	Primary

End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 49)

End point values	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[45]	28[46]		
Units: Beats per minute				
least squares mean (standard error)				
Day 1 weighted HR (0-2 hr), n=26, 28	76.39 (± 1.311)	79.2 (± 1.285)		
Day 14 weighted mean HR (0-2 hr), n=23, 26	76.11 (± 1.309)	77.67 (± 1.264)		
Day 14 weighted mean HR (0-8 hr), n=23, 26	80.54 (± 1.458)	80.65 (± 1.404)		

Notes:

[45] - All Subjects Population,only those participants available at the specified time points were analyzed

[46] - All Subjects Population,only those participants available at the specified time points were analyzed

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo v VI 25 µg
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[47]
Parameter estimate	Mean difference (final values)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	5.7

Notes:

[47] - Estimation based analysis. Day 1 weighted HR (0-2 hr). The estimated value represents the treatment difference: VI 25 µg minus placebo.

Statistical analysis title	Analysis 2
Comparison groups	Placebo v VI 25 µg
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[48]
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	3.7

Notes:

[48] - Estimation based analysis. Day 14 weighted HR (0-2 hr). The estimated value represents the treatment difference: VI 25 µg minus placebo.

Statistical analysis title	Analysis 3
Comparison groups	Placebo v VI 25 µg
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[49]
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	3.6

Notes:

[49] - Estimation based analysis. Day 14 weighted HR (0-8 hr). The estimated value represents the treatment difference: VI 25 µg minus placebo.

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

End point description:

The electrocardiographic (ECG) parameter QT duration corrected using Fridericia's formula (QTcF) was measured at Day 1 and Day 14 of the respective treatment period. hr=hour. For 0-8 hr parameters, treatment, period, participant Baseline, and period Baseline were fitted as fixed effects, and participant was fitted as a random effect. For 0-2 hr parameters, 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. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg (n=28).

End point type	Primary

End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 49)

End point values	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[50]	28[51]		
Units: milliseconds				
least squares mean (standard error)				
Day 1 maximum QTcF (0-2 hr), n=26, 28	405.6 (± 2.29)	406.6 (± 2.22)		
Day 14 maximum QTcF (0-2 hr), n=24, 26	406.1 (± 2.06)	407.7 (± 2)		
Day 14 maximum QTcF (0-8 hr), n=24, 26	407.8 (± 1.87)	409.2 (± 1.82)		

Notes:

[50] - All Subjects Population,only those participants available at the specified time points were analyzed

[51] - All Subjects Population,only those participants available at the specified time points were analyzed

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo v VI 25 µg
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[52]
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	6.6

Notes:

[52] - Estimation based analysis. Day 1 maximum QTcF (0-2 hr). The estimated value represents the treatment difference: VI 25 µg minus placebo.

Statistical analysis title	Analysis 2
Comparison groups	Placebo v VI 25 µg
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[53]
Parameter estimate	Mean difference (final values)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	6.3

Notes:

[53] - Estimation based analysis. Day 14 maximum QTcF (0-2 hr). The estimated value represents the treatment difference: VI 25 µg minus placebo.

Statistical analysis title	Analysis 3
Comparison groups	Placebo v VI 25 µg
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[54]
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	5.7

Notes:

[54] - Estimation based analysis. Day 14 maximum QTcF (0-8 hr). The estimated value represents the treatment difference: VI 25 µg minus placebo.

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

End point title	Weighted mean QTcF at Day 1 and Day 14 of the respective treatment period

End point description:

The electrocardiographic (ECG) parameter QT duration corrected using Fridericia's formula (QTcF) was measured at Day 1 and Day 14 of the respective treatment period. hr=hour. Actual relative times were used for the calculation except where actual times were missing. If any actual times were missing, planned relative times were used for these observations. For 0-8 hr parameters, treatment, period, participant Baseline, and period Baseline were fitted as fixed effects, and participant was fitted as a random effect. For 0-2 hr parameters, 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. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg (n=28).

End point type	Primary

End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 49)

End point values	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[55]	28[56]		
Units: milliseconds				
least squares mean (standard error)				
Day 1 weighted mean QTcF (0-2 hr), n=26, 28	394.21 (± 2.007)	396.22 (± 1.96)		
Day 14 weighted mean QTcF (0-2 hr), n=23, 26	395.09 (± 2.122)	398.03 (± 2.024)		
Day 14 weighted mean QTcF (0-8 hr), n=23, 26	393.43 (± 1.867)	396.62 (± 1.793)		

Notes:

[55] - All Subjects Population,only those participants available at the specified time points were analyzed

[56] - All Subjects Population,only those participants available at the specified time points were analyzed

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo v VI 25 µg
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[57]
Parameter estimate	Mean difference (final values)
Point estimate	2.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.59
upper limit	6.61

Notes:

[57] - Estimation based analysis. Day 1 weighted QTcF (0-2 hr). The estimated value represents the treatment difference: VI 25 µg minus placebo.

Statistical analysis title	Analysis 2
Comparison groups	Placebo v VI 25 µg

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[58]
Parameter estimate	Mean difference (final values)
Point estimate	2.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.93
upper limit	7.81

Notes:

[58] - Estimation based analysis. Day 14 weighted QTcF (0-2 hr). The estimated value represents the treatment difference: VI 25 µg minus placebo.

Statistical analysis title	Analysis 3
Comparison groups	Placebo v VI 25 µg
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[59]
Parameter estimate	Mean difference (final values)
Point estimate	3.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	7.08

Notes:

[59] - Estimation based analysis. Day 14 weighted QTcF (0-8 hr). The estimated value represents the treatment difference: VI 25 µg minus placebo.

Secondary: AUC(0-t) and AUC(0-8) on Day 14 of the respective treatment period

End point title	AUC(0-t) and AUC(0-8) on Day 14 of the respective treatment period

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 8 hours AUC(0-8) 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, 4, 6, and 8 hours post-dose for participants who were >=20 kilograms and pre-dose; 10 min and 30 min post-dose; and 1, 2, and 4 hours post-dose for participants who were <=20 kilograms on Day 14 of the respective treatment period. Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the Pharmacokinetic Population. Pharmacokinetic (PK) Population: all participants in the All Subjects Population for whom a PK sample was obtained and analyzee. Only those participants available at the specified time points were analyzed (represented by n=X,X in the category titles).

End point type	Secondary

End point timeframe:

Day 14 of the respective treatment period (up to Study Day 49)

End point values	VI 25 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	25[60]			
Units: picograms*hour per milliliter (pg*hr/mL)				
geometric mean (confidence interval 95%)				
AUC(0-t), n=0,25 AUC(0-8), n=0,19	132.8 (96 to 183.8) 181.7 (145 to 227.7)			

Notes:

[60] - PK Population:all participants in All Subjects Population for whom a PK sample was obtained/analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax on Day 14 of the respective treatment period

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

End point description:

Cmax is defined as the maximum observed 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, 4, 6, and 8 hours post-dose for participants who were >=20 kilograms and pre-dose; 10 min and 30 min post-dose; and 1, 2, and 4 hours post-dose for participants who were <=20 kilograms on Day 14 of the respective treatment period.

End point type	Secondary

End point timeframe:

Day 14 of the respective treatment period (up to Study Day 49)

End point values	VI 25 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	25[61]			
Units: picograms per milliliter (pg/mL)				
geometric mean (confidence interval 95%)	97.44 (64.83 to 146.45)			

Notes:

[61] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: tmax, t1/2, and t at Day 14 of the respective treatment period

End point title	tmax, t1/2, and t at Day 14 of the respective treatment period

End point description:

tmax is defined as the time to reach the observed maximum concentration, t1/2 is defined as the time required to reduce the plasma concentration to one half its initial value, and t 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, 4, 6, and 8 hours post-dose for participants who were >=20 kilograms and pre-dose; 10 min and 30 min

post-dose; and 1, 2, and 4 hours post-dose for participants who were <=20 kilograms on Day 14 of the respective treatment period. PK Population. 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

End point timeframe:

Day 14 of the respective treatment period (up to Study Day 49)

End point values	VI 25 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	25[62]			
Units: hours				
median (full range (min-max))				
tmax, n=23	0.2 (0 to 1)			
t1/2, n=14	3.131 (1.06 to 6.32)			
t, n=23	6 (1 to 8.13)			

Notes:

[62] - PK Population. Only those participants available at the specified time points were analyzed (n=X).

Statistical analyses

No statistical analyses for this end point

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

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

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, 4, 6, and 8 hours post-dose for participants who were >=20 kilograms and pre-dose; 10 min and 30 min post-dose; and 1, 2, and 4 hours post-dose for participants who were <=20 kilograms on Day 14 of the respective treatment period. 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 times were used for these observations. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg. Treatment and period were fitted as fixed effects and participant was fitted as a random effect.

End point type	Secondary

End point timeframe:

Day 14 of the respective treatment period (up to Study Day 49)

End point values	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[63]	27[64]		
Units: Millimoles per liter (mmol/L)				
least squares mean (standard error)				
Maximum Glucose (0-2 hr), n=24, 26	5.55 (± 0.184)	5.57 (± 0.182)		

Maximum Glucose (0-8 hr), n=24, 26	6.22 (± 0.187)	6.03 (± 0.183)		
Weighted Mean Glucose (0-2 hr), n=21, 25	5.02 (± 0.114)	5.06 (± 0.109)		
Weighted Mean Glucose (0-8 hr), n=19, 24	5.26 (± 0.108)	5.21 (± 0.1)		
Minimum Potassium (0-2 hr), n=23, 26	4.05 (± 0.04)	4 (± 0.038)		
Minimum Potassium (0-8 hr), n=24, 26	3.89 (± 0.06)	3.87 (± 0.059)		
Weighted Mean Potassium (0-2 hr), n=19, 22	4.21 (± 0.049)	4.23 (± 0.046)		
Weighted Mean Potassium (0-8 hr), n=17, 22	4.05 (± 0.052)	4.11 (± 0.049)		

Notes:

[63] - All Subjects Population,only those participants available at the specified time points were analyzed

[64] - All Subjects Population,only those 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

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. All Subjects Population. Only those participants available at the specified time point were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 49)

End point values	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[65]	27[66]		
Units: centimeters squared (cm^2)				
arithmetic mean (standard deviation)				
Day 1, n=15, 13	5.65 (± 1.834)	4.42 (± 2.31)		
Day 14, n=14, 15	5.47 (± 1.661)	5.16 (± 2.139)		

Notes:

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

[66] - All Subjects Population. Only those participants available at the specified time point 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

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. All Subjects Population. Only those participants available at the specified time point were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 49)

End point values	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[67]	27[68]		
Units: centimeters (cm)				
arithmetic mean (standard deviation)				
Day 1, n=15, 13	18.4 (± 1.502)	18.26 (± 1.824)		
Day 14, n=14, 15	18.46 (± 1.395)	18.41 (± 1.276)		

Notes:

[67] - All Subjects Population. Only those participants available at the specified time point were analyzed
[68] - All Subjects Population. Only those participants available at the specified time point 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

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 (centimeters cubed [cm^3]) 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. All Subjects Population. Only those participants available at the specified time point were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 49)

End point values	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[69]	27[70]		
Units: cm^3				
arithmetic mean (standard deviation)				
Day 1, n=15, 13	102.33 (± 32.451)	78.6 (± 39.296)		
Day 14, n=14, 15	102.26 (± 36.322)	93.35 (± 37.19)		

Notes:

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

[70] - All Subjects Population. Only those participants available at the specified time point 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

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. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg.

End point type	Secondary

End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 49)

End point values	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[71]	27[72]		
Units: Liters per minute (L/min)				
arithmetic mean (standard deviation)				
Day 1, Average flow rate, n=23, 25	38.84 (± 9.44)	42.23 (± 10.952)		
Day 14, Average flow rate, n=23, 25	40.45 (± 10.538)	42.08 (± 10.191)		
Day 1, PIFR, n=23, 25	58.27 (± 14.258)	61.41 (± 16.513)		

Day 14, PIFR, n=23, 25	60.93 (± 14.901)	61.79 (± 15.348)		

Notes:

[71] - All Subjects Population. Only those participants available at the specified time point were analyzed
[72] - All Subjects Population. Only those participants available at the specified time point were analyzed

Statistical analyses

No statistical analyses for this end point

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

End point title	Inhalation time on Day 1 and Day 14 of the respective treatment period

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. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg.

End point type	Secondary

End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 49)

End point values	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[73]	27[74]		
Units: Seconds (sec)				
arithmetic mean (standard deviation)				
Day 1, n=23, 25	1.45 (± 0.604)	1.36 (± 0.551)		
Day 14, n=23, 25	1.35 (± 0.528)	1.34 (± 0.476)		

Notes:

[73] - All Subjects Population. Only those participants available at the specified time point were analyzed
[74] - All Subjects Population. Only those participants available at the specified time point were analyzed

Statistical analyses

No statistical analyses for this end point

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

End point title	Inhaled volume on Day 1 and Day 14 of the respective treatment period

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 inhalaled volume was determined. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the

summary of VI 25 µg.

End point type	Secondary

End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 49)

End point values	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[75]	27[76]		
Units: Liters				
arithmetic mean (standard deviation)				
Day 1, n=23, 25	0.93 (± 0.433)	0.92 (± 0.343)		
Day 14, n=23, 25	0.9 (± 0.426)	0.95 (± 0.417)		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Peak pressure drop on Day 1 and Day 14 of the respective treatment period

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. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg.

End point type	Secondary

End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 49)

End point values	Placebo	VI 25 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[77]	27[78]		
Units: Kilopascal (kpa)				
arithmetic mean (standard deviation)				
Day 1, n=23, 25	2.97 (± 1.275)	3.33 (± 1.632)		
Day 14, n=23, 25	3.23 (± 1.479)	3.33 (± 1.35)		

Notes:

[77] - All Subjects Population. Only those participants available at the specified time point were analyzed
[78] - All Subjects Population. Only those participants available at the specified time point were analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Total emitted dose (TED) on Day 1 and Day 14 of the respective treatment period

End point title	Total emitted dose (TED) on Day 1 and Day 14 of the respective treatment period

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 ororpharyngeal 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. All Subjects Population. Only those participants available at the specified time point were analyzed. Subject 2308 received VI 25 µg in both treatment periods, and contributed twice to the summary of VI 25 µg.

End point type	Secondary

End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 49)

End point values	VI 25 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	25[79]			
Units: micrograms				
arithmetic mean (standard deviation)				
Nominal TED	20.28 (± 0.177)			
Minimum TED	20.24 (± 0.188)			
Maximum TED	20.31 (± 0.173)			

Notes:

[79] - All Subjects Population. Only those participants available at the specified time point were analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Ex-throat dose (ETD) and ETD <2 microns on Day 1 and Day 14 of the respective treatment period

End point title	Ex-throat dose (ETD) and ETD <2 microns on Day 1 and Day 14 of the respective treatment period

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 ororpharyngeal 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.

End point type	Secondary

End point timeframe:

Day 1 and Day 14 of the respective treatment period (up to Study Day 49)

End point values	VI 25 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	15[80]			
Units: micrograms				
arithmetic mean (standard deviation)				
Nominal ETD	9 (± 0.697)			
Minimum ETD	8.94 (± 0.652)			
Maximum ETD	9.06 (± 0.747)			
ETD <2 microns	4.19 (± 1.079)			
Minimum ETD <2 microns	4.1 (± 1.011)			
Maximum ETD <2 microns	4.29 (± 1.157)			

Notes:

[80] - All Subjects Population. Only those participants available at the specified time point were analyzed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
On-treatment adverse events were reported.	
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

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
All participants who received matching placebo in one or both of the two 14-day treatment periods. Matching placebo 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	VI 25 µg
Reporting group description:	
All participants who received VI 25µg in one or both of the two 14-day treatment periods. Inhaled VI 25µg 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	Placebo	VI 25 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 27 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	VI 25 µg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 26 (23.08%)	9 / 27 (33.33%)	
Injury, poisoning and procedural complications			
Limb Injury			
subjects affected / exposed	0 / 26 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Spinal Column Injury			

subjects affected / exposed	0 / 26 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Cardiac disorders			
Sinus Bradycardia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 26 (7.69%)	2 / 27 (7.41%)	
occurrences (all)	2	2	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 26 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Chest Pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 26 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	0 / 26 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Psychiatric disorders			
Conversion Disorder			
subjects affected / exposed	1 / 26 (3.85%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Disorientation			

subjects affected / exposed	1 / 26 (3.85%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 26 (0.00%)	3 / 27 (11.11%)	
occurrences (all)	0	3	
Otitis media			
subjects affected / exposed	0 / 26 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	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