



## Clinical trial results:

**A randomized, double-blind, placebo-controlled, two-way crossover 14-day study to investigate the safety, tolerability, pharmacodynamics and pharmacokinetics of repeat dose inhaled fluticasone furoate 100 mcg in children aged 5-11 years with persistent asthma**

### Summary

EudraCT number	2012-000753-31
Trial protocol	Outside EU/EEA
Global end of trial date	29 January 2011

### Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	25 February 2015

### Trial information

#### Trial identification

Sponsor protocol code	HZA102942
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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)	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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	29 January 2011
Is this the analysis of the primary completion data?	No

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Global end of trial reached?	Yes
Global end of trial date	29 January 2011
Was the trial ended prematurely?	No

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Notes:

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**General information about the trial**

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Main objective of the trial:

To determine the safety and tolerability following administration of fluticasone furoate 100 µg (via a novel dry powder inhaler) once daily for 14 days in 5-11 year-old subjects.

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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.

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Background therapy: -

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Evidence for comparator: -

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Actual start date of recruitment	17 May 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	27
EEA total number of subjects	0

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Notes:

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**Subjects enrolled per age group**

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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)	27
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	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 treatment sequences (fluticasone furoate [FF] 100 µg followed by placebo; placebo followed by FF 100 µg). Results are reported by intervention, regardless of the age of the participant.

### Period 1

Period 1 title	Treatment Period 1 (14 days):Overall
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Subject, Carer, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Sequence 1: FF 100 µg followed by Placebo

Arm description:

Participants received fluticasone furoate (FF) 100 micrograms (µg) in Treatment Period 1 and matching placebo in Treatment Period 2. Inhaled FF 100 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	Fluticasone furoate; placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

FF 100ug or Pbo once daily x 14 days; 7 day w/o; crossover

<b>Arm title</b>	Sequence 2: Placebo followed by FF 100 µg
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Arm description:

Participants received placebo in Treatment Period 1 and FF 100 µg in Treatment Period 2. Inhaled FF 100 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	Fluticasone furoate; placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

FF 100ug or Pbo once daily x 14 days; 7 day w/o; crossover

<b>Number of subjects in period 1</b>	Sequence 1: FF 100 µg followed by Placebo	Sequence 2: Placebo followed by FF 100 µg
Started	14	13
Completed	12	12
Not completed	2	1
Adverse event, non-fatal	1	-
Protocol deviation	1	1

## Period 2

Period 2 title	Washout Period (>=7 days)
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
<b>Arm title</b>	Sequence 1: FF 100 µg followed by Placebo

### Arm description:

Participants received fluticasone furoate (FF) 100 micrograms (µg) in Treatment Period 1 and matching placebo in Treatment Period 2. Inhaled FF 100 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	Fluticasone furoate; placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

### Dosage and administration details:

FF 100ug or Pbo once daily x 14 days; 7 day w/o; crossover

<b>Arm title</b>	Sequence 2: Placebo followed by FF 100 µg
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### Arm description:

Participants received placebo in Treatment Period 1 and FF 100 µg in Treatment Period 2. Inhaled FF 100 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	Fluticasone furoate; placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

### Dosage and administration details:

FF 100ug or Pbo once daily x 14 days; 7 day w/o; crossover

<b>Number of subjects in period 2</b>	Sequence 1: FF 100 µg followed by Placebo	Sequence 2: Placebo followed by FF 100 µg
Started	12	12
Completed	12	12

### Period 3

Period 3 title	Treatment Period 2 (14 days)
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
<b>Arm title</b>	Sequence 1: FF 100 µg followed by Placebo

#### Arm description:

Participants received fluticasone furoate (FF) 100 micrograms (µg) in Treatment Period 1 and matching placebo in Treatment Period 2. Inhaled FF 100 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	Fluticasone furoate; placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

#### Dosage and administration details:

FF 100ug or Pbo once daily x 14 days; 7 day w/o; crossover

<b>Arm title</b>	Sequence 2: Placebo followed by FF 100 µg
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#### Arm description:

Participants received placebo in Treatment Period 1 and FF 100 µg in Treatment Period 2. Inhaled FF 100 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:Other
Investigational medicinal product name	Fluticasone furoate; placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

#### Dosage and administration details:

FF 100ug or Pbo once daily x 14 days; 7 day w/o; crossover

<b>Number of subjects in period 3</b>	Sequence 1: FF 100 µg followed by Placebo	Sequence 2: Placebo followed by FF 100 µg
Started	12	12
Completed	11	11
Not completed	1	1
Physician decision	1	1

## Baseline characteristics

### Reporting groups

Reporting group title	Treatment Period 1 (14 days):Overall
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Reporting group description:

Participants received either fluticasone furoate (FF) 100 micrograms ( $\mu\text{g}$ ) or matching placebo in the first of two 14-day treatment periods, followed by the other therapy (the therapy not received in the first treatment period) in the second 14-day treatment period. Inhaled FF 100  $\mu\text{g}$  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 (14 days):Overall	Total	
Number of subjects	27	27	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	8.2		
standard deviation	$\pm 2.08$	-	
Gender categorical			
Units: Subjects			
Female	13	13	
Male	14	14	
Race			
Units: Subjects			
African American/African Heritage	9	9	
White	16	16	
African American/African Heritage & White	1	1	
Unknown; Child Was Adopted	1	1	

## End points

### End points reporting groups

Reporting group title	Sequence 1: FF 100 µg followed by Placebo
Reporting group description: Participants received fluticasone furoate (FF) 100 micrograms (µg) in Treatment Period 1 and matching placebo in Treatment Period 2. Inhaled FF 100 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 FF 100 µg
Reporting group description: Participants received placebo in Treatment Period 1 and FF 100 µg in Treatment Period 2. Inhaled FF 100 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: FF 100 µg followed by Placebo
Reporting group description: Participants received fluticasone furoate (FF) 100 micrograms (µg) in Treatment Period 1 and matching placebo in Treatment Period 2. Inhaled FF 100 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 FF 100 µg
Reporting group description: Participants received placebo in Treatment Period 1 and FF 100 µg in Treatment Period 2. Inhaled FF 100 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: FF 100 µg followed by Placebo
Reporting group description: Participants received fluticasone furoate (FF) 100 micrograms (µg) in Treatment Period 1 and matching placebo in Treatment Period 2. Inhaled FF 100 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 FF 100 µg
Reporting group description: Participants received placebo in Treatment Period 1 and FF 100 µg in Treatment Period 2. Inhaled FF 100 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	FF 100 µg
Subject analysis set type	Safety analysis
Subject analysis set description: All participants who received FF 100 µg in one or both of the 14-day treatment periods. Inhaled 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
Subject analysis set type	Sub-group analysis
Subject analysis set description: All participants who received FF 100 µg in one or both of the 14-day treatment periods. Inhaled 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.	

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

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End point title	Number of participants with any adverse event (AE) or any serious adverse event (SAE) during the Treatment Period <sup>[1]</sup>
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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.

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End point type	Primary
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End point timeframe:

From the start of study medication until Week 11 (Visit 6)/Early Withdrawal

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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	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[2]</sup>	26 <sup>[3]</sup>		
Units: Participants				
Any AE	4	8		
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

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**Statistical analyses**

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No statistical analyses for this end point

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

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End point title	Basophil, eosinophil, lymphocyte, monocyte, total neutrophil, platelet, and white blood cell count values at Day 14 of respective treatment period <sup>[4]</sup>
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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 respective treatment period.

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End point type	Primary
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End point timeframe:

Day 14 of respective treatment period (up to Study Day 44)

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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.

<b>End point values</b>	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[5]</sup>	26 <sup>[6]</sup>		
Units: 10 <sup>9</sup> cells per liter (GI/L)				
arithmetic mean (standard deviation)				
Basophils, n=23, 21	0.022 (± 0.0153)	0.022 (± 0.0154)		
Eosinophils, n=23, 21	0.308 (± 0.2204)	0.252 (± 0.2182)		
Lymphocytes, n=23, 21	2.595 (± 0.7834)	2.43 (± 0.6563)		
Monocytes, n=23, 21	0.28 (± 0.1669)	0.27 (± 0.1204)		
Total neutrophils, n=23, 21	2.74 (± 1.2091)	3.209 (± 1.3103)		
Platelets, n=23, 20	266.4 (± 48.59)	263.3 (± 55.9)		
WBCs, n=23, 21	5.94 (± 1.696)	6.18 (± 1.513)		

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 <sup>[7]</sup>
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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
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End point timeframe:

Day 14 of the respective treatment period (up to Study Day 44)

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.

<b>End point values</b>	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[8]</sup>	26 <sup>[9]</sup>		
Units: Grams per liter (g/L)				
arithmetic mean (standard deviation)				
Hemoglobin, n=23, 21	129.1 (± 7.15)	129.6 (± 6.5)		
MCHC, n=23, 21	336.4 (± 7.66)	336.6 (± 7.8)		

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 <sup>[10]</sup>
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End point description:

Blood samples were collected for the measurement of reticulocyte 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 44)

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	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[11]</sup>	26 <sup>[12]</sup>		
Units: 10 <sup>12</sup> cells per liter (TI/L)				
arithmetic mean (standard deviation)				
Reticulocytes, n=23, 21	0.04952 (± 0.024497)	0.04499 (± 0.021309)		
RBCs, n=23, 21	4.43 (± 0.277)	4.46 (± 0.296)		

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 44)

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.

<b>End point values</b>	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23 <sup>[14]</sup>	21 <sup>[15]</sup>		
Units: percentage of red blood cells in blood				
arithmetic mean (standard deviation)	0.384 (± 0.02621)	0.3854 (± 0.02296)		

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 <sup>[16]</sup>
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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 44)

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.

<b>End point values</b>	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23 <sup>[17]</sup>	21 <sup>[18]</sup>		
Units: 10 <sup>15</sup> femtoliters (fL) per cell				
arithmetic mean (standard deviation)	86.8 (± 4.05)	86.9 (± 4.4)		

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 <sup>[19]</sup>
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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 44)

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.

<b>End point values</b>	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23 <sup>[20]</sup>	21 <sup>[21]</sup>		
Units: 10 <sup>12</sup> picograms (pg) per cell				
arithmetic mean (standard deviation)	29.18 (± 1.279)	29.24 (± 1.458)		

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 <sup>[22]</sup>
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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 44)

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.

<b>End point values</b>	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[23]</sup>	26 <sup>[24]</sup>		
Units: International units per liter (IU/L)				
arithmetic mean (standard deviation)				
ALT, n=22, 20	12.2 (± 3.06)	13 (± 6.04)		
ALP, n=22, 20	257.8 (± 59.24)	260.7 (± 64.15)		
AST, n=22, 19	26.8 (± 4.39)	26.1 (± 4.53)		
GGT, n=22, 20	14.3 (± 3.58)	15.4 (± 4.5)		

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 <sup>[25]</sup>
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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 44)

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	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[26]</sup>	26 <sup>[27]</sup>		
Units: Grams per liter				
arithmetic mean (standard deviation)				
Albumin, n=22, 20	43 (± 2.26)	42.9 (± 1.83)		
Total protein, n=22, 20	67.8 (± 2.98)	67.8 (± 2.57)		

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 <sup>[28]</sup>
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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 44)

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	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[29]</sup>	26 <sup>[30]</sup>		
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				

Calcium, n=20, 19	2.371 ( $\pm$ 0.0791)	2.366 ( $\pm$ 0.0626)		
Chloride, n=22, 20	105.2 ( $\pm$ 1.93)	104.7 ( $\pm$ 1.72)		
CO2 content/bicarbonate, n=20, 19	17.4 ( $\pm$ 2.04)	17.8 ( $\pm$ 1.86)		
Glucose, n=22, 20	5.13 ( $\pm$ 0.614)	4.86 ( $\pm$ 0.319)		
Potassium, n=20, 19	4.24 ( $\pm$ 0.254)	4.24 ( $\pm$ 0.289)		
Sodium, n=22, 20	138.3 ( $\pm$ 1.55)	137.4 ( $\pm$ 1.54)		
Urea/BUN, n=22, 20	4.66 ( $\pm$ 0.993)	4.83 ( $\pm$ 1.331)		

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, creatinine, and uric acid values at Day 14 of the respective treatment period

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

Blood samples were collected for the measurement of total 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 44)

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	FF 100 $\mu$ g		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[32]</sup>	26 <sup>[33]</sup>		
Units: Micromoles per liter ( $\mu$ mol/L)				
arithmetic mean (standard deviation)				
Total bilirubin, n= 22, 20	5.9 ( $\pm$ 2.27)	5.6 ( $\pm$ 1.23)		
Creatinine, n= 22, 20	39.89 ( $\pm$ 7.775)	40.62 ( $\pm$ 8.421)		
Uric acid, n= 22, 20	237.7 ( $\pm$ 65.46)	234.5 ( $\pm$ 70.97)		

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 <sup>[34]</sup>
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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

End point timeframe:

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

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	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[35]</sup>	25 <sup>[36]</sup>		
Units: liters/minute				
arithmetic mean (standard deviation)				
Day 1, Baseline, n=25, 25	242.3 (± 77.68)	238.4 (± 64.98)		
Day 1, 15 minutes post-dose, n=25, 25	242.1 (± 78.98)	238.2 (± 58.97)		
Day 1, 30 minutes post-dose, n=25, 25	249.2 (± 78.07)	246 (± 62.65)		
Day 1, 1 hour post-dose, n=25, 25	247.7 (± 72.54)	247 (± 64.75)		
Day 1, 2 hours post-dose, n=25, 25	252.3 (± 89.08)	252.6 (± 61.77)		
Day 14, Pre-dose, n=24, 23	242 (± 73.6)	240.6 (± 83.88)		
Day 14, 30 minutes post-dose, n=23, 23	246.1 (± 81.17)	238.8 (± 88.78)		
Day 14, 1 hours post-dose, n=23, 23	247 (± 77.95)	237.6 (± 78.66)		
Day 14, 2 hours post-dose, n=23, 23	249.5 (± 74.09)	242.3 (± 72.02)		
Day 14, 4 hours post-dose, n=23, 23	250.6 (± 82.43)	246.2 (± 70.43)		
Day 14, 7 hours post-dose, n=23, 23	246.3 (± 79.07)	232.1 (± 59.82)		
Day 14, 12 hours post-dose, n=23, 23	241.9 (± 75.8)	245.6 (± 76.68)		

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: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) at Baseline and Day 14 of the respective treatment period

End point title Systolic blood pressure (SBP) and diastolic blood pressure (DBP) at Baseline and Day 14 of the respective treatment period<sup>[37]</sup>

End point description:

SBP and DBP were measured at Baseline and Day 14 of the respective treatment period. Baseline is defined as the pre-dose measurement at Day 1 for each period.

End point type Primary

End point timeframe:

Baseline and Day 14 of the respective treatment period (up to Study Day 44)

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.

<b>End point values</b>	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[38]</sup>	26 <sup>[39]</sup>		
Units: Millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Day 1 SBP, Predose, n=25, 26	103.1 (± 9.29)	102.9 (± 9.68)		
Day 1 SBP, 30 minutes, n=25, 26	101.2 (± 8.57)	103.8 (± 10.44)		
Day 1 SBP, 1 hour, n=25, 26	102.7 (± 11.11)	105.2 (± 11.19)		
Day 1 SBP, 2 hours, n=25, 26	102.9 (± 9.98)	103.9 (± 9.04)		
Day 14 SBP, Predose, n=24, 23	101.8 (± 8.04)	102.1 (± 9.92)		
Day 14 SBP, 1 hour, n=23, 23	102.6 (± 9.14)	103.1 (± 8.04)		
Day 14 SBP, 4 hours, n=23, 23	102 (± 9.07)	102.7 (± 9.43)		
Day 14 SBP, 7 hours, n=23, 23	103.4 (± 9.34)	103.9 (± 9.88)		
Day 14 SBP, 12 hours, n=23, 23	103.2 (± 7.42)	106.3 (± 10.61)		
Day 1 DBP, Predose, n=25, 26	62 (± 9.71)	61.7 (± 7.66)		
Day 1 DBP, 30 minutes, n=25, 26	63 (± 9.09)	62.6 (± 6.39)		
Day 1 DBP, 1 hour, n=25, 26	61.4 (± 8.69)	62.3 (± 8.73)		
Day 1 DBP, 2 hours, n=25, 26	63 (± 8.34)	61.2 (± 8.39)		
Day 14 DBP, Predose, n=24, 23	61.3 (± 6.91)	61.4 (± 6.81)		
Day 14 DBP, 1 hour, n=23, 23	63.9 (± 10.14)	62.7 (± 6.88)		
Day 14 DBP, 4 hours, n=23, 23	60.4 (± 8.81)	60.5 (± 6.73)		
Day 14 DBP, 7 hours, n=23, 23	61.8 (± 9.27)	62.3 (± 8.23)		
Day 14 DBP, 12 hours, n=23, 23	62 (± 8.1)	63.9 (± 8.68)		

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: Heart rate at Baseline and Day 14 of the respective treatment period

End point title	Heart rate at Baseline and Day 14 of the respective treatment period <sup>[40]</sup>
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End point description:

Heart rate (HR) was measured at Baseline and Day 14 of the respective treatment period. Baseline is defined as the pre-dose measurement at Day 1 for each period.

End point type	Primary
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End point timeframe:

Baseline and Day 14 of the respective treatment period (up to Study Day 44)

Notes:

[40] - 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.

<b>End point values</b>	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[41]</sup>	26 <sup>[42]</sup>		
Units: Beats per minute				
arithmetic mean (standard deviation)				
Day 1, Baseline, n=25, 26	78.7 (± 13.18)	75.9 (± 11.48)		
Day 1, 30 minutes, n=25, 26	78.5 (± 13.99)	75.5 (± 10.9)		
Day 1, 1 hour, n=25, 26	78.6 (± 12.62)	77.6 (± 11.49)		
Day 1, 2 hours, n=25, 26	80.6 (± 13.3)	79.6 (± 11.78)		
Day 14, Predose, n=24, 23	76.8 (± 13.52)	74.5 (± 10.6)		
Day 14, 1 hour, n=23, 23	80.3 (± 14.76)	76.2 (± 8.6)		
Day 14, 4 hours, n=23, 23	78.2 (± 10.46)	77.7 (± 9.77)		
Day 14, 7 hours, n=23, 23	83.1 (± 14.65)	81.2 (± 12.13)		
Day 14, 12 hours, n=23, 23	83.6 (± 11.7)	81.1 (± 10.71)		

Notes:

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

[42] - 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 the indicated electrocardiographic (ECG) parameters at the indicated time points on Day 14 of the respective treatment period

End point title	Change from Baseline in the indicated electrocardiographic (ECG) parameters at the indicated time points on Day 14 of the respective treatment period <sup>[43]</sup>
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End point description:

PR, QRS, QT, QTcB, QTcF, and RR were measured at Baseline and Day 14 of the respective treatment period. Baseline is defined as the pre-dose measurement at Day 1 for each period. Change from Baseline was calculated as the value at Day 14 minus the Baseline value. QTcB is the QT duration corrected for heart rate by Bazett's formula. QTcF is the QT duration corrected for heart rate by Fridericia's formula.

End point type	Primary
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End point timeframe:

Baseline and Day 14 of the respective treatment period (up to Study Day 44)

Notes:

[43] - 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.

<b>End point values</b>	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[44]</sup>	26 <sup>[45]</sup>		
Units: milliseconds (msec)				
arithmetic mean (standard deviation)				
Day 1 PR Interval, 30 minutes, n=25, 26	6.4 (± 6.37)	7.5 (± 7.54)		
Day 1 PR Interval, 1 hour, n=25, 26	7.3 (± 6.68)	8.4 (± 7.17)		
Day 1 PR Interval, 2 hours, n=25, 26	8 (± 8.61)	9.5 (± 10.48)		
Day 14 PR Interval, Predose, n=24, 23	7.8 (± 6.76)	9.6 (± 9.82)		
Day 14 PR Interval, 1 hour, n=23, 23	8.7 (± 6.74)	8.3 (± 6.03)		
Day 14 PR Interval, 4 hours, n=23, 23	6.4 (± 3.7)	8.9 (± 6.86)		

Day 14 PR Interval, 7 hour, n=23, 23	8.3 (± 6.56)	10.2 (± 10.09)	
Day 14 PR Interval, 12 hours, n=22, 23	7.2 (± 7.5)	9.7 (± 6.54)	
Day 1 QRS Interval, 30 minutes, n=25, 26	4.6 (± 3.46)	5.2 (± 4.7)	
Day 1 QRS Interval, 1 hour, n=25, 26	4.1 (± 2.84)	4.4 (± 3.86)	
Day 1 QRS Interval, 2 hours, n=25, 26	4 (± 2.64)	4.5 (± 3.61)	
Day 14 QRS Interval, Predose, n=24, 23	4.2 (± 3.71)	4.7 (± 4.29)	
Day 14 QRS Interval, 1 hour, n=23, 23	5.7 (± 3.54)	5.3 (± 4.71)	
Day 14 QRS Interval, 4 hours, n=23, 23	5.6 (± 3.85)	4.9 (± 3.93)	
Day 14 QRS Interval, 7 hours, n=23, 23	6.1 (± 5.25)	4.3 (± 4.22)	
Day 14 QRS Interval, 12 hours, n=23, 23	5 (± 4.7)	4.8 (± 4.02)	
Day 1 QT Interval, 30 minutes, n=25, 26	9.8 (± 8.14)	10.5 (± 9.57)	
Day 1 QT Interval, 1 hour, n=25, 26	13.1 (± 11.04)	12.7 (± 11.53)	
Day 1 QT Interval, 2 hours, n=25, 26	17.5 (± 13.88)	15.5 (± 13.83)	
Day 14 QT Interval, Predose, n=24, 23	12.5 (± 9.81)	15.5 (± 13.34)	
Day 14 QT Interval, 1 hour, n=23, 23	11.4 (± 6.45)	15.9 (± 11.11)	
Day 14 QT Interval, 4 hours, n=23, 23	13.3 (± 9.65)	16.7 (± 12.52)	
Day 14 QT Interval, 7 hours, n=23, 23	14.7 (± 10.94)	15.3 (± 11.93)	
Day 14 QT Interval, 12 hours, n=23, 23	14.7 (± 10.42)	24.8 (± 14.93)	
Day 1 QTcB Interval, 30 minutes, n=25, 26	15.4 (± 14.44)	14.2 (± 11.64)	
Day 1 QTcB Interval, 1 hour, n=25, 26	17.3 (± 13.46)	17.7 (± 13.18)	
Day 1 QTcB Interval, 2 hours, n=25, 26	13.6 (± 11.07)	18.2 (± 17.54)	
Day 14 QTcB Interval, Predose, n=24, 23	20.7 (± 15.54)	17.9 (± 14.92)	
Day 14 QTcB Interval, 1 hour, n=23, 23	16.6 (± 9.43)	16.2 (± 9.71)	
Day 14 QTcB Interval, 4 hours, n=23, 23	14.7 (± 9.13)	16.8 (± 9.23)	
Day 14 QTcB Interval, 7 hours, n=23, 23	14.5 (± 10.14)	19.6 (± 12.03)	
Day 14 QTcB Interval, 12 hours, n=23, 23	13.8 (± 10.7)	18.5 (± 15.7)	
Day 1 QTcF Interval, 30 minutes, n=25, 26	10.8 (± 9.31)	11.8 (± 9.3)	
Day 1 QTcF Interval, 1 hour, n=25, 26	11.6 (± 9.57)	12.6 (± 10)	
Day 1 QTcF Interval, 2 hours, n=25, 26	10.4 (± 8.36)	15.4 (± 12.88)	
Day 14 QTcF Interval, Predose, n=24, 23	14.2 (± 9.92)	12.6 (± 10.99)	
Day 14 QTcF Interval, 1 hour, n=23, 23	9.3 (± 6.09)	11.4 (± 9.56)	
Day 14 QTcF Interval, 4 hours, n=23, 23	7.8 (± 6.97)	15.7 (± 7.41)	
Day 14 QTcF Interval, 7 hours, n=23, 23	9.3 (± 7.77)	15 (± 9.51)	
Day 14 QTcF Interval, 12 hours, n=23, 23	8.8 (± 5.84)	15.8 (± 11.61)	
Day 1 RR Interval, 30 minutes, n=25, 26	70.4 (± 66.47)	54.2 (± 44.61)	
Day 1 RR Interval, 1 hour, n=25, 26	93.5 (± 64.97)	90.7 (± 52.94)	
Day 1 RR Interval, 2 hours, n=25, 26	102 (± 61.66)	80.4 (± 71.51)	
Day 14 RR Interval, Predose, n=24, 23	106 (± 73.2)	103.5 (± 78.48)	
Day 14 RR Interval, 1 hour, n=23, 23	92.5 (± 64.45)	87.7 (± 63.3)	
Day 14 RR Interval, 4 hours, n=23, 23	92.1 (± 65.93)	63.6 (± 47.14)	
Day 14 RR Interval, 7 hours, n=23, 23	89.6 (± 63.06)	74.5 (± 78.18)	

Day 14 RR Interval, 12 hours, n=23, 23	94.4 (± 73.45)	110.3 (± 101.24)		
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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

No statistical analyses for this end point

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

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

Area under the concentration-time (AUC(0-t)) curve from time zero (pre-dose) to the last time of quantifiable concentration of FF on Day 14 of the respective treatment period was measured. Samples were collected at the following times: pre-dose; 30 minutes, 1, 2, 4, 7, and 12 hours post-dose on Day 14 of the respective treatment period. Due to non-quantifiable values, it was not possible to derive AUC(0-12).

End point type	Secondary
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End point timeframe:

Day 14 of the respective treatment period

<b>End point values</b>	FF 100 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	23 <sup>[46]</sup>			
Units: picograms*hour per milliliter (pg*hr/mL)				
geometric mean (confidence interval 95%)	91.29 (63.24 to 131.78)			

Notes:

[46] - Pharmacokinetic (PK) Pop: all participants in the All Subjects Pop for whom a PK sample was 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
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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; 30 minutes, 1, 2, 4, 7, and 12 hours post-dose on Day 14 of the respective treatment period.

End point type	Secondary
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End point timeframe:

Day 14 of the respective treatment period

<b>End point values</b>	FF 100 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	23 <sup>[47]</sup>			
Units: picograms per milliliter (pg/mL)				
geometric mean (confidence interval 95%)	24.68 (20.24 to 30.1)			

Notes:

[47] - Pharmacokinetic (PK) Pop: all participants in the All Subjects Pop for whom a PK sample was analyzed

### Statistical analyses

No statistical analyses for this end point

### Secondary: tmax and t at Day 14 of the respective treatment period

End point title	tmax and t at 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 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; 30 minutes, 1, 2, 4, 7, and 12 hours post-dose on Day 14 of the respective treatment period.

End point type	Secondary
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End point timeframe:

Day 14 of the respective treatment period

<b>End point values</b>	FF 100 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	22 <sup>[48]</sup>			
Units: hours				
arithmetic mean (standard deviation)				
tmax	0.863 (± 0.7926)			
time (t)	6.953 (± 4.0875)			

Notes:

[48] - Pharmacokinetic (PK) Pop: all participants in the All Subjects Pop for whom a PK sample was analyzed

### Statistical analyses

No statistical analyses for this end point

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

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

Serum cortisol weighted mean was determined for each participant over the time period 0-12 hours on Day 14 of the respective treatment period. Samples were collected at the following times: pre-dose; 30 minutes, 1, 2, 4, 7, and 12 hours post-dose on Day 14 of the respective treatment period.

End point type	Secondary
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End point timeframe:

Day 14 of the respective treatment period

<b>End point values</b>	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22 <sup>[49]</sup>	23 <sup>[50]</sup>		
Units: nanomoles per Liter				
geometric mean (confidence interval 95%)	178.76 (157.43 to 202.97)	150.41 (132.91 to 170.22)		

Notes:

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

[50] - 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 Days 1 and 14 of the respective treatment period

End point title	Average oropharyngeal cross-sectional area on Days 1 and 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. 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
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End point timeframe:

Days 1 and 14 of the respective treatment period

<b>End point values</b>	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[51]</sup>	26 <sup>[52]</sup>		
Units: centimeters squared (cm <sup>2</sup> )				
arithmetic mean (standard deviation)				
Day 1, n=14, 18	4.06 (± 1.875)	4.24 (± 1.677)		
Day 14, n= 12, 12	5.49 (± 1.586)	4.58 (± 1.497)		

Notes:

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

[52] - 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 Days 1 and 14 of the respective treatment period

End point title	Distance of assessment on Days 1 and 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
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End point timeframe:

Days 1 and 14 of the respective treatment period

End point values	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[53]</sup>	26 <sup>[54]</sup>		
Units: centimeters (cm)				
arithmetic mean (standard deviation)				
Day 1, n=14, 18	18.63 (± 1.736)	18.69 (± 1.432)		
Day 14, n= 12, 12	19.37 (± 1.823)	18.61 (± 1.942)		

Notes:

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

[54] - 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 Days 1 and 14 of the respective treatment period

End point title	Oropharyngeal Volume on Days 1 and 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 (cm<sup>3</sup>) 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
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End point timeframe:

Days 1 and 14 of the respective treatment period

<b>End point values</b>	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[55]</sup>	26 <sup>[56]</sup>		
Units: cubic centimeters (cm <sup>3</sup> )				
arithmetic mean (standard deviation)				
Day 1, n=14, 18	74.19 (± 32.402)	78.86 (± 31.092)		
Day 14, n= 12, 12	106.31 (± 33.188)	86.22 (± 34.363)		

Notes:

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

[56] - 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 Days 1 and 14 of the respective treatment period

End point title	Average flow rate and Peak Inspiratory Flow Rate (PIFR) 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. 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

<b>End point values</b>	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[57]</sup>	26 <sup>[58]</sup>		
Units: Liters per minute (L/min)				
arithmetic mean (standard deviation)				
Day 1 Average flow rate, n=21, 20	35.38 (± 11.441)	34.65 (± 10.84)		
Day 14 Average flow rate, n=21, 22	36.25 (± 11.243)	36.17 (± 12.772)		
Day 1 PIFR, n=21, 20	51.83 (± 17.286)	52.9 (± 16.028)		
Day 14 PIFR, n=21, 22	55.7 (± 16.589)	54.76 (± 17.986)		

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

End point title	Inhalation time 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. 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

End point values	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[59]</sup>	26 <sup>[60]</sup>		
Units: Seconds				
arithmetic mean (standard deviation)				
Day 1, n=21, 20	1.71 (± 0.534)	1.93 (± 0.861)		
Day 14, n= 21, 22	1.6 (± 0.802)	1.61 (± 0.858)		

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: 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

<b>End point values</b>	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[61]</sup>	26 <sup>[62]</sup>		
Units: Liters				
arithmetic mean (standard deviation)				
Day 1, n=21, 20	0.99 (± 0.461)	1.07 (± 0.48)		
Day 14, n= 21, 22	1 (± 0.58)	0.95 (± 0.541)		

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: 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

<b>End point values</b>	Placebo	FF 100 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[63]</sup>	26 <sup>[64]</sup>		
Units: Kilopascal (kpa)				
arithmetic mean (standard deviation)				
Day 1, n=21, 20	2.44 (± 1.63)	2.53 (± 1.56)		
Day 14, n= 21, 22	2.78 (± 1.543)	2.74 (± 1.609)		

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

End point title	Total emitted dose (TED) on Days 1 and 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.

End point type	Secondary
End point timeframe:	
Day 1 and Day 14 of the respective treatment period	

End point values	FF 100 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	26 <sup>[65]</sup>			
Units: micrograms				
arithmetic mean (standard deviation)				
Day 1, Nominal TED, n=0, 20	85.35 (± 1.576)			
Day 14, Nominal TED, n=0, 22	85.57 (± 1.857)			
Day 1, Minimum TED, n=0, 20	84.84 (± 1.617)			
Day 14, Minimum TED, n=0, 22	85.17 (± 1.905)			
Day 1, Maximum TED, n=0, 20	85.86 (± 1.639)			
Day 14, Maximum TED, n=0, 22	85.97 (± 1.861)			

Notes:

[65] - 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 Days 1 and 14 of the respective treatment period

End point title	Ex-throat dose (ETD) and ETD <2 microns on Days 1 and 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.

End point type	Secondary
End point timeframe:	
Day 1 and Day 14 of the respective treatment period	

<b>End point values</b>	FF 100 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	26 <sup>[66]</sup>			
Units: micrograms				
arithmetic mean (standard deviation)				
Day 1, Nominal ETD, n=0, 17	29.37 (± 2.874)			
Day 14, Nominal ETD, n=0, 12	29.83 (± 2.528)			
Day 1, Minimum ETD, n=0, 17	28.47 (± 3.241)			
Day 14, Minimum ETD, n=0, 12	29.35 (± 2.664)			
Day 1, Maximum ETD, n=0, 17	30.26 (± 2.598)			
Day 14, Maximum ETD, n=0, 12	30.26 (± 2.472)			
Day 1, ETD <2 microns, n=0, 17	5.13 (± 0.498)			
Day 14, ETD <2 microns, n=0, 12	5.07 (± 0.455)			
Day 1, Minimum ETD <2 microns, n=0, 17	4.96 (± 0.459)			
Day 14, Minimum ETD <2 microns, n=0, 12	4.99 (± 0.448)			
Day 1, Maximum ETD <2 microns, n=0, 17	5.3 (± 0.559)			
Day 14, Maximum ETD <2 microns, n=0, 12	5.17 (± 0.476)			

Notes:

[66] - 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

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.1
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### Reporting groups

Reporting group title	Placebo
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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 Novel 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:

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

<b>Serious adverse events</b>	Placebo	FF 100 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (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: 0 %

<b>Non-serious adverse events</b>	Placebo	FF 100 µg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 25 (16.00%)	8 / 26 (30.77%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 25 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Product taste abnormal			
subjects affected / exposed	1 / 25 (4.00%)	1 / 26 (3.85%)	
occurrences (all)	1	1	

Pyrexia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 26 (3.85%) 1	
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 26 (0.00%) 0	
Dyspepsia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 26 (3.85%) 2	
Toothache subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	1 / 26 (3.85%) 1	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 26 (3.85%) 1	
Nasal congestion subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 26 (3.85%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 26 (0.00%) 0	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	1 / 26 (3.85%) 1	
Acute tonsillitis subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 26 (3.85%) 1	
Influenza subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 26 (3.85%) 1	
Otitis externa			

subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Otitis media			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported