Clinical trial results:
A repeat-dose, open-label, randomized, incomplete block design in pediatric subjects with asthma, ages 4 - 11 years, to compare systemic exposure and pharmacodynamics of fluticasone propionate and salmeterol following Advair® HFA 45/21 mcg (2 inhalations), Advair HFA 45/21 mcg (2 inhalations) with Aerochamber Plus Spacer and Advair Diskus 100/50 twice daily.

Summary

EudraCT number	2015-004866-27
Trial protocol	Outside EU/EEA
Global end of trial date	02 February 2007

Results information

Result version number	v1 (current)
This version publication date	19 December 2016
First version publication date	19 December 2016

Trial information

Trial identification

Sponsor protocol code	SAS105519

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, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1-866 4357343, GSKClinicalSupportHD@gsk.com

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	Final
Date of interim/final analysis	11 July 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 February 2007
Global end of trial reached?	Yes
Global end of trial date	02 February 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to compare the systemic exposure and pharmacodynamics of therapeutic doses of Advair HFA

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 October 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: 31
Worldwide total number of subjects	31
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)	0
Children (2-11 years)	31
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 repeat-dose, open-label randomized, incomplete block design study in pediatric participants with asthma, aged 4-11 years to compare systemic exposure and pharmacodynamics of Advair HFA (A), Advair DISKUS (B), and Advair HFA with Aerochamber Plus Spacer (C) in two treatment periods, with a follow-up period within 24 hours post last dose.

Pre-assignment

Screening details:

Following Baseline assessments, participants received Advair HFA 45/21 microgram (µg) (two inhalations), Advair DISKUS 100/50 µg (one inhlation), or Advair HFA with Aerochamber Plus Spacer 45/21 µg (two inhalations) twice daily for 21 days, in accordance with the treatment sequence to which they were randomized (AB,BA,AC,CA,BC,or CB).

Period 1

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

Arms

Arm title	All study treatments

Arm description:

Participants were randomized to one of the 6 possible treatment arms (AB, BC, AC, CA, BC, or CB): Treatment regimen A: two inhalations of ADVAIR HFA 45/21 µg, which was a combination of 45 µg of fluticasone propionate (FP) and 21 µg of salmeterol administered via a metered dose inhaler (MDI), treatment regimen B: Advair HFA 42/21 µg with Aerochamber Plus Spacer, or treatment regimen C: Adavir DISKUS 100/50 µg twice daily (BID) for 21 days (on outpatient basis except on Day 21) in both treatment periods without any washout period.

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

Dosage and administration details:

Advair HFA 45/21 µg was supplied as an HFA-propelled 120-actuation MDI desgined to deliver approximately 21 µg salmeterol and 42 µg FP per actuation. Two inhalations from this device twice daily (BID) for 21 days.

Investigational medicinal product name	ADVAIR HFA with Aerochamber Plus Spacer
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Advair HFA 45/21 µg was supplied as supplied as a 6 mutli-dose powder inhaler (MDPI) to deliver 45 µg of salmeterol and 21 µg of fluticasone propionate (FP). Two inhalations from the DISKUS device twice daily (BID) for 21 days

Investigational medicinal product name	ADVAIR DISKUS
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of ADVAIR DISKUS 100/50mcg (Fluticasone, Salmeterol) will be administered twice daily for 21 days

Number of subjects in period 1	All study treatments
Started	31
Completed	28
Not completed	3
Consent withdrawn by subject	2
Missing	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	31	31	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	7.16		
standard deviation	± 2.423	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	24	24	
Race Units: Subjects			
AfricanAmerican/African Heritage	2	2	
Asian-South East Asian Heritage	1	1	
Native Hawaiian or Other Pacific Islander	1	1	
White-Arabic/North African Heritage	2	2	
White-White/Caucasian/European Heritage	25	25	

End points

End points reporting groups

Reporting group title	All study treatments

Reporting group description:

Participants were randomized to one of the 6 possible treatment arms (AB, BC, AC, CA, BC, or CB): Treatment regimen A: two inhalations of ADVAIR HFA 45/21 µg, which was a combination of 45 µg of fluticasone propionate (FP) and 21 µg of salmeterol administered via a metered dose inhaler (MDI), treatment regimen B: Advair HFA 42/21 µg with Aerochamber Plus Spacer, or treatment regimen C: Adavir DISKUS 100/50 µg twice daily (BID) for 21 days (on outpatient basis except on Day 21) in both treatment periods without any washout period.

Subject analysis set title	Advair HFA
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to one of the 6 possible treatment arms (AB, BA, AC, CA, BC, or CB): two inhalations of ADVAIR HFA 45/21 µg , which was supplied as a HFA-propelled 120-actuation metered dose inhaler (MDI) desgined to deliver 45 µg of fluticasone propionate (FP) and 21 µg of salmeterol twice daily (BID) for 21 days (on outpatient basis except on Day 21) along with either Advair HFA with Aerochamber Plus Spacer or Adavir DISKUS. After this treatment period 1, participants received a repeat dosing of the same sequence for 21 days without any washout period.

Subject analysis set title	Advair HFA with Spacer
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to one of the 6 possible treatment arms (AB, BA, AC, CA, BC, or CB): two inhalations of ADVAIR HFA 45/21 µg with Aerochamber Plus Spacer, which was supplied as a metered dose inhaler (MDI) designed to deliver 45 µg of FP and 21 µg of salmeterol twice daily (BID) for 21 days (on outpatient basis except on Day 21) along with either Advair HFA or Adavir DISKUS. After this treatment period 1, participants received a repeat dosing of the same sequence for 21 days without any washout period.

Subject analysis set title	Advair DISKUS
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to one of the 6 possible treatment arms (AB, BA, AC, CA, BC or CB): one inhalation of ADVAIR DISKUS 100/50 µg, which was supplied as a 60-dose multi-dose powder inhaler (MPDI) designed to deliver 100 µg of FP and 50 µg of salmeterol twice daily (BID) for 21 days (on outpatient basis except on Day 21) along with either Advair HFA with Aerochamber Plus Spacer or Adavir HFA. After this treatment period 1, participants received a repeat dosing of the same sequence for 21 days without any washout period.

Primary: Weighted mean serum cortisol (SC) over 0 to 12 hours (h; 0-12 h) post-dose for fluticasone propionate (FP)

End point title	Weighted mean serum cortisol (SC) over 0 to 12 hours (h; 0-12 h) post-dose for fluticasone propionate (FP)

End point description:

Participants' blood samples were collected and analyzed for SC levels. The serum cortisol weighted mean, calculated by dividing the area under the concentration curve (AUC) over the 0-12 h period by the sample collection time interval, was determined at Baseline and at the end of each treatment period. Only participants data available at the analysis time point were analyzed (represented as n=X, X, X in category title. Pharmacodynamic (PD) parameter population was defined as all participants who received treatment during both periods and for whom PD parameters were derived for both periods.

End point type	Primary

End point timeframe:

Baseline and 0, 2, 4, 8, and 12 h post-dose on Day 21 of each treatment period

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[1]	19[2]	20[3]	
Units: Nanomoles per liter (nmol/L)				
geometric mean (confidence interval 95%)	0.86 (0.77 to 0.96)	0.78 (0.7 to 0.86)	0.87 (0.79 to 0.97)	

Notes:

[1] - Pharmacodynamic (PD) Parameter Population

[2] - Pharmacodynamic (PD) Parameter Population

[3] - Pharmacodynamic (PD) Parameter Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advair DISKUS v Advair HFA
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Ratio of adjusted geometric means
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.12
Variability estimate	Standard error of the mean
Dispersion value	0.062

Notes:

[4] - If the two-sided CI for the ratio of geometric means for the two formulations is contained within the range of 0.7 to 1.43, the two formulations were deemed comparable.

Statistical analysis title	Statistical analysis 2
Comparison groups	Advair DISKUS v Advair HFA with Spacer
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Ratio of adjusted geometric means
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.01
Variability estimate	Standard error of the mean
Dispersion value	0.061

Notes:

[5] - If the two-sided CI for the ratio of geometric means for the two formulations is contained within the range of 0.7 to 1.43, the two formulations were deemed comparable.

Statistical analysis title	Statistical analysis 3
Comparison groups	Advair HFA with Spacer v Advair HFA

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Ratio of adjusted geometric means
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.03
Variability estimate	Standard error of the mean
Dispersion value	0.064

Notes:

[6] - If the two-sided CI for the ratio of geometric means for the two formulations is contained within the range of 0.7 to 1.43, the two formulations were deemed comparable.

Primary: Serum cortisol minimum (Cmin) over 0-12 h post-dose for FP

End point title	Serum cortisol minimum (Cmin) over 0-12 h post-dose for FP

End point description:

Blood samples of participants were collected for the evaluation of Cmin. Any differences in systemic exposure as a result of the absorbed steroid component of the three differing inhaled treatments should also result in differences in serum cortisol concentrations. Only participants data available at the analysis time point were analyzed (represented as n=X, X, X in category title).

End point type	Primary

End point timeframe:

At Baseline and 0, 2, 4, 8, and 12 h post-dose on Day 21 of each treatment period

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[7]	19[8]	20[9]	
Units: Nanomoles/liter (nmol/L)				
geometric mean (confidence interval 95%)	0.9 (0.69 to 1.18)	0.67 (0.52 to 0.87)	1.09 (0.84 to 1.4)	

Notes:

[7] - Pharmacodynamic (PD) Parameter Population

[8] - Pharmacodynamic (PD) Parameter Population

[9] - Pharmacodynamic (PD) Parameter Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advair HFA v Advair DISKUS
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[10]
Parameter estimate	Ratio of adjusted geometric means
Point estimate	0.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.2
Variability estimate	Standard error of the mean
Dispersion value	0.185

Notes:

[10] - If the two-sided CI for the ratio of geometric means for the two formulations is contained within the range of 0.7 to 1.43, the two formulations were deemed comparable.

Statistical analysis title	Statistical analysis 2
Comparison groups	Advair DISKUS v Advair HFA with Spacer
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[11]
Parameter estimate	Ratio of adjusted geometric means
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.89
Variability estimate	Standard error of the mean
Dispersion value	0.183

Notes:

[11] - If the two-sided CI for the ratio of geometric means for the two formulations is contained within the range of 0.7 to 1.43, the two formulations were deemed comparable.

Statistical analysis title	Statistical analysis 3
Comparison groups	Advair HFA with Spacer v Advair HFA
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other[12]
Parameter estimate	Ratio of adjusted geometric means
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.09
Variability estimate	Standard error of the mean
Dispersion value	0.189

Notes:

[12] - If the two-sided CI for the ratio of geometric means for the two formulations is contained within the range of 0.7 to 1.43, the two formulations were deemed comparable.

Secondary: Maximum mean change from Baseline of the QT Interval Corrected According to Bazett’s Formula (QTcB) at 9 hours post-dose

End point title	Maximum mean change from Baseline of the QT Interval Corrected According to Bazett’s Formula (QTcB) at 9 hours post-dose

End point description:

Twelve-lead electrocardiogram was performed to measure QTcB at Baseline, pre-dose and at 15 min, 45 min, 1.5 h, 3h, 6 h and 9 h post-dose on Day 21 of each treatment period and maximum value for QTcB was derived during the 0-9 h period. Baseline was defined as the derived parameter from the Baseline assessment. Only participants data available at the analysis time point were analyzed (represented as n=X, X, X in category title). Pharmacodynamic (PD) parameter population was defined as all participants who received treatment during both periods and for whom PD parameters were derived for both periods.

End point type	Secondary

End point timeframe:

At Baseline, and pre-dose, 15 min, 45 min, 1.5 h, 3 h, 6 h, and 9 h on Day 21 of each treatment period

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[13]	19[14]	20[15]	
Units: Milliseconds (ms)				
arithmetic mean (standard error)	3.6 (± 2.2)	-2.2 (± 2.14)	0.4 (± 2.08)	

Notes:

[13] - Pharmacodynamic (PD) Parameter Population

[14] - Pharmacodynamic (PD) Parameter Population

[15] - Pharmacodynamic (PD) Parameter Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advair HFA v Advair DISKUS
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of adjusted means
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	8.8
Variability estimate	Standard error of the mean
Dispersion value	2.73

Statistical analysis title	Statistical analysis 2
Comparison groups	Advair DISKUS v Advair HFA with Spacer
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of adjusted means
Point estimate	-2.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8
upper limit	2.9
Variability estimate	Standard error of the mean
Dispersion value	2.69

Statistical analysis title	Statistical analysis 3
Comparison groups	Advair HFA with Spacer v Advair HFA
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of adjusted means
Point estimate	-5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.5
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	2.82

Secondary: Weighted mean change from Baseline of the QT Interval Corrected According to Bazett's Formula (QTcB) at 9 hours post-dose

End point title	Weighted mean change from Baseline of the QT Interval Corrected According to Bazett's Formula (QTcB) at 9 hours post-dose

End point description:

Twelve-lead electrocardiograms were performed to measure QTcB at Baseline, pre-dose and 15 min, 45 min, 1.5 h, 3h, 6 h and 9 h post-dose on Day 21 of each treatment period. Baseline was defined as the derived parameter from the Baseline assessment. Weighted mean (WM) was derived by calculating the area under curve (AUC), and then dividing by the relevant time interval. The data are presented as the adjusted means of WM. Only participants data available at the analysis time point were analyzed (represented as n=X, X, X in category title).

End point type	Secondary

End point timeframe:

At Baseline, and pre-dose, 15 min, 45 min, 1.5 h, 3 h, 6 h, and 9 h on Day 21 of each treatment period

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[16]	19[17]	20[18]	
Units: Milliseconds (ms)				
arithmetic mean (standard error)	5 (± 1.61)	0.1 (± 1.62)	1 (± 1.53)	

Notes:
[16] - PD Parameter Population
[17] - PD Parameter Population
[18] - PD Parameter Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advair HFA v Advair DISKUS
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of adjusted means
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	7.9
Variability estimate	Standard error of the mean
Dispersion value	1.9

Statistical analysis title	Statistical analysis 2
Comparison groups	Advair DISKUS v Advair HFA with Spacer
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of adjusted means
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	3
Variability estimate	Standard error of the mean
Dispersion value	1.9

Statistical analysis title	Statistical analysis 3
Comparison groups	Advair HFA with Spacer v Advair HFA

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of adjusted means
Point estimate	-4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.1
upper limit	-0.8
Variability estimate	Standard error of the mean
Dispersion value	2.03

Secondary: Maximum mean change from Baseline of the QT Interval Corrected According to Fridericia's Formula (QTcF) at 9 hours post-dose

End point title	Maximum mean change from Baseline of the QT Interval Corrected According to Fridericia's Formula (QTcF) at 9 hours post-dose

End point description:

Twelve-lead electrocardiograms (ECGs) were performed to measure QT interval corrected according to Fridericia's formula (QTcF) at Baseline, pre-dose and 15 minutes (min), 45 min, 1.5 hours (h), 3h, 6 h and 9 h post-dose on Day 21 of each treatment period and the maximum values for QTcF were derived during the 0-9 h period. Baseline was defined as the derived parameter from the Baseline assessment. The data are presented as adjusted means of the maximum QTcF. Only participants data available at the analysis time point were analyzed (represented as n=X, X, X in category title).

End point type	Secondary

End point timeframe:

At Baseline, and pre-dose, 15 min, 45 min, 1.5 h, 3 h, 6 h, and 9 h on Day 21 of each treatment period

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[19]	19[20]	20[21]	
Units: Milliseconds (ms)				
arithmetic mean (standard error)	-0.9 (± 1.88)	-4 (± 1.83)	-4.4 (± 1.79)	

Notes:

[19] - PD Parameter Population

[20] - PD Parameter Population

[21] - PD Parameter Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advair HFA v Advair DISKUS

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of adjusted means
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	8
Variability estimate	Standard error of the mean
Dispersion value	2.26

Statistical analysis title	Statistical analysis 2
Comparison groups	Advair DISKUS v Advair HFA with Spacer
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of adjusted means
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	5
Variability estimate	Standard error of the mean
Dispersion value	2.24

Statistical analysis title	Statistical analysis 3
Comparison groups	Advair HFA with Spacer v Advair HFA
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of adjusted means
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	1.8
Variability estimate	Standard error of the mean
Dispersion value	2.35

Secondary: Weighted mean change from Baseline of the QT Interval Corrected

According to Fridericia's Formula (QTcF) at 9 hours post-dose	
End point title	Weighted mean change from Baseline of the QT Interval Corrected According to Fridericia's Formula (QTcF) at 9 hours post-dose

End point description:

Twelve-lead ECGs (electrocardiograms) were performed to measure QTcF at Baseline, pre-dose and 15 minutes (min), 45 min, 1.5 h, 3h, 6 h and 9 h post-dose on Day 21 of each treatment period. Baseline was defined as the derived parameter from the Baseline assessment. Weighted mean (WM) was derived by calculating the AUC, and then dividing by the relevant time interval. Data are presented as the adjusted means of WM. Only participants data available at the analysis time point were analyzed (represented as n=X, X, X in category title).

End point type	Secondary

End point timeframe:

At Baseline, and pre-dose, 15 min, 45 min, 1.5 h, 3 h, 6 h, and 9 h on Day 21 of each treatment period

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[22]	18[23]	20[24]	
Units: Milliseconds (ms)				
arithmetic mean (standard error)	1.9 (± 1.28)	-3.3 (± 1.28)	-3.6 (± 1.2)	

Notes:

[22] - PD Parameter Population

[23] - PD Parameter Population

[24] - PD Parameter Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advair HFA v Advair DISKUS
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of adjusted means
Point estimate	5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	8.9
Variability estimate	Standard error of the mean
Dispersion value	1.65

Statistical analysis title	Statistical analysis 2
Comparison groups	Advair DISKUS v Advair HFA with Spacer

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of adjusted means
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	3.7
Variability estimate	Standard error of the mean
Dispersion value	1.65

Statistical analysis title	Statistical analysis 3
Comparison groups	Advair HFA with Spacer v Advair HFA
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of adjusted means
Point estimate	-5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	-1.7
Variability estimate	Standard error of the mean
Dispersion value	1.74

Secondary: Maximum mean change from Baseline of the supine heart rate at 9 hours post-dose

End point title	Maximum mean change from Baseline of the supine heart rate at 9 hours post-dose

End point description:

Heart rate was recorded at Screening, prior to dosing, and at 15 minutes, 45 minutes, 1.5, 3, 6 and 9 h post-dose on Day 21of each treatment period. Baseline was defined as the derived parameter from the Baseline assessment. Heart rate measurement was taken in a supine position having rested in this position for at least 10 min before each reading. The maximum observed value of heart rate was measured and data are presented as adjusted mean of maximum heart rate. Only participants data available at the analysis time point were analyzed (represented as n=X, X, X in category title).

End point type	Secondary

End point timeframe:

At Baseline, and pre-dose, 15 min, 45 min, 1.5 h, 3 h, 6 h, and 9 h on Day 21 of each treatment period

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[25]	19[26]	20[27]	
Units: Beats per minute (bpm)				
arithmetic mean (standard error)	3.7 (± 2.31)	-0.1 (± 2.26)	4.8 (± 2.19)	

Notes:

[25] - PD Parameter Population

[26] - PD Parameter Population

[27] - PD Parameter Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advair HFA v Advair DISKUS
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of adjusted means
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	4.6
Variability estimate	Standard error of the mean
Dispersion value	2.82

Statistical analysis title	Statistical analysis 2
Comparison groups	Advair DISKUS v Advair HFA with Spacer
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of adjusted means
Point estimate	-5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	2.79

Statistical analysis title	Statistical analysis 3
Comparison groups	Advair HFA with Spacer v Advair HFA

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of adjusted means
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	2.1
Variability estimate	Standard error of the mean
Dispersion value	2.92

Secondary: Weighted Mean change from Baseline of supine heart rate at 9 hours post-dose

End point title	Weighted Mean change from Baseline of supine heart rate at 9 hours post-dose

End point description:

Heart rate was recorded at Screening, prior to dosing, and at 15 min, 45 min, 1.5, 3, 6 and 9 h post-dose on Day 21of each treatment period. Baseline was defined as the derived parameter from the Baseline assessment. Heart rate measurement was taken in a supine position having rested in this position for at least 10 min before each reading. Weighted mean (WM) was derived by calculating the AUC, and then dividing by the relevant time interval. Only participants data available at the analysis time point were analyzed (represented as n=X, X, X in category title).

End point type	Secondary

End point timeframe:

At Baseline, and pre-dose, 15 min, 45 min, 1.5 h, 3 h, 6 h, and 9 h on Day 21 of each treatment period

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[28]	18[29]	20[30]	
Units: Bpm				
arithmetic mean (standard error)	4.1 (± 1.52)	3.2 (± 1.53)	5.8 (± 1.44)	

Notes:

[28] - PD Parameter Population

[29] - PD Parameter Population

[30] - PD Parameter Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advair HFA v Advair DISKUS

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of treatment ratios
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	2.4
Variability estimate	Standard error of the mean
Dispersion value	2.03

Statistical analysis title	Statistical analysis 2
Comparison groups	Advair DISKUS v Advair HFA with Spacer
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of treatment ratios
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	1.5
Variability estimate	Standard error of the mean
Dispersion value	2.03

Statistical analysis title	Statistical analysis 3
Comparison groups	Advair HFA with Spacer v Advair HFA
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of treatment ratios
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	3.4
Variability estimate	Standard error of the mean
Dispersion value	2.13

Secondary: Maximum change from Baseline for supine systolic blood pressure (SBP)

at 9 hours post-dose	
End point title	Maximum change from Baseline for supine systolic blood pressure (SBP) at 9 hours post-dose

End point description:

Blood pressure (BP) measurement included supine SBP and diastolic BP (DBP). SBP was recorded at screening, prior to dosing, and at 15 min, 45 min, 1.5,2, 4, 6 and 9 h post-dose on Day 21 of the each treatment period. The maximum observed values for SBP from the time of the morning dose on Day 21 to 9 h post-dose were measured and the data are presented as adjusted mean of maximum SBP. Baseline was defined as the derived parameter from the Baseline assessment. Only participants data available at the analysis time point were analyzed (represented as n=X, X, X in category title).

End point type	Secondary

End point timeframe:

At Baseline, and pre-dose, 15 min, 45 min, 1.5 h, 3 h, 6 h, and 9 h on Day 21 of each treatment period

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[31]	19[32]	20[33]	
Units: Millimeters of mercury (mmHg)				
arithmetic mean (standard error)	0.4 (± 1.46)	0.7 (± 1.43)	-1.5 (± 1.39)	

Notes:

[31] - PD Parameter Population

[32] - PD Parameter Population

[33] - PD Parameter Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advair HFA v Advair DISKUS
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of treatment ratios
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	5.3
Variability estimate	Standard error of the mean
Dispersion value	1.72

Statistical analysis title	Statistical analysis 2
Comparison groups	Advair HFA with Spacer v Advair DISKUS

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of treatment ratios
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	5.7
Variability estimate	Standard error of the mean
Dispersion value	1.71

Statistical analysis title	Statistical analysis 3
Comparison groups	Advair HFA with Spacer v Advair HFA
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of treatment ratios
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	4
Variability estimate	Standard error of the mean
Dispersion value	1.79

Secondary: Minimum change from Baseline of the supine diastolic BP (DBP) at 9 hours post-dose

End point title	Minimum change from Baseline of the supine diastolic BP (DBP) at 9 hours post-dose

End point description:

Blood pressure (BP) measurement included supine SBP and DBP. DBP were recorded at screening, prior to dosing, and at 15 min, 45 min, 1.5,2, 4, 6 and 9 h post-dose on Day 21 of the each treatment period. Baseline was defined as the derived parameter from the Baseline assessment. The minimum observed values from the time of the morning dose on Day 21 to 9 hours post dose were measured and the data are presented as adjusted mean of minimum DBP. Only participants data available at the analysis time point were analyzed (represented as n=X, X, X in category title).

End point type	Secondary

End point timeframe:

At Baseline, and pre-dose, 15 min, 45 min, 1.5 h, 3 h, 6 h, and 9 h on Day 21 of each treatment period

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[34]	19[35]	20[36]	
Units: mmHg				
arithmetic mean (standard error)	-3.3 (± 1.03)	1 (± 1.01)	-1.3 (± 0.98)	

Notes:

[34] - PD Parameter Population

[35] - PD Parameter Population

[36] - PD Parameter Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advair DISKUS v Advair HFA
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of treatment ratios
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	1.33

Statistical analysis title	Statistical analysis 2
Comparison groups	Advair DISKUS v Advair HFA with Spacer
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of treatment ratios
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	4.9
Variability estimate	Standard error of the mean
Dispersion value	1.31

Statistical analysis title	Statistical analysis 3
Comparison groups	Advair HFA v Advair HFA with Spacer

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of treatment ratios
Point estimate	4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	7
Variability estimate	Standard error of the mean
Dispersion value	1.37

Secondary: Weighted mean change from Baseline for supine SBP at 9 hours post-dose

End point title	Weighted mean change from Baseline for supine SBP at 9 hours post-dose

End point description:

Blood pressure (BP) measurement included supine SBP and DBP. SBP was recorded at screening, prior to dosing, and at 15 min, 45 min, 1.5,2, 4, 6 and 9 h post-dose on Day 21 of the each treatment period. Weighted mean (WM) was derived by calculating the AUC, and then dividing by the relevant time interval. Baseline was defined as the derived parameter from the Baseline assessment. The data are presented as adjusted mean of WM SBP. Only participants data available at the analysis time point were analyzed (represented as n=X, X, X in category title).

End point type	Secondary

End point timeframe:

At Baseline, and pre-dose, 15 min, 45 min, 1.5 h, 3 h, 6 h, and 9 h on Day 21 of each treatment period

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[37]	19[38]	20[39]	
Units: mmHg				
arithmetic mean (standard error)	0.6 (± 1.37)	1.1 (± 1.34)	-2.2 (± 1.3)	

Notes:

[37] - PD Parameter Population

[38] - PD Parameter Population

[39] - PD Parameter Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advair HFA v Advair DISKUS

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of treatment ratios
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	6.2
Variability estimate	Standard error of the mean
Dispersion value	1.7

Statistical analysis title	Statistical analysis 2
Comparison groups	Advair DISKUS v Advair HFA with Spacer
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of treatment ratios
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	6.8
Variability estimate	Standard error of the mean
Dispersion value	1.68

Statistical analysis title	Statistical analysis 3
Comparison groups	Advair HFA with Spacer v Advair HFA
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of treatment ratios
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	4.1
Variability estimate	Standard error of the mean
Dispersion value	1.76

Secondary: Weighted mean change from Baseline for supine DBP at 9 hours post-

dose	
End point title	Weighted mean change from Baseline for supine DBP at 9 hours post-dose

End point description:

Blood pressure (BP) measurement included SBP and DBP. DBP was recorded at screening, prior to dosing, and at 15 min, 45 min, 1.5,2, 4, 6 and 9 h post-dose on Day 21 of the each treatment period. Weighted mean (WM) was derived by calculating the AUC, and then dividing by the relevant time interval. Baseline was defined as the derived parameter from the Baseline assessment. The data are presented as adjusted mean of WM DBP. Only participants data available at the analysis time point were analyzed (represented as n=X, X, X in category title).

End point type	Secondary

End point timeframe:

At Baseline, and pre-dose, 15 min, 45 min, 1.5 h, 3 h, 6 h, and 9 h on Day 21 of each treatment period

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[40]	19[41]	20[42]	
Units: mmHg				
arithmetic mean (standard error)	-1.7 (± 0.89)	-0.9 (± 0.87)	-1.7 (± 0.85)	

Notes:

[40] - PD Parameter Population

[41] - PD Parameter Population

[42] - PD Parameter Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advair HFA v Advair DISKUS
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of treatment ratios
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	2.2
Variability estimate	Standard error of the mean
Dispersion value	1.09

Statistical analysis title	Statistical analysis 2
Comparison groups	Advair DISKUS v Advair HFA with Spacer

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of treatment ratios
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	3.1
Variability estimate	Standard error of the mean
Dispersion value	1.09

Statistical analysis title	Statistical analysis 3
Comparison groups	Advair HFA with Spacer v Advair HFA
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference of treatment ratios
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	3.2
Variability estimate	Standard error of the mean
Dispersion value	1.14

Secondary: Area under the concentration-time curve from time 0 to the last quantifiable concentration (AUC[last]) for FP

End point title	Area under the concentration-time curve from time 0 to the last quantifiable concentration (AUC[last]) for FP

End point description:

Blood samples were collected to determine the plasma concentrations of FP from pre-dose up to 12 hour post-dose of each treatment period to derive the AUC(0-t). Blood samples for PK analysis of FP were obtained on Day 21 at pre-dose and 30 minutes (min), 1 hour (h), 2,4,8, and12 h post FP dose administration. For 8 and 12 h post dose, two 4 mL blood samples were collected. Pharmacokinetic (PK) Parameter Population was defined as all participants who received treatment during both treatment periods and for whom PK parameters were derived for both periods.

End point type	Secondary

End point timeframe:

At pre-morning dose, 30 min, 1, 2, 4, 8, and 12 h post-dose on Day 21 of Treatments periods 1 and 2

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[43]	19[44]	20[45]	
Units: Picograms hrs per milliliter (pg.hr/mL)				
geometric mean (confidence interval 95%)	24.063 (9.624 to 60.165)	107.381 (45.714 to 252.236)	137.592 (69.258 to 273.245)	

Notes:

[43] - PK Parameter Population

[44] - PK Parameter Population

[45] - PK Parameter Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advair HFA v Advair DISKUS
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric means
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.37
Variability estimate	Standard error of the mean
Dispersion value	0.512

Statistical analysis title	Statistical analysis 2
Comparison groups	Advair HFA v Advair HFA with Spacer
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric means
Point estimate	4.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	10.2
Variability estimate	Standard error of the mean
Dispersion value	0.529

Statistical analysis title	Statistical analysis 3
Comparison groups	Advair HFA with Spacer v Advair DISKUS

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric means
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.54
Variability estimate	Standard error of the mean
Dispersion value	0.507

Secondary: AUC(last) for Salmeterol

End point title	AUC(last) for Salmeterol

End point description:

Blood samples were collected to determine the plasma concentrations of Salmeterol from pre-dose up to 4 hour post-dose of each treatment period to derive the AUC(0-t). Blood samples for PK analysis of salmeterol were obtained on Day 21 at pre-dose and 30 minutes (min), 1 hour (h), 2 h, and 4 h post salmeterol dose administration. One 4 mL sample was also collected at 10 min post dose on Day 21.

End point type	Secondary

End point timeframe:

At pre-morning dose, 10 minutes (min), 30 min, 1, 2, and 4 h post-dose on Day 21 of Treatments periods 1 and 2

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[46]	19[47]	20[48]	
Units: pg.hr/mL				
geometric mean (confidence interval 95%)	125.702 (70.339 to 224.639)	103.417 (53.576 to 199.623)	110.139 (55.383 to 219.03)	

Notes:

[46] - PK Parameter Population

[47] - PK Parameter Population

[48] - PK Parameter Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advair HFA v Advair DISKUS
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric means
Point estimate	1.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	2.32
Variability estimate	Standard error of the mean
Dispersion value	0.437

Statistical analysis title	Statistical analysis 2
Comparison groups	Advair HFA v Advair HFA with Spacer
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric means
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.75
Variability estimate	Standard error of the mean
Dispersion value	0.448

Statistical analysis title	Statistical analysis 3
Comparison groups	Advair HFA with Spacer v Advair DISKUS
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric means
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.9
Variability estimate	Standard error of the mean
Dispersion value	0.431

Secondary: Maximum observed plasma concentration (Cmax) at steady state for FP	
End point title	Maximum observed plasma concentration (Cmax) at steady state for FP

End point description:

Blood samples were collected to determine the plasma concentrations of FP from pre-dose up to 12 hour post-dose of each treatment period to derive the Cmax. Blood samples for PK analysis of FP were obtained on Day 21 at pre-dose and 30 minutes (min), 1 hour (h), 2 h, 4 h, 8 h, 12 h post FP dose

administration. For 8 and 12 h post dose, two 4 mL blood samples were collected.

End point type	Secondary

End point timeframe:

At pre-morning dose, 30 min, 1, 2, 4, 8, and 12 h post-dose on Day 21 of Treatments periods 1 and 2

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[49]	19[50]	20[51]	
Units: Picogram per millimeter (pg/mL)				
geometric mean (confidence interval 95%)	15.705 (8.493 to 29.043)	35.048 (20.359 to 60.335)	54.369 (33.078 to 89.362)	

Notes:

[49] - PK Parameter Population

[50] - PK Parameter Population

[51] - PK Parameter Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advair HFA v Advair DISKUS
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric means
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.47
Variability estimate	Standard error of the mean
Dispersion value	0.33

Statistical analysis title	Statistical analysis 2
Comparison groups	Advair HFA v Advair HFA with Spacer
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric means
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	3.74

Variability estimate	Standard error of the mean
Dispersion value	0.342

Statistical analysis title	Statistical analysis 3
Comparison groups	Advair HFA with Spacer v Advair DISKUS
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric means
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	0.98
Variability estimate	Standard error of the mean
Dispersion value	0.327

Secondary: Cmax at steady state for salmeterol

End point title	Cmax at steady state for salmeterol

End point description:

Blood samples were collected to determine the plasma concentrations of Salmeterol from pre-dose up to 4 hour post-dose of each treatment period to derive the Cmax. Blood samples for PK analysis of salmeterol were obtained on Day 21 at pre-dose and 30 minutes (min), 1 hour (h), 2 h, and 4 h post salmeterol dose administration. One 4 mL sample was also collected at 10 min post dose on Day 21.

End point type	Secondary

End point timeframe:

At pre-morning dose, 10 minutes (min), 30 min, 1, 2, and 4 h post-dose on Day 21 of Treatments periods 1 and 2

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[52]	19[53]	20[54]	
Units: pg/mL				
geometric mean (confidence interval 95%)	73.932 (51.987 to 105.14)	121.196 (77.467 to 189.61)	96.53 (60.422 to 154.215)	

Notes:

[52] - PK Parameter Population

[53] - PK Parameter Population

[54] - PK Parameter Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advair HFA v Advair DISKUS
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric means
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.25
Variability estimate	Standard error of the mean
Dispersion value	0.291

Statistical analysis title	Statistical analysis 2
Comparison groups	Advair HFA v Advair HFA with Spacer
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric means
Point estimate	1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	2.67
Variability estimate	Standard error of the mean
Dispersion value	0.298

Statistical analysis title	Statistical analysis 3
Comparison groups	Advair HFA with Spacer v Advair DISKUS
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric means
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	2.01
Variability estimate	Standard error of the mean
Dispersion value	0.287

Secondary: Time to occurrence of Cmax (Tmax) at steady state for FP and salmeterol

End point title	Time to occurrence of Cmax (Tmax) at steady state for FP and salmeterol

End point description:

Blood samples were collected to determine the plasma concentrations of FP and salmeterol from pre-dose up to 12 h post-dose of each treatment period to derive tmax. Blood samples of participants were collected for evaluating Tmax. Tmax is a measure of the time required to reach the maximum concentration of the drug. Blood samples for PK analysis were obtained on Day 21 at pre-dose and 30 minutes (min), 1 hour (h), 2 h, 4 h, 8 h, 12 h post FP dose administration. One 4 mL sample was also collected at 10 min post dose on Day 21. For 8 and 12 h post dose, two 4 mL blood samples were collected.

End point type	Secondary

End point timeframe:

At pre-morning dose, 10 minutes (min), 30 min, 1, 2, 4, 8, and 12 h post-dose on Day 21 of Treatments periods 1 and 2

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[55]	19[56]	20[57]	
Units: Hour (hr)				
median (full range (min-max))				
Fluticasone propionate	0.74 (0.47 to 2.02)	0.98 (0 to 8.17)	0.5 (0 to 1)	
Salmeterol	0.2 (0.03 to 2.02)	0.17 (0.08 to 0.22)	0.175 (0.13 to 1.97)	

Notes:

[55] - PK Parameter Population

[56] - PK Parameter Population

[57] - PK Parameter Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of paritcipants with any adverse event (AE) or serious adverse event (SAE)

End point title	Number of paritcipants with any adverse event (AE) or serious adverse event (SAE)

End point description:

An AE is defined as any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Any AE with onset after the start dose of the study medication and on or before the follow-up phone call were collected. All Subjects Population was defined as all participants who received at least one study treatment.

End point type	Secondary

End point timeframe:

From the first dose of the study medication until follow-up period (Up to 7 weeks)

End point values	Advair HFA	Advair HFA with Spacer	Advair DISKUS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21[58]	19[59]	20[60]	
Units: Participants				
Adverse event	13	9	14	
Serious adverse event	0	0	0	

Notes:

[58] - All Subjects Population

[59] - All Subjects Population

[60] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from start of IP (Session 1) until Week 7 including the follow-up period.

Adverse event reporting additional description:

On-treatment SAEs and non-serious AEs are reported for all Subjects Population, comprised of all participants who received at least one dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Advair HFA

Reporting group description:

Participants were randomized to one of the 6 possible treatment arms (AB, BA, AC, CA, BC, or CB): two inhalations of ADVAIR HFA 45/21 µg , which was supplied as a HFA-propelled 120-actuation metered dose inhaler (MDI) desgined to deliver 45 µg of fluticasone propionate (FP) and 21 µg of salmeterol twice daily (BID) for 21 days (on outpatient basis except on Day 21) along with either Advair HFA with Aerochamber Plus Spacer or Adavir DISKUS. After this treatment period 1, participants received a repeat dosing of the same sequence for 21 days without any washout period.

Reporting group title	Advair HFA with Spacer

Reporting group description:

Participants were randomized to one of the 6 possible treatment arms (AB, BA, AC, CA, BC, or CB): two inhalations of ADVAIR HFA 45/21 µg with Aerochamber Plus Spacer, which was supplied as a metered dose inhaler (MDI) designed to deliver 45 µg of FP and 21 µg of salmeterol twice daily (BID) for 21 days (on outpatient basis except on Day 21) along with either Advair HFA or Adavir DISKUS. After this treatment period 1, participants received a repeat dosing of the same sequence for 21 days without any washout period.

Reporting group title	Advair DISKUS

Reporting group description:

Participants were randomized to one of the 6 possible treatment arms (AB, BA, AC, CA, BC or CB): one inhalation of ADVAIR DISKUS 100/50 µg, which was supplied as a 60-dose multi-dose powder inhaler (MPDI) desgined to deliver 100 µg of FP and 50 µg of salmeterol twice daily (BID) for 21 days (on outpatient basis except on Day 21) along with either Advair HFA with Aerochamber Plus Spacer or Adavir HFA. After this treatment period 1, participants received a repeat dosing of the same sequence for 21 days without any washout period.

Serious adverse events	Advair HFA	Advair HFA with Spacer	Advair DISKUS
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Advair HFA	Advair HFA with Spacer	Advair DISKUS
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 21 (61.90%)	9 / 19 (47.37%)	14 / 20 (70.00%)
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	0 / 21 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 21 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 19 (0.00%)	2 / 20 (10.00%)
occurrences (all)	2	0	2
Chest pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 21 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 21 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 21 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 21 (42.86%)	3 / 19 (15.79%)	5 / 20 (25.00%)
occurrences (all)	23	4	9

Rhinorrhoea			
subjects affected / exposed	4 / 21 (19.05%)	3 / 19 (15.79%)	5 / 20 (25.00%)
occurrences (all)	7	3	9
Nasal congestion			
subjects affected / exposed	5 / 21 (23.81%)	1 / 19 (5.26%)	2 / 20 (10.00%)
occurrences (all)	9	1	5
Wheezing			
subjects affected / exposed	2 / 21 (9.52%)	1 / 19 (5.26%)	2 / 20 (10.00%)
occurrences (all)	2	1	3
Dyspnoea			
subjects affected / exposed	1 / 21 (4.76%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Asthma			
subjects affected / exposed	1 / 21 (4.76%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Pharyngolaryngeal pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 21 (4.76%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 19 (0.00%)	4 / 20 (20.00%)
occurrences (all)	1	0	4
Gastroenteritis viral			
subjects affected / exposed	2 / 21 (9.52%)	0 / 19 (0.00%)	2 / 20 (10.00%)
occurrences (all)	2	0	2
Viral infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1

Ear Infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	1 / 21 (4.76%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2006	The purpose of this amendment was to change the study design to include a third arm to evaluate the systemic exposure and pharmacodynamics of ADVAIR HFA following administration using the Aerochamber plus Spacer. GlaxoSmithKline plans to use the Aerochamber Plus Spacer in a 12-week safety study (SFA 106484). Since systemic exposure of an inhaled drug product can vary gently depending on the mechanism of administration, the FDA recommended an assessment of the difference of systemic exposure with and without a spacer to be included in this clinical pharmacology protocol. This protocol has also been modified to remove inconsistencies in study procedures and to make clarification to the inclusion/exclusion criteria.
09 November 2006	Based on feedback at a recent investigators meeting, the inclusion criteria regarding minimum weight for eligibility in this study will be amended to facilitate in the 4 to 7 years age range. The protocol states that 1/3 of the subjects must be ≤7 years of age. However, the current weight restriction would make it difficult to reach this enrollment target. Furthermore, this amendment will clarify exclusion criteria regarding inhaled corticosteroid use.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported