Clinical trial results:
A repeat-dose, open-label, 2-session study to assess the systemic exposure to, and pharmacodynamics of, fluticasone propionate HFA inhalation aerosol 88 mcg administered twice-daily for 28 days delivered via an MDI and valved holding chamber with facemask to subjects ages 6 months to <12 months who have experienced 2 or more wheezing episodes in the preceding 6 months

Summary

EudraCT number	2015-004884-35
Trial protocol	Outside EU/EEA
Global end of trial date	12 April 2007

Results information

Result version number	v1 (current)
This version publication date	22 January 2017
First version publication date	22 January 2017

Trial information

Trial identification

Sponsor protocol code	FAS106533

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)	No
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	19 July 2007
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 April 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the effect of administration of FP HFA MDI 88 mcg BID on 12 h serum cortisol in pediatric subjects, ages 6 months to <12 months, who have experienced 2 or more wheezing episodes in the preceding 6 months.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 August 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	23
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	23
Children (2-11 years)	0
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 an open-label, repeat-dose, 2-session study to assess the systemic exposure to, and pharmacodynamics of, fluticasone propionate hydrofluoroalkane (FP HFA) inhalation administered twice-daily, via an metered-dose inhaler (MDI), to participants, aged 6 months to <12 months, who had experienced 2 wheezing episodes in the preceding 6 months.

Pre-assignment

Screening details:

The study consisted of 2 sessions followed by a follow-up call. The total duration of the study was approximately 8 weeks.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Overall Study

Arm description:

Placebo twice daily (BID) for 14 days followed by FP HFA 44 microgram (mcg) BID for 28 days

Arm type	Experimental
Investigational medicinal product name	Fluticasone propionate (FP) hydrofluoroalkane (HFA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

This consists of a white to off-white suspension of FP (micronized) in a liquefied HFA propellant. A metered dose inhaler (MDI) is a small hand held pressurized canister device that contains both medications, in this case, FP, and a propellant. In Session 2, it was administered at 44 mcg (two inhalations BID given 30 seconds apart for 28 days) using a Aerochamber Plus with an infant mask

Investigational medicinal product name	Placebo HFA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

This consists of a liquefied HFA propellant (placebo). An MDI is a small hand held pressurized canister device that contains both medications, in this case, FP, and a propellant. In Session 1, two inhalations were administered BID 30 seconds apart for 14 days, using a Aerochamber Plus with an infant mask

Number of subjects in period 1	Overall Study
Started	23
Completed Session 1	21
Completed	18
Not completed	5
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Medication not administered	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description:

In
Session 1, participants received two inhalations of placebo HFA BID 30 seconds apart from Day 1 to 14, via a MDI and a valved holding chamber (AeroChamber Plus) with infant mask. In Session 2, participants received 2 inhalations of 44 mcg FP HFA BID 30 seconds apart from Day 1 to 28, via a MDI and a valved holding chamber (AeroChamber Plus) with infant mask. Doses were given at about the same time of day approximately 12 hours apart.

Reporting group values	Overall Study	Total	
Number of subjects	23	23	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	9.4		
standard deviation	± 1.59	-	
Gender categorical Units:			
Male	18	18	
Female	5	5	
Race, Customized Units: Subjects			
African American/African Heritage	8	8	
White-Arabic/North African Heritage	1	1	
White-White/Caucasian/European Heritage	12	12	
Mixed Race	2	2	

End points

End points reporting groups

Reporting group title	Overall Study
Reporting group description:	
Placebo twice daily (BID) for 14 days followed by FP HFA 44 microgram (mcg) BID for 28 days	
Subject analysis set title	Placebo HFA
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
In Session 1, participants received two inhalations of placebo HFA BID 30 seconds apart from Day 1 to 14, via a MDI and a valved holding chamber (AeroChamber Plus) with infant mask.	
Subject analysis set title	FP HFA 44 microgram
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
In Session 2, participants received 2 inhalations of 44 mcg FP HFA BID 30 seconds apart from Day 1 to 28, via a MDI and a valved holding chamber (AeroChamber Plus) with infant mask. Doses were given at about the same time of day approximately 12 hours apart.	

Primary: Weighted mean serum cortisol over 0 to 12 hours (h) (0-12 h) post dose

End point title	Weighted mean serum cortisol over 0 to 12 hours (h) (0-12 h) post dose
End point description:	
Blood samples of participants were collected at the following time points: 0, 2, 4, 8, and 12 hour following the morning dose on Day 14 of Session 1 and Day 28 of Session 2. The primary outcome compared serum cortisol weighted mean(0-12h) between treatments after 28 days of FP HFA MDI 88 mcg with 14 days of placebo, obtained from the repeated measures analysis. . Only those participants available at the specified time points were analyzed. Pharmacodynamic (PD) Population: all participants in the Safety Population (comprised of all participants who received at least one dose of placebo in session 1) who had serum cortisol results for session 1 Day 14 or session 2 Day 28 were included.	
End point type	Primary
End point timeframe:	
Day 14 and Day 28	

End point values	Placebo HFA	FP HFA 44 microgram		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21[1]	17[2]		
Units: Nanomoles per liter (nmol/L)				
geometric mean (standard error)	191.65 (± 0.108)	184.58 (± 0.12)		

Notes:

[1] - PD Population

[2] - PD Population

Statistical analyses

Statistical analysis title	Statistical Analysis - 1
Comparison groups	FP HFA 44 microgram v Placebo HFA

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Ratio of geometric means
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.31

Notes:

[3] - Non-inferiority was demonstrated if the lower limit of the two-sided 95% confidence interval for the ratio of the geometric mean for the two treatment arms was greater than 0.7.

Secondary: Minimum serum cortisol concentration (Cmin) over 0 to 12 h

End point title	Minimum serum cortisol concentration (Cmin) over 0 to 12 h

End point description:

Blood samples for serum cortisol were collected at the following timepoints: 0, 2, 4, 8, and 12 hour following the morning dose on Day 14 of Session 1 and Day 28 of Session 2. Cmin was derived from the serum cortisol concentration data. Any difference in systemic exposure of the two treatments was considered to also result in differences in serum cortisol concentrations. Only those participants available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Day 14 and Day 28

End point values	Placebo HFA	FP HFA 44 microgram		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17[4]	14[5]		
Units: nmol/L				
geometric mean (confidence interval 95%)	103.25 (74.47 to 143.15)	91.56 (64 to 131)		

Notes:

[4] - PD Population

[5] - PD Population

Statistical analyses

Statistical analysis title	Statistical Analysis - 1
Comparison groups	Placebo HFA v FP HFA 44 microgram
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Ratio of geometric means
Point estimate	0.887
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.579
upper limit	1.359

Notes:

[6] - Non-inferiority was not demonstrated if the lower confidence limit was greater than 0.7

Secondary: Maximum plasma concentration at steady-state (Cmax) for FP

End point title	Maximum plasma concentration at steady-state (Cmax) for FP

End point description:

Plasma FP samples were collected at the following times: 1 h post-dose following morning dose on Day 14 (Session 1) and 0, 1, 4, 8 and 12 h post-dose on Day 28 (Session 2) and analyzed for Cmax of FP in the blood. Cmax was used to estimate the time at which the activity of the drug was at its maximum. Pharmacokinetic (PK) Parameter Population: All participants in the PK Concentration Population (included all participants in the Safety Population who had PK results for Session 1 Day 14 or Session 2 Day 28) who had derived PK parameters for session 2 Day 28 were included.

End point type	Secondary

End point timeframe:

Day 14 and Day 28

End point values	FP HFA 44 microgram			
Subject group type	Subject analysis set			
Number of subjects analysed	17[7]			
Units: Picogram/milliliter (pg/mL)				
geometric mean (confidence interval 95%)	24.6 (13.4 to 45)			

Notes:

[7] - PK Parameter Population

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration versus time curve within a dosing interval at steady-state (AUC[0-t]) for FP

End point title	Area under the plasma concentration versus time curve within a dosing interval at steady-state (AUC[0-t]) for FP

End point description:

Plasma FP samples were collected at the following times: 1 h post-dose following morning dose on Day 14 (Session 1) and 0, 1, 4, 8 and 12 h post-dose on Day 28 (Session 2) and analyzed for AUC(0-t) of FP in the blood. AUC(0-t) is a measure of the plasma drug concentration from pre-dose to the last measurable concentration.

End point type	Secondary

End point timeframe:

Day 14 and Day 28

End point values	FP HFA 44 microgram			
Subject group type	Subject analysis set			
Number of subjects analysed	17[8]			
Units: Hours per picogram per milliliter				
geometric mean (confidence interval 95%)	75 (33.8 to 166.3)			

Notes:

[8] - PK Parameter Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Plasma Concentration at steady state (tmaxss) for FP

End point title	Time to Reach Maximum Observed Plasma Concentration at steady state (tmaxss) for FP

End point description:

Plasma FP samples were collected at the following times: 1 h post-dose following morning dose on Day 14 (Session 1) and 0, 1, 4, 8 and 12 h post-dose on Day 28 (Session 2) and analyzed for tmax of FP in the blood. Tmax is a measure of the time required to reach the maximum concentration of the drug

End point type	Secondary

End point timeframe:

Day 14 and Day 28

End point values	FP HFA 44 microgram			
Subject group type	Subject analysis set			
Number of subjects analysed	17[9]			
Units: Hour (hr)				
median (full range (min-max))	1 (0 to 4)			

Notes:

[9] - PK parameter population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any adverse events (AEs) and any serious averse events (SAE) during the treatment period

End point title	Number of participants with any adverse events (AEs) and any serious averse events (SAE) during the treatment period

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. SAEs assessed included medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, and is a significant medical event in the investigator's judgment. Safety Population: all participants who received at least one dose of placebo in session 1.

End point type	Secondary

End point timeframe:

Up to 4 weeks

End point values	Placebo HFA	FP HFA 44 microgram		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[10]	21[11]		
Units: Participants				
number (not applicable)				
Any AE	22	19		
Any SAE	1	0		

Notes:

[10] - Safety Population

[11] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected from the time a parent/guardian consents for their infant to participate in the study to the end of the the treatment period (approximately 8 weeks including screening and follow-up).

Adverse event reporting additional description:

SAEs and non-serious AEs were reported for the Safety Population, comprised all participants who received at least one dose of placebo in session 1.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Fluticasone propionate HFA

Reporting group description:

In Session 2, participants received 2 inhalations of 44 mcg FP HFA BID 30 seconds apart from Day 1 to 28, via a MDI and a valved holding chamber (AeroChamber Plus) with infant mask. Doses were given at about the same time of day approximately 12 hours apart.

Reporting group title	Placebo HFA

Reporting group description:

In Session 1, participants received two inhalations of placebo HFA BID 30 seconds apart from Day 1 to 14, via a MDI and a valved holding chamber (AeroChamber Plus) with infant mask.

Serious adverse events	Fluticasone propionate HFA	Placebo HFA	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 23 (4.35%)	
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: 5 %

Non-serious adverse events	Fluticasone propionate HFA	Placebo HFA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 21 (90.48%)	22 / 23 (95.65%)	

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 21 (28.57%)	8 / 23 (34.78%)	
occurrences (all)	10	11	
Irritability			
subjects affected / exposed	1 / 21 (4.76%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 21 (4.76%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 21 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Teething			
subjects affected / exposed	3 / 21 (14.29%)	1 / 23 (4.35%)	
occurrences (all)	4	1	
Vomiting			
subjects affected / exposed	2 / 21 (9.52%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 21 (66.67%)	17 / 23 (73.91%)	
occurrences (all)	32	58	
Rhinorrhoea			
subjects affected / exposed	13 / 21 (61.90%)	15 / 23 (65.22%)	
occurrences (all)	23	25	
Nasal congestion			
subjects affected / exposed	6 / 21 (28.57%)	12 / 23 (52.17%)	
occurrences (all)	12	16	
Wheezing			

subjects affected / exposed	8 / 21 (38.10%)	10 / 23 (43.48%)	
occurrences (all)	22	26	
Dyspnoea			
subjects affected / exposed	1 / 21 (4.76%)	3 / 23 (13.04%)	
occurrences (all)	1	3	
Respiratory tract congestion			
subjects affected / exposed	1 / 21 (4.76%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Grunting			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Sneezing			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Middle insomnia			
subjects affected / exposed	11 / 21 (52.38%)	9 / 23 (39.13%)	
occurrences (all)	17	27	
Crying			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Ear infection			
subjects affected / exposed	1 / 21 (4.76%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	1 / 21 (4.76%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Eye infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Influenza			

subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Streptococcal sepsis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Varicella			
subjects affected / exposed	1 / 21 (4.76%)	0 / 23 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 October 2006	The purpose of this amendment is to make changes to the Rationale, Endpoints, Hypotheses, Study Design, Dose Rationale and Sample Size Assumptions sections of the protocol as well as include additional information to the Background Section of the protocol and remove section 10.2.2 which no longer applies to this protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported