



Clinical trial results:

A randomised, double-blind, two-way crossover study to investigate the effect of inhaled fluticasone furoate on short-term growth in paediatric subjects with asthma

Summary

EudraCT number	2015-000841-22
Trial protocol	DK
Global end of trial date	21 December 2015

Results information

Result version number	v1 (current)
This version publication date	03 July 2016
First version publication date	03 July 2016

Trial information

Trial identification

Sponsor protocol code	HZA107112
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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 +4357343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1-866 +4357343,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 April 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	21 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of two weeks treatment with inhaled fluticasone furoate versus placebo once daily on short-term lower-leg growth using a knemometer.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 September 2015
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	Denmark: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	60
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:

Study consisted of run-in period of two-weeks followed by two treatment periods of 14 days each (+/- 4 days) separated by a 14-day washout period and a follow-up visit of approximately 7 days post last dose. The total participation time in the study was approximately 9 Weeks.

Pre-assignment

Screening details:

A total of 60 participants were randomized to receive one of the two treatment sequences; placebo followed by inhaled fluticasone furoate or inhaled fluticasone furoate followed by placebo. All 60 participants received at least one single dose of study medication.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo followed by fluticasone furoate

Arm description:

Participants received oral inhalation of 50 microgram (mcg) fluticasone furoate (FF) once daily (OD) or placebo for 14 days in either of the treatment periods in a two-way crossover design. Sequence 1 participants received oral inhalation of placebo OD for 14 days +/- 4 days in Treatment Period 1, followed by oral inhalation of FF 50 mcg, OD for 14 days +/- 4 days in Treatment Period 2. The two treatment periods were separated by a two-week wash-out period. Additionally, all participants were provided a salbutamol inhaler for symptomatic relief of asthma symptoms during the 2-week run-in, washout, and treatment periods as needed.

Arm type	Experimental
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 once daily (OD) for 14 days +/- 4 days. Each dose was administered via dry powder inhaler.

Investigational medicinal product name	Fluticasone furoate 50 mcg Dry Powder Inhaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone furoate 50 mcg was administered once daily (OD) for 14 days +/- 4 days. Each dose was administered via dry powder inhaler.

Arm title	Fluticasone furoate followed by placebo
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Arm description:

Participants received oral inhalation of 50 microgram (mcg) fluticasone furoate (FF) once daily (OD) or placebo for 14 days in either of the treatment periods in a two-way crossover design. Sequence 2 participants received oral inhalation of FF 50 mcg, OD for 14 days +/- 4 days in Treatment Period 1 followed by oral inhalation of placebo, OD for 14 days +/- 4 days in Treatment Period 2. The two treatment periods were separated by a two-week wash-out period. Additionally, all participants were

provided a salbutamol inhaler for symptomatic relief of asthma symptoms during the 2-week run-in, washout, and treatment periods as needed.

Arm type	Experimental
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 once daily (OD) for 14 days +/- 4 days. Each dose was administered via dry powder inhaler.

Investigational medicinal product name	Fluticasone furoate 50 mcg Dry Powder Inhaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone furoate 50 mcg was administered once daily (OD) for 14 days +/- 4 days. Each dose was administered via dry powder inhaler.

Number of subjects in period 1	Placebo followed by fluticasone furoate	Fluticasone furoate followed by placebo
Started	30	30
Completed	29	30
Not completed	1	0
Adverse event, non-fatal	1	-

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo followed by fluticasone furoate

Arm description:

The two treatment periods were separated by a two-week wash-out period in which all participants did not receive study medication, but were provided a salbutamol inhaler for symptomatic relief of asthma symptoms.

Arm type	Experimental
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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 once daily (OD) for 14 days +/- 4 days. Each dose was administered via dry powder inhaler.

Investigational medicinal product name	Fluticasone furoate 50 mcg Dry Powder Inhaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone furoate 50 mcg was administered once daily (OD) for 14 days +/- 4 days. Each dose was administered via dry powder inhaler.

Arm title	Fluticasone furoate followed by placebo
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Arm description:

The two treatment periods were separated by a two-week wash-out period in which all participants did not receive study medication, but were provided a salbutamol inhaler for symptomatic relief of asthma symptoms.

Arm type	Experimental
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 once daily (OD) for 14 days +/- 4 days. Each dose was administered via dry powder inhaler.

Investigational medicinal product name	Fluticasone furoate 50 mcg Dry Powder Inhaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone furoate 50 mcg was administered once daily (OD) for 14 days +/- 4 days. Each dose was administered via dry powder inhaler.

Number of subjects in period 2	Placebo followed by fluticasone furoate	Fluticasone furoate followed by placebo
Started	29	30
Completed	28	30
Not completed	1	0
Adverse event, non-fatal	1	-

Period 3

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo followed by fluticasone furoate

Arm description:

Participants received oral inhalation of 50 microgram (mcg) fluticasone furoate (FF) once daily (OD) or placebo for 14 days in either of the treatment periods in a two-way crossover design. Sequence 1 participants received oral inhalation of placebo OD for 14 days +/- 4 days in Treatment Period 1, followed by oral inhalation of FF 50 mcg, OD for 14 days +/- 4 days in Treatment Period 2. The two treatment periods were separated by a two-week wash-out period. Additionally, all participants were provided a salbutamol inhaler for symptomatic relief of asthma symptoms during the 2-week run-in, washout, and treatment periods as needed.

Arm type	Experimental
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 once daily (OD) for 14 days +/- 4 days. Each dose was administered via dry powder inhaler.

Investigational medicinal product name	Fluticasone furoate 50 mcg Dry Powder Inhaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone furoate 50 mcg was administered once daily (OD) for 14 days +/- 4 days. Each dose was administered via dry powder inhaler.

Arm title	Fluticasone furoate followed by placebo
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Arm description:

Participants received oral inhalation of 50 microgram (mcg) fluticasone furoate (FF) once daily (OD) or placebo for 14 days in either of the treatment periods in a two-way crossover design. Sequence 2 participants received oral inhalation of FF 50 mcg, OD for 14 days +/- 4 days in Treatment Period 1 followed by oral inhalation of placebo, OD for 14 days +/- 4 days in Treatment Period 2. The two treatment periods were separated by a two-week wash-out period. Additionally, all participants were provided a salbutamol inhaler for symptomatic relief of asthma symptoms during the 2-week run-in, washout, and treatment periods as needed.

Arm type	Experimental
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 once daily (OD) for 14 days +/- 4 days. Each dose was administered via dry powder inhaler.

Investigational medicinal product name	Fluticasone furoate 50 mcg Dry Powder Inhaler
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone furoate 50 mcg was administered once daily (OD) for 14 days +/- 4 days. Each dose was administered via dry powder inhaler.

Number of subjects in period 3	Placebo followed by fluticasone furoate	Fluticasone furoate followed by placebo
Started	28	30
Completed	28	30

Baseline characteristics

Reporting groups

Reporting group title	Double-blind treatment Period 1
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Reporting group description:

Participants received oral inhalation of 50 microgram (mcg) fluticasone furoate (FF) once daily (OD) or placebo for 14 days in either of the treatment periods in a two-way crossover design. Sequence 1 participants received oral inhalation of placebo OD for 14 days +/- 4 days in Period 1, followed by oral inhalation of FF 50 mcg, OD for 14 days +/- 4 days in Period 2. Sequence 2 participants received oral inhalation of FF 50 mcg, OD for 14 days +/- 4 days in Period 1 followed by oral inhalation of placebo, OD for 14 days +/- 4 days in Period 2. The two treatment periods were separated by a two-week wash-out period. Additionally, all participants were provided a salbutamol inhaler for symptomatic relief of asthma symptoms during the 2-week run-in, washout, and treatment periods as needed.

Reporting group values	Double-blind treatment Period 1	Total	
Number of subjects	60	60	
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	8.7 ± 1.53	-	
Gender categorical Units: Subjects			
Female	24	24	
Male	36	36	
Race, Customized Units: Subjects			
Asian - Central/South Asian Heritage	1	1	
White - White/Caucasian/European Heritage	59	59	

End points

End points reporting groups

Reporting group title	Placebo followed by fluticasone furoate
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Reporting group description:

Participants received oral inhalation of 50 microgram (mcg) fluticasone furoate (FF) once daily (OD) or placebo for 14 days in either of the treatment periods in a two-way crossover design. Sequence 1 participants received oral inhalation of placebo OD for 14 days +/- 4 days in Treatment Period 1, followed by oral inhalation of FF 50 mcg, OD for 14 days +/- 4 days in Treatment Period 2. The two treatment periods were separated by a two-week wash-out period. Additionally, all participants were provided a salbutamol inhaler for symptomatic relief of asthma symptoms during the 2-week run-in, washout, and treatment periods as needed.

Reporting group title	Fluticasone furoate followed by placebo
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Reporting group description:

Participants received oral inhalation of 50 microgram (mcg) fluticasone furoate (FF) once daily (OD) or placebo for 14 days in either of the treatment periods in a two-way crossover design. Sequence 2 participants received oral inhalation of FF 50 mcg, OD for 14 days +/- 4 days in Treatment Period 1 followed by oral inhalation of placebo, OD for 14 days +/- 4 days in Treatment Period 2. The two treatment periods were separated by a two-week wash-out period. Additionally, all participants were provided a salbutamol inhaler for symptomatic relief of asthma symptoms during the 2-week run-in, washout, and treatment periods as needed.

Reporting group title	Placebo followed by fluticasone furoate
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Reporting group description:

The two treatment periods were separated by a two-week wash-out period in which all participants did not receive study medication, but were provided a salbutamol inhaler for symptomatic relief of asthma symptoms.

Reporting group title	Fluticasone furoate followed by placebo
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Reporting group description:

The two treatment periods were separated by a two-week wash-out period in which all participants did not receive study medication, but were provided a salbutamol inhaler for symptomatic relief of asthma symptoms.

Reporting group title	Placebo followed by fluticasone furoate
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Reporting group description:

Participants received oral inhalation of 50 microgram (mcg) fluticasone furoate (FF) once daily (OD) or placebo for 14 days in either of the treatment periods in a two-way crossover design. Sequence 1 participants received oral inhalation of placebo OD for 14 days +/- 4 days in Treatment Period 1, followed by oral inhalation of FF 50 mcg, OD for 14 days +/- 4 days in Treatment Period 2. The two treatment periods were separated by a two-week wash-out period. Additionally, all participants were provided a salbutamol inhaler for symptomatic relief of asthma symptoms during the 2-week run-in, washout, and treatment periods as needed.

Reporting group title	Fluticasone furoate followed by placebo
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Reporting group description:

Participants received oral inhalation of 50 microgram (mcg) fluticasone furoate (FF) once daily (OD) or placebo for 14 days in either of the treatment periods in a two-way crossover design. Sequence 2 participants received oral inhalation of FF 50 mcg, OD for 14 days +/- 4 days in Treatment Period 1 followed by oral inhalation of placebo, OD for 14 days +/- 4 days in Treatment Period 2. The two treatment periods were separated by a two-week wash-out period. Additionally, all participants were provided a salbutamol inhaler for symptomatic relief of asthma symptoms during the 2-week run-in, washout, and treatment periods as needed.

Subject analysis set title	Placebo
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants received oral inhalation of placebo OD for 14 days +/- 4 days during Period 1 or Period 2

Subject analysis set title	Fluticasone furoate
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants received oral inhalation of FF 50 mcg, OD for 14 days +/- 4 days during Period 1 or Period 2

Primary: Mean growth rate in lower-leg growth (mm/week), as determined by knemometry

End point title	Mean growth rate in lower-leg growth (mm/week), as determined by knemometry
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End point description:

Lower leg growth rate was assessed in growth population as change in the lower leg length from start to end of each 2-week treatment period, divided by time interval (number of days) between the two measurements, multiplied by 7. The Growth Population is defined as the Intent-To-Treat (ITT) population excluding participants having any of the following: did not fulfill growth-specific criteria; did not have growth assessment(s) at any defined time point; withdrawal from study due to adverse events related to major trauma to the legs, major surgery, or severe dehydration; received protocol prohibited medications that may affect short term growth, prior to randomization and during the study; protocol deviations defined in exclusion criteria for growth population. ITT Population consists of all randomized participants who received at least one dose of study drug.

End point type	Primary
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End point timeframe:

Over a two week (14 day) treatment period for FF 50mcg OD and Placebo respectively

End point values	Placebo	Fluticasone furoate		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58 ^[1]	58 ^[2]		
Units: millimeter per week				
least squares mean (standard error)	0.3638 (\pm 0.02793)	0.3118 (\pm 0.02793)		

Notes:

[1] - Growth Population

[2] - Growth Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

Analysis performed using ANCOVA with covariates period-level baseline and subject-level baseline lower-leg length, age, gender, treatment and period.

Please note: To clarify system limitations, the comparison groups for statistical analysis are fluticasone furoate vs. placebo. Although the system adds the subjects in each analysis group together (total 116 below), there are only 58 subjects measured in this analysis as this is a crossover study with the same 58 subjects in each arm.

Comparison groups	Fluticasone furoate v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
Method	ANCOVA
Parameter estimate	Adjusted Mean Difference
Point estimate	-0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1217
upper limit	0.0176

Notes:

[3] - Non-inferiority would be demonstrated if the lower limit of the confidence interval (0.025,1-sided significance test level) for the mean difference in lower-leg growth rate of FF 50 mcg OD versus Placebo was greater than -0.20mm/week.

Secondary: Number of participants with any adverse events (AE) and any serious adverse event (SAE).

End point title	Number of participants with any adverse events (AE) and any serious adverse event (SAE).
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End point description:

An AE is any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. 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, is a congenital anomaly/birth defect. Number of participants with AEs and SAEs have been presented. Two participants randomized to Sequence 1 (Placebo/FF), were treated with placebo in Period 1; however, neither received FF in Period 2, due to premature withdrawal.

End point type	Secondary
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End point timeframe:

From the start of study treatment until follow-up (assessed up to 54 days)

End point values	Placebo	Fluticasone furoate		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60 ^[4]	58 ^[5]		
Units: Participants	14	7		

Notes:

[4] - ITT Population

[5] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs and non-serious AEs were collected from start of study medication through the Study Phase (7 weeks post-dose) and assessed up to 54 days. AEs reported during the wash-out and follow-up period are considered post-treatment and are not presented.

Adverse event reporting additional description:

On-treatment Serious Adverse Events (SAEs) and non-serious Adverse Events (AEs) are reported for the ITT Population, which comprises 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
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Participants received oral inhalation of placebo OD for 14 days +/- 4 days during Period 1 or Period 2

Reporting group title	Fluticasone furoate
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Reporting group description:

Participants received oral inhalation of FF 50 mcg, OD for 14 days +/- 4 days during Period 1 or Period 2

Serious adverse events	Placebo	Fluticasone furoate	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Fluticasone furoate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 60 (25.00%)	7 / 58 (12.07%)	
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	8 / 60 (13.33%) 9	3 / 58 (5.17%) 4	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	0 / 58 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3 3 / 60 (5.00%) 3	2 / 58 (3.45%) 2 2 / 58 (3.45%) 2	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 60 (8.33%) 5	4 / 58 (6.90%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported