Clinical trial results:
Clinical assessment of fluticasone propionate/ salmeterol xinafoate HFA MDI in 6-month to 4-year-old Japanese patients with bronchial asthma

Summary

EudraCT number	2016-003479-22
Trial protocol	Outside EU/EEA
Global end of trial date	

Results information

Result version number	v1
This version publication date	21 December 2016
First version publication date	21 December 2016

Trial information

Trial identification

Sponsor protocol code	200860

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?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	17 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 June 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of fluticasone propionate (FP)/ salmeterol xinafoate (SLM) hydrofluoroalkane (HFA) MDI 50/25 µg 1 or 2 inhalation bid for 8 weeks in comparison with FP HFA MDI 50 µg 1 or 2 inhalation bid in 6-month to 4-year-old Japanese patients with bronchial asthma.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 May 2014
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	Japan: 370
Worldwide total number of subjects	370
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)	67
Children (2-11 years)	303
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 study evaluated the efficacy and safety of (FP)/salmeterol xinafoate (SLM) HFA twice-daily (BID) via metered-dose inhaler (MDI) for 8 weeks in comparison with FP HFA MDI in 6-months to 4-years-old Japanese participants (par.) with infantile bronchial asthma. The results presented are based on the Interim Analysis.

Pre-assignment

Screening details:

Eligible par. at screening entered a 2-week run-in period to receive FP HFA MDI 50 µg, followed by 8-week double-blind treatment period (TP) 1 to receive FP/SLM HFA MDI 50/25 µg or FP HFA MDI 50 µg. In TP2, par. received FP/SLM HFA MDI 50/25 µg for 16 weeks (open-label phase). The total duration of the study was 27 weeks with follow-up.

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, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	FP HFA 50 µg

Arm description:

In TP1, participants were randomized to receive one or two inhalations of FP HFA 50 µg BID for 8 weeks via a MDI using AeroChamber Plus with face mask. Salbutamol was provided as a rescue medication.

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

Dosage and administration details:

FP HFA was administered via pressurized Metered-Dose Inhaler at 50 µg BID (one or two inhalations given using AeroChamber Plus with face mask) for 2 weeks in run-in period and 8 weeks in TP1

Arm title	FP/SLM HFA 50/25 µg

Arm description:

In TP1, participants were randomized to receive one or two inhalations of FP/SLM HFA 50/25 µg BID for 8 weeks via a MDI using AeroChamber Plus with face mask. Salbutamol was provided as a rescue medication.

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

Dosage and administration details:

FP/SLM HFA was administered via pressurized Metered-Dose Inhaler at 50/25µg BID (one or two inhalations given using AeroChamber Plus with face mask) for 8 weeks in TP1 and 16 weeks in TP2

Number of subjects in period 1[1]	FP HFA 50 µg	FP/SLM HFA 50/25 µg
Started	150	150
Completed	142	148
Not completed	8	2
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	-
Par. Reached Stopping Criteria	5	2
Protocol deviation	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 370 participants were enrolled of which 300 participants were randomized.

Baseline characteristics

Reporting groups	
Reporting group title	FP HFA 50 µg
Reporting group description:	
In TP1, participants were randomized to receive one or two inhalations of FP HFA 50 µg BID for 8 weeks via a MDI using AeroChamber Plus with face mask. Salbutamol was provided as a rescue medication.	
Reporting group title	FP/SLM HFA 50/25 µg
Reporting group description:	
In TP1, participants were randomized to receive one or two inhalations of FP/SLM HFA 50/25 µg BID for 8 weeks via a MDI using AeroChamber Plus with face mask. Salbutamol was provided as a rescue medication.	

Reporting group values	FP HFA 50 µg	FP/SLM HFA 50/25 µg	Total
Number of subjects	150	150	300
Age categorical Units: Subjects			
Age continuous			
Age continuous description			
Units: months			
arithmetic mean	38.4	40.5	
standard deviation	± 14.1	± 14.07	-
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	60	55	115
Male	90	95	185
Race/Ethnicity, Customized Units: Subjects			
Asian - Japanese Heritage	150	150	300

End points

End points reporting groups

Reporting group title	FP HFA 50 µg
Reporting group description:	
In TP1, participants were randomized to receive one or two inhalations of FP HFA 50 µg BID for 8 weeks via a MDI using AeroChamber Plus with face mask. Salbutamol was provided as a rescue medication.	
Reporting group title	FP/SLM HFA 50/25 µg
Reporting group description:	
In TP1, participants were randomized to receive one or two inhalations of FP/SLM HFA 50/25 µg BID for 8 weeks via a MDI using AeroChamber Plus with face mask. Salbutamol was provided as a rescue medication.	

Primary: Mean change from Baseline in total asthma symptom score (daytime plus night time) at the end of the Treatment Period 1 (TP1)

End point title	Mean change from Baseline in total asthma symptom score (daytime plus night time) at the end of the Treatment Period 1 (TP1)
End point description:	
The participant's parent or legally acceptable representative made entries asthma symptom experienced by the participant in a patient diary twice daily (day time and night time) in the form of scores on a 4-point rating scale from Baseline (Week -1) until end of TP1 (Week 8). The Baseline value is a mean value of the last 7 consecutive days during the run-in period (excluding the day of Visit 2 [Randomization]).The end of the TP1 value is a mean value of the last 7 consecutive days during the TP1 (excluding the last day of the TP1). Change from Baseline is the difference between the value of the endpoint at the time point of interest and the Baseline value. Participants who completed TP1 were analyzed.	
End point type	Primary
End point timeframe:	
Baseline and Week 8	

End point values	FP HFA 50 µg	FP/SLM HFA 50/25 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142[1]	148[2]		
Units: Scores on a scale				
least squares mean (standard error)	-3.01 (± 0.545)	-3.97 (± 0.534)		

Notes:

[1] - ITT Population: all randomized par. who received at least one dose of study medication.

[2] - ITT Population: all randomized par. who received at least one dose of study medication.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FP HFA 50 µg v FP/SLM HFA 50/25 µg

Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.206
Method	ANCOVA
Parameter estimate	Difference in Least square means
Point estimate	-0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.47
upper limit	0.54

Secondary: Mean change from Baseline in night-time asthma symptoms score at the end of Treatment Period 1 (TP1)

End point title	Mean change from Baseline in night-time asthma symptoms score at the end of Treatment Period 1 (TP1)

End point description:

The participant's parent or legally acceptable representative recorded asthma symptoms experienced by the participant during the night in a patient diary in the form of scores on a 4-point rating scale from Baseline (Week -1) until end of TP1 (Week 8). Scores ranged from 0 (none) to 3 (severe). Change from Baseline in the asthma symptom scores at night time at the end of TP1 was analyzed. The Baseline value is a mean value of the last 7 consecutive days during the run-in period (excluding the day of Visit 2 [Randomization]).The end of the TP1 value is a mean value of the last 7 consecutive days during the TP1 (excluding the last day of the TP1). Change from Baseline is the difference between the value of the endpoint at the time point of interest and the Baseline value. Participants who completed TP1 were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	FP HFA 50 µg	FP/SLM HFA 50/25 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142[3]	148[4]		
Units: Scores on a scale				
least squares mean (standard error)	-1.61 (± 0.292)	-2.1 (± 0.286)		

Notes:

[3] - ITT Population

[4] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FP/SLM HFA 50/25 µg v FP HFA 50 µg

Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.235
Method	ANCOVA
Parameter estimate	Difference in Least sqaure means
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.29
upper limit	0.32

Secondary: Mean change from Baseline in daytime asthma symptoms score at the end of Treatment Period 1 (TP1)

End point title	Mean change from Baseline in daytime asthma symptoms score at the end of Treatment Period 1 (TP1)

End point description:

The participant's parent or legally acceptable representative recorded asthma symptoms experienced by the participant during the day in a patient diary in the form of scores on a 4-point rating scale from Baseline (Week -1) until end of TP1 (Week 8). Scores ranged from 0 (none) to 3 (severe). Change from Baseline in the asthma symptom scores at day time at the end of TP1 was analyzed. The Baseline value is a mean value of the last 7 consecutive days during the run-in period (excluding the day of Visit 2 [Randomization]).The end of the TP1 value is a mean value of the last 7 consecutive days during the TP1 (excluding the last day of the TP1). Change from Baseline is the difference between the value of the endpoint at the time point of interest and the Baseline value. Participants who completed TP1 were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	FP HFA 50 µg	FP/SLM HFA 50/25 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142[5]	148[6]		
Units: Scores on a scale				
least squares mean (standard error)	-1.39 (± 0.287)	-1.87 (± 0.281)		

Notes:

[5] - ITT Population

[6] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FP HFA 50 µg v FP/SLM HFA 50/25 µg

Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.236
Method	ANCOVA
Parameter estimate	Difference in Least-Sqaure means
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.27
upper limit	0.31

Secondary: Number of participants with at least one asthma exacerbation in Treatment Period 1 (TP1)

End point title	Number of participants with at least one asthma exacerbation in Treatment Period 1 (TP1)

End point description:

The definition of exacerbations was amended during the study. <Original> An exacerbation is defined as deterioration of asthma requiring the use of systemic corticosteroids (oral, parenteral, or depot) for at least 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. <Amendment> An asthma exacerbation is defined as deterioration of asthma requiring the use of prednisone or hydrocortisone equivalent systemic corticosteroids for at least 3 days, or requiring the use of dexamethasone or betametasone equivalent systemic corticosteroids (oral, intravenous or intramuscular), or requiring the use of systemic depot corticosteroids once, or an in-patient hospitalization that required treatment for respiratory symptom with wheezing, or emergency department visit due to asthma that required intravenous systemic corticosteroids.

End point type	Secondary

End point timeframe:

Treatment Period 1

End point values	FP HFA 50 µg	FP/SLM HFA 50/25 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147[7]	150[8]		
Units: Participants	8	4		

Notes:

[7] - ITT Population

[8] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FP/SLM HFA 50/25 µg v FP HFA 50 µg

Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	1.6

Secondary: Mean change from Baseline in Japanese Pediatric Asthma Control Program (JPAC) score at the end of Treatment Period 1 (TP1)

End point title	Mean change from Baseline in Japanese Pediatric Asthma Control Program (JPAC) score at the end of Treatment Period 1 (TP1)

End point description:

Severity and control statuses based on Japanese pediatric guideline for the treatment and management of asthma (JPGL) can be assessed according to JPAC. Theoretically range of JPAC score was 0 (poor control) to 18 (complete control) point. JPAC questionnaire was recorded at Baseline (Week -2) and Week 8 by the participant's parent or legally acceptable representative who knew the participant's asthma for the last month. Change from Baseline is the difference between the value of the endpoint at the time point of interest and the Baseline value. Participants who completed TP1 were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	FP HFA 50 µg	FP/SLM HFA 50/25 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142[9]	148[10]		
Units: Scores on a scale				
least squares mean (standard error)	-0.3 (± 0.25)	0.4 (± 0.24)		

Notes:

[9] - ITT Population

[10] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FP HFA 50 µg v FP/SLM HFA 50/25 µg
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.041
Method	ANCOVA
Parameter estimate	Difference in Least-Square Means
Point estimate	0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1.4

Secondary: Change from Baseline in use of rescue medication (number of occasions used during a 24-hour period) in Treatment Period 1 (TP1)

End point title	Change from Baseline in use of rescue medication (number of occasions used during a 24-hour period) in Treatment Period 1 (TP1)

End point description:

The number of inhalations of rescue salbutamol inhalation aerosol (medication used to relieve symptoms immediately) used during the day and night was recorded by the participant's parent or legally acceptable representative twice daily in a patient diary from Baseline (Week -1) until Week 8. A 24-hour period in which a participant's responses to both the morning and evening assessments indicated no use of rescue medication was considered as rescue free. Participants who were rescue free for 24-hour periods during the 8 weeks in TP1 were assessed. The Baseline value was derived from the last 7 days of the patient diary prior to the randomization of the participant. Change from Baseline is the difference between the value of the endpoint at the time point of interest and the Baseline value.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	FP HFA 50 µg	FP/SLM HFA 50/25 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142[11]	148[12]		
Units: Occasions per 24 hours				
least squares mean (standard error)	0.07 (± 0.048)	0.01 (± 0.047)		

Notes:

[11] - ITT Population

[12] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FP/SLM HFA 50/25 µg v FP HFA 50 µg
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.335
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.07

Secondary: Change from Baseline in use of rescue medication (percentage of days with rescue-free 24-hour period) at the end of Treatment Period 1 (TP1)

End point title	Change from Baseline in use of rescue medication (percentage of days with rescue-free 24-hour period) at the end of Treatment Period 1 (TP1)

End point description:

The number of inhalations of rescue salbutamol inhalation aerosol (medication used to relieve symptoms immediately) used during the day and night was recorded by the participant's parent or legally acceptable representative twice daily in a patient diary. A 24-hour period in which a participant's responses to both the morning and evening assessments indicated no use of rescue medication was considered as rescue free. Participants who were rescue free for 24-hour periods during the 4-week Treatment Period were assessed. The Baseline value was derived from the last 7 days of the patient diary prior to the randomization of the participant. Change from Baseline is calculated as the average value during the 8 weeks in TP1 minus the value at Baseline. Participants who completed TP1 were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	FP HFA 50 µg	FP/SLM HFA 50/25 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142[13]	148[14]		
Units: Percentage of rescue-free 24-hour period				
least squares mean (standard error)	-2.9 (± 2.16)	-0.3 (± 2.11)		

Notes:

[13] - ITT Population

[14] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FP HFA 50 µg v FP/SLM HFA 50/25 µg
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.389
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	8.6

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All on-treatment serious adverse events (SAEs) and non-serious AEs were collected in Treatment Period 1.

Adverse event reporting additional description:

On-treatment AEs and SAEs are reported for the ITT Population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	FP/SLM HFA 50/25 µg

Reporting group description:

In TP1, participants were randomized to receive one or two inhalations of FP/SLM HFA 50/25 µg BID for 8 weeks via a MDI using AeroChamber Plus with face mask. Salbutamol was provided as a rescue medication.

Reporting group title	FP HFA 50 µg

Reporting group description:

In TP1, participants were randomized to receive one or two inhalations of FP HFA 50 µg BID for 8 weeks via a MDI using AeroChamber Plus with face mask. Salbutamol was provided as a rescue medication.

Serious adverse events	FP/SLM HFA 50/25 µg	FP HFA 50 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 150 (0.67%)	5 / 150 (3.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 150 (0.00%)	4 / 150 (2.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
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	FP/SLM HFA 50/25 µg	FP HFA 50 µg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 150 (53.33%)	82 / 150 (54.67%)	
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract inflammation			
subjects affected / exposed	10 / 150 (6.67%)	18 / 150 (12.00%)	
occurrences (all)	13	25	
Asthma			
subjects affected / exposed	4 / 150 (2.67%)	10 / 150 (6.67%)	
occurrences (all)	4	10	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	28 / 150 (18.67%)	17 / 150 (11.33%)	
occurrences (all)	35	19	
Nasopharyngitis			
subjects affected / exposed	18 / 150 (12.00%)	24 / 150 (16.00%)	
occurrences (all)	22	33	
Bronchitis			
subjects affected / exposed	14 / 150 (9.33%)	13 / 150 (8.67%)	
occurrences (all)	18	15	
Gastroenteritis			
subjects affected / exposed	11 / 150 (7.33%)	13 / 150 (8.67%)	
occurrences (all)	14	13	
Pharyngitis			

subjects affected / exposed	11 / 150 (7.33%)	9 / 150 (6.00%)	
occurrences (all)	14	12	
Hand-foot-and-mouth disease			
subjects affected / exposed	9 / 150 (6.00%)	4 / 150 (2.67%)	
occurrences (all)	9	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2015	The primary purpose of this amendment is to change the wording related to the definition of inclusion criteria, re-screening criteria, permitted medications and non- drug therapies, prohibited medications and non-drug therapies, asthma exacerbation, withdrawal criteria and rescue medication and to clarify ambiguous description based on the comments from Safety Review Team.
26 January 2016	The primary objectives of this amendment is to set up interim analyses with the view to posting and disclosing study result summary on the clinical trial registries within 6 months after primary compression achievement of the last subject, change administrative aspects of the trail, and make adjustments to ambiguous descriptions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported