

**Clinical trial results:****Study HZA114971, A Multicentre Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effects of a One-Year Regimen of Orally Inhaled Fluticasone Furoate 50 mcg once daily on Growth Velocity in Prepubertal, Paediatric Subjects with Asthma****Summary**

EudraCT number	2016-002551-22
Trial protocol	PL
Global end of trial date	04 June 2021

Results information

Result version number	v1 (current)
This version publication date	19 December 2021
First version publication date	19 December 2021

Trial information**Trial identification**

Sponsor protocol code	114971
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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, TW8 9GS
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000431-PIP08-06
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	24 August 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the magnitude of effect (with a level of precision) of inhaled FF 50 micrograms (mcg) versus inhaled placebo once daily (OD) on growth velocity in prepubertal children over one year of treatment

Protection of trial subjects:

In order to minimise pain and distress, it was agreed with both Food and drug Administration (FDA) and European Medicines Agency (EMA) not to do any blood tests in this study. Furthermore, participants were on a background of open-label montelukast tablets to avoid a "no treatment" arm to reduce the risk of uncontrolled asthma in the placebo group.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 30
Country: Number of subjects enrolled	Poland: 70
Country: Number of subjects enrolled	Romania: 16
Country: Number of subjects enrolled	Russian Federation: 172
Country: Number of subjects enrolled	South Africa: 39
Country: Number of subjects enrolled	United States: 150
Worldwide total number of subjects	477
EEA total number of subjects	86

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)	477

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:

This was a multicenter, randomized, double-blind, placebo-controlled study to evaluate the effects of a one-year regimen of orally inhaled fluticasone furoate (FF) 50 micrograms (mcg) once daily on growth velocity in prepubertal, pediatric participants with asthma.

Pre-assignment

Screening details:

Total 477 participants were enrolled in this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received a single-blind placebo inhaler during a 16-week run-in period. After run-in period inhaled placebo was administered once daily (OD) in the morning for 52 weeks during the double-blind treatment period. Participants also received open-label montelukast one tablet orally in the evening (4 milligrams [mg] for participants who were 5 years old and 5 mg for participants who were greater than or equal to [\geq] 6 years old) as background therapy from the run-in period through to the end of follow-up (8 weeks) period.

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

Dosage and administration details:

Placebo was administered as dry white powder Lactose for inhalation using ELLIPTA inhaler

Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Montelukast was administered as 4 milligram (mg) in (5 year old participants) or 5 mg (\geq 6 year old participants) orally once daily in evening.

Arm title	FF 50 mcg
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Arm description:

Participants received received a single-blind placebo inhaler during a 16-week run-in period. After run-in period inhaled FF 50 mcg was administered via ELLIPTA inhaler once daily in the morning for 52 weeks during double-blind treatment period. Participants also received open-label montelukast one tablet orally in the evening (4 mg for participants who were 5 years old and 5 mg for participants who were \geq 6 years old) as background therapy from the run-in period through to the end of follow-up (8 weeks) period.

Arm type	Experimental
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Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Montelukast was administered as 4 milligram (mg) in (5 year old participants) or 5 mg (≥ 6 year old participants) orally once daily in evening.

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

Dosage and administration details:

Fluticasone furoate was administered as 50 microgram (mcg) dry white powder for inhalation using ELLIPTA inhaler

Number of subjects in period 1	Placebo	FF 50 mcg
Started	239	238
Completed	196	205
Not completed	43	33
Consent withdrawn by subject	30	21
Site Closed	12	11
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received a single-blind placebo inhaler during a 16-week run-in period. After run-in period inhaled placebo was administered once daily (OD) in the morning for 52 weeks during the double-blind treatment period. Participants also received open-label montelukast one tablet orally in the evening (4 milligrams [mg] for participants who were 5 years old and 5 mg for participants who were greater than or equal to [\geq] 6 years old) as background therapy from the run-in period through to the end of follow-up (8 weeks) period.	
Reporting group title	FF 50 mcg
Reporting group description:	
Participants received received a single-blind placebo inhaler during a 16-week run-in period. After run-in period inhaled FF 50 mcg was administered via ELLIPTA inhaler once daily in the morning for 52 weeks during double-blind treatment period. Participants also received open-label montelukast one tablet orally in the evening (4 mg for participants who were 5 years old and 5 mg for participants who were ≥ 6 years old) as background therapy from the run-in period through to the end of follow-up (8 weeks) period.	

Reporting group values	Placebo	FF 50 mcg	Total
Number of subjects	239	238	477
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	239	238	477
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	6.1	6.3	-
standard deviation	± 1.07	± 1.02	-
Sex: Female, Male Units: Participants			
Female	84	94	178
Male	155	144	299
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	13	13	26
Asian - Central/South Asian Heritage	0	1	1
Multiple	18	20	38
White - Arabic/North African Heritage	3	3	6
White - Mixed Race	1	0	1

White - White/Caucasian/European Heritage	204	201	405
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End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants received a single-blind placebo inhaler during a 16-week run-in period. After run-in period inhaled placebo was administered once daily (OD) in the morning for 52 weeks during the double-blind treatment period. Participants also received open-label montelukast one tablet orally in the evening (4 milligrams [mg] for participants who were 5 years old and 5 mg for participants who were greater than or equal to [\geq] 6 years old) as background therapy from the run-in period through to the end of follow-up (8 weeks) period.	
Reporting group title	FF 50 mcg
Reporting group description: Participants received a single-blind placebo inhaler during a 16-week run-in period. After run-in period inhaled FF 50 mcg was administered via ELLIPTA inhaler once daily in the morning for 52 weeks during double-blind treatment period. Participants also received open-label montelukast one tablet orally in the evening (4 mg for participants who were 5 years old and 5 mg for participants who were ≥ 6 years old) as background therapy from the run-in period through to the end of follow-up (8 weeks) period.	

Primary: Growth Velocity (centimeter per year) over the double-blind treatment period, as determined by stadiometry

End point title	Growth Velocity (centimeter per year) over the double-blind treatment period, as determined by stadiometry
End point description: Three reproducible height measurement were taken using stadiometer at each visit, recorded to nearest 1/10th of centimeter. Each set of triplicate measurements was averaged to derive 1 estimated height per participant (Participant) per visit. Growth velocity (GV) was calculated over double-blind (DB) treatment period (up to 52 weeks) by fitting regression line to averaged height measurement at each visit. Slope of regression line was participant's GV for DB treatment period. Treatment policy estimand was assessed including all on- and post-treatment data. Baseline was included as covariate calculated based on stadiometric height measurement recorded at V1 (wk -16), 3 (wk -8), 5 (wk 0), data from at least 2 of visits was used to fit simple linear regression line against time and slope of fitted regression line was GV. Growth Pop. was ITT participant who have stadiometric height assessment from 3 post-randomization, on-treatment clinic visit (including height measurement after V5 (wk 0) up to, incl V18 (wk 52), without excl.) during DB period.	
End point type	Primary
End point timeframe: Up to 52 weeks	

End point values	Placebo	FF 50 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226 ^[1]	231 ^[2]		
Units: Centimeter per year				
least squares mean (standard error)	6.065 (\pm 0.1090)	5.905 (\pm 0.1078)		

Notes:

[1] - Growth Population

[2] - Growth Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	FF 50 mcg v Placebo
Number of subjects included in analysis	457
Analysis specification	Pre-specified
Analysis type	other ^[3]
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.462
upper limit	0.142

Notes:

[3] - Analysis was performed using an analysis of covariance (ANCOVA) model adjusting for baseline growth velocity, age at Visit 1, gender and country.

Secondary: Percentage of participants below the third percentile of growth velocity during double-blind treatment period

End point title	Percentage of participants below the third percentile of growth velocity during double-blind treatment period
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End point description:

Three reproducible height measurements were taken using stadiometer at each visit & were recorded to nearest 1/10th of a centimeter. Each set of triplicate measurements was averaged to derive one estimated height per participant per visit. Growth velocity was calculated for each participant over double-blind(DB) treatment(upto 52weeks) period by fitting regression line to height measurements recorded for that participant during period. Each participant's DB treatment period growth velocity was calculated based on all on & off treatment height data & was programmatically compared to data values from Standards from Birth to Maturity for Height, Weight, Height Velocity, established in British Children (1965) & further updated for North American children (1985) using 3rd percentile value of age closest to participant's age at end of endpoint (i.e. either end of participant's DB treatment period [Visit 18 Wk 52] / withdrawal from study [Early Withdrawal Visit]). Percentage values presented is rounded off

End point type	Secondary
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End point timeframe:

Up to 52 weeks

End point values	Placebo	FF 50 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226 ^[4]	231 ^[5]		
Units: Percentage of participants	9	7		

Notes:

[4] - Growth Population

[5] - Growth Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with change in growth velocity quartiles from Baseline to endpoint

End point title	Percentage of participants with change in growth velocity quartiles from Baseline to endpoint
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End point description:

Growth velocity(GV)quartile(GVQ)(1st quartile(1Q)=1st-25th percentile,2Q=26th-50th percentile,3Q=51st-75th percentile,4Q=76th-100th percentile)was determined at Baseline&endpoint.Endpoint was slope of simple linear regression of average stadiometric height recorded at wk28upto wk52.Baseline GVwas calculated as slope from simple linear regression of average stadiometric height recorded at wk-16,-8&0.Baseline GV was programmatically compared to reference for standard height data using participant's estimated age at wk0&age in reference data closest to actual age of participant to determine Baseline GVQ.Endpoint GV was programmatically compared to reference data using participant's age at endpoint&age in reference data closest to actual age of participant to determine endpoint GVQ.Any increase/decrease indicates any increase/decrease in quartiles with reference to Baseline.Only participants with data available at specified datapoints were analyzed.Percentage value is rounded off.

End point type	Secondary
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End point timeframe:

Baseline and Endpoint (Week 28[Visit 12]up to and including Week 52 [Visit 18])

End point values	Placebo	FF 50 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216 ^[6]	223 ^[7]		
Units: Percentage of Participants				
Any increase	33	32		
Any decrease	34	38		

Notes:

[6] - Growth Population.

[7] - Growth Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Growth velocity over the first 12 weeks of double-blind treatment period

End point title	Growth velocity over the first 12 weeks of double-blind treatment period
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End point description:

Growth velocity(GV)was calculated for each participant over double-blind (DB) period by fitting regression line to height measurements recorded for participant during period.Slope of this regression line was participant's GV for DB treatment period.In order to be included in this analysis,participant must have data from Visit(V)8(Wk12) stadiometric height assessment.Baseline was included as covariate which was calculated based on stadiometric height measurements recorded at V1(wk - 16),3(wk-8),&5(wk0),data from at least two of this visits were used to fit simple linear regression line against time&slope of fitted regression line was participant's Baseline GV.All available height data collected during DB treatment period uptoV8(Wk12) while participant was on randomized DB treatment was considered.ANCOVA model was used to estimate mean treatment difference in GV over 1st 12wks of DB treatment period.Only those participants with data available at specified data points were

End point type	Secondary
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End point timeframe:

Up to 12 weeks [Visit 8] of double-blind treatment period

End point values	Placebo	FF 50 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210 ^[8]	211 ^[9]		
Units: Centimeter per year				
least squares mean (standard error)	6.222 (± 0.1845)	6.281 (± 0.1841)		

Notes:

[8] - Growth Population.

[9] - Growth Population.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v FF 50 mcg
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	other ^[10]
Parameter estimate	LS Mean Difference
Point estimate	0.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.455
upper limit	0.572

Notes:

[10] - Analysis was performed using an ANCOVA model adjusting for Baseline growth velocity, age at Visit 1(wk -16), gender and country.

Secondary: Change in Height Standard Deviation Scores (SDS) from Baseline to Endpoint

End point title	Change in Height Standard Deviation Scores (SDS) from Baseline to Endpoint
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End point description:

Each participant's SDS for each of 3 required stadiometric height measurements was calculated as:(observed height measurement-standard median height for age at Visit [week-16]) divided by (/) ([standard 95th height percentile for age at visit-standard 5th height percentile for age at visit]/[2*1.645]).Standard median, 95th percentile, & 5th percentile values were obtained from standard tables (Guidance for Industry Orally Inhaled & Intranasal Corticosteroid). SDS for each height stadiometric measurement at each visit was calculated using percentiles from standard tables & averaged for each participant before being summarized by treatment group. A reduction in SDS over time indicates growth deceleration & an increase in SDS over time means growth acceleration.Baseline was defined as height SD score at Visit 5 (week 0). Endpoint was defined as height SD score at Visit 18 (week52) (on- & off-treatment data). Change from Baseline was calculated as Endpoint value minus

End point type	Secondary
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End point timeframe:

Baseline (Week 0 [Visit 5]) and up to Endpoint (Week 52 [Visit 18])

End point values	Placebo	FF 50 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196 ^[11]	202 ^[12]		
Units: Standard Deviation Score				
arithmetic mean (standard deviation)	-0.02 (± 0.281)	-0.04 (± 0.281)		

Notes:

[11] - Growth Population.

[12] - Growth Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with non-serious adverse events (AEs) and serious adverse events (SAEs)

End point title	Number of participants with non-serious adverse events (AEs) and serious adverse events (SAEs)
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End point description:

An AE is 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 SAE is defined as any untoward medical occurrence that, at any dose which results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, other situations as per investigator's judgement. Intent-to-Treat Population comprised of all randomized participants who received at least one dose of study treatment.

End point type	Secondary
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End point timeframe:

Up to 76 weeks

End point values	Placebo	FF 50 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239 ^[13]	238 ^[14]		
Units: Participants				
Any SAEs	8	6		
Any Non-serious AEs	105	99		

Notes:

[13] - Intent-to-Treat Population

[14] - Intent-to-Treat Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with on-treatment asthma exacerbations over double-blind treatment period

End point title	Number of participants with on-treatment asthma exacerbations over double-blind treatment period
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End point description:

An exacerbation is defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or a single depot corticosteroid injection, or an in-patient hospitalization or emergency department (ED) visit due to asthma that required systemic

corticosteroids. Number of participants with on-treatment asthma exacerbations during double-blind treatment period is presented.

End point type	Secondary
End point timeframe:	
Up to 52 weeks	

End point values	Placebo	FF 50 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239 ^[15]	238 ^[16]		
Units: Participants	22	7		

Notes:

[15] - Intent-to-Treat Population

[16] - Intent-to-Treat Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All cause mortality, non-serious adverse events (AEs) and serious AEs were collected up to 76 weeks

Adverse event reporting additional description:

All-cause mortality, non-serious AEs and SAEs were collected in Intent-to-Treat Population which was comprised of all randomized participants who received at least one dose of study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	FF 50 mcg
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Reporting group description:

Participants received a single-blind placebo inhaler during a 16-week run-in period. After run-in period inhaled FF 50 mcg was administered via ELLIPTA inhaler once daily in the morning for 52 weeks during double-blind treatment period. Participants also received open-label montelukast one tablet orally in the evening (4 mg for participants who were 5 years old and 5 mg for participants who were ≥ 6 years old) as background therapy from the run-in period through to the end of follow-up (8 weeks) period.

Reporting group title	Placebo
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Reporting group description:

Participants received a single-blind placebo inhaler during a 16-week run-in period. After run-in period inhaled placebo was administered once daily (OD) in the morning for 52 weeks during the double-blind treatment period. Participants also received open-label montelukast one tablet orally in the evening (4 milligrams [mg] for participants who were 5 years old and 5 mg for participants who were ≥ 6 years old) as background therapy from the run-in period through to the end of follow-up (8 weeks) period.

Serious adverse events	FF 50 mcg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 238 (2.52%)	8 / 239 (3.35%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	0 / 238 (0.00%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Faecaloma			
subjects affected / exposed	1 / 238 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Testicular appendage torsion			
subjects affected / exposed	0 / 238 (0.00%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 238 (0.00%)	2 / 239 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 238 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Adenoviral haemorrhagic cystitis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 238 (0.00%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 238 (0.42%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 238 (0.00%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 238 (0.00%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	FF 50 mcg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	99 / 238 (41.60%)	105 / 239 (43.93%)	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 238 (4.20%)	12 / 239 (5.02%)	
occurrences (all)	17	24	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	13 / 238 (5.46%)	18 / 239 (7.53%)	
occurrences (all)	15	23	
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	8 / 238 (3.36%)	9 / 239 (3.77%)	
occurrences (all)	9	11	
Cough			

subjects affected / exposed occurrences (all)	12 / 238 (5.04%) 15	15 / 239 (6.28%) 23	
Rhinorrhoea subjects affected / exposed occurrences (all)	3 / 238 (1.26%) 3	8 / 239 (3.35%) 10	
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	9 / 238 (3.78%) 11	12 / 239 (5.02%) 13	
Influenza subjects affected / exposed occurrences (all)	11 / 238 (4.62%) 11	7 / 239 (2.93%) 8	
Nasopharyngitis subjects affected / exposed occurrences (all)	23 / 238 (9.66%) 26	25 / 239 (10.46%) 31	
Pharyngitis subjects affected / exposed occurrences (all)	3 / 238 (1.26%) 3	9 / 239 (3.77%) 10	
Respiratory tract infection viral subjects affected / exposed occurrences (all)	10 / 238 (4.20%) 11	4 / 239 (1.67%) 7	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	29 / 238 (12.18%) 63	33 / 239 (13.81%) 57	
Rhinitis subjects affected / exposed occurrences (all)	16 / 238 (6.72%) 18	18 / 239 (7.53%) 26	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2016	Amendment 1: Remove the term local growth charts and replace with United States Centers for Disease Control (US CDC) charts for inclusion criteria 4 and 5; Amend the text for inclusion criterion 7 to provide clarity on the time window used for re-scheduling the spirometry assessment at screening (Visit 1); Remove the term World Health Organisation (WHO) growth charts and replace with North America Longitudinal Standard Growth Velocity Charts for randomization criterion 1c; Amended typographical error in Section 5.5.4 and to clarify that the participant will be withdrawn from study treatment (for consistency with Section 5.5.1); Amend the text and provide clarity on the procedure around oropharyngeal exams in Section 7.3.5; Amend the time and events table to show an 'x' for body weight at Visit 3 as this was missing; Remove word "continuously" in Section 9.1; Add a supportive completer's analysis of growth velocity over the 1-year double-blind treatment period, based on participants who completed the double-blind treatment period while remaining on study treatment, in Section 9.4.1.1
06 March 2019	Amendment 2: Removal of the upper limit of the Forced Expiratory Flow in 1 second (FEV1) from inclusion criterion 7 (Section 5.1); Removal of calcitriol from exclusion criteria 3 (Section 5.2) and from the prohibited medications Table 3 (Section 6.10.2); Update of text in Section 5.3 (Screening/Baseline/Run-in Failures) to allow rescreening of participants who have failed screening.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported