Clinical trial results:
Randomised, double-blind, double-dummy, parallel-group, comparative study of salmeterol/FP 50/100mcg bd inhalation powder via Diskus with oral Montelukast (5mg QD) chewable tablets in Children 6-14 years.

Summary

EudraCT number	2015-004898-32
Trial protocol	Outside EU/EEA
Global end of trial date	30 April 2007

Results information

Result version number	v1 (current)
This version publication date	28 December 2016
First version publication date	28 December 2016

Trial information

Trial identification

Sponsor protocol code	SAM103848

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	Final
Date of interim/final analysis	06 August 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary study objective was to demonstrate the superior clinical effectiveness of Salmeterol/Fluticasone Propionate (SFC) compared with montelukast in the management of persistent asthma in children aged 6-14 years. Please note: In the age table the actual number of adolescent (between the ages of 12-17) participants is 90 participants. Two participants were missing age information from all study demographic tables, with no clear explanation about why that data was missing. Because the system does not allow us to note missing information, the 2 participants of unknown age were added to the adolescent age category.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 October 2005
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	Mexico: 163
Country: Number of subjects enrolled	Peru: 113
Country: Number of subjects enrolled	Argentina: 97
Country: Number of subjects enrolled	Costa Rica: 92
Country: Number of subjects enrolled	Ecuador: 32
Country: Number of subjects enrolled	Venezuela, Bolivarian Republic of: 24
Country: Number of subjects enrolled	Colombia: 20
Country: Number of subjects enrolled	Turkey: 7
Worldwide total number of subjects	548
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)	456
Adolescents (12-17 years)	92
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted from 08 Dec 2005 to 30 Apr 2007 at 27 centres across 8 countries.

Pre-assignment

Screening details:

A total of 607 participants were screened and 548 participants were enrolled in the study. During run in period, participants received salbutamol metered dose inhaler (MDI) for 2 weeks

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg

Arm description:

During treatment period, participants received 1 inhalation of salmeterol/fluticasone propionate (SALM/ FP) 50/100 micrograms (mcg) dry powder inhaler (DPI) twice daily (BID) plus placebo for montelukast 5 milligram (mg) chewable tablet once daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Salmeterol/Fluticasone propionate (SALM/FP)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One oral inhalation of 50/100 mcg of SFC via dry powder inhaler twice daily (morning and evening)

Arm title	Montelukast 5 mg once daily

Arm description:

During treatment period, participants received montlukast 5 mg chewable tablet once daily plus a placebo for SALM/FP 50/100 mcg DPI BID for 12 weeks.

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

Dosage and administration details:

One chewable tablet 5 mg orally once daily (evening)

Number of subjects in period 1	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg	Montelukast 5 mg once daily
Started	281	267
Completed	263	244
Not completed	18	23
Consent withdrawn by subject	4	3
Asthma exacerbation	-	7
Adverse event, non-fatal	2	3
Unspecified	4	2
Lost to follow-up	5	3
Protocol deviation	3	4
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg
Reporting group description:	
During treatment period, participants received 1 inhalation of salmeterol/fluticasone propionate (SALM/ FP) 50/100 micrograms (mcg) dry powder inhaler (DPI) twice daily (BID) plus placebo for montelukast 5 milligram (mg) chewable tablet once daily for 12 weeks.	
Reporting group title	Montelukast 5 mg once daily
Reporting group description:	
During treatment period, participants received montlukast 5 mg chewable tablet once daily plus a placebo for SALM/FP 50/100 mcg DPI BID for 12 weeks.	

Reporting group values	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg	Montelukast 5 mg once daily	Total
Number of subjects	281	267	548
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	9.3	9.3	
standard deviation	± 2.15	± 2.12	-
Gender categorical			
Units:			
Female	125	88	213
Male	156	179	335
Race, Customized			
Units: Subjects			
White	27	28	55
Black	1	1	2
Asian	1	0	1
American Hispanic	233	225	458
Other	19	13	32

End points

End points reporting groups

Reporting group title	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg
Reporting group description:	
During treatment period, participants received 1 inhalation of salmeterol/fluticasone propionate (SALM/ FP) 50/100 micrograms (mcg) dry powder inhaler (DPI) twice daily (BID) plus placebo for montelukast 5 milligram (mg) chewable tablet once daily for 12 weeks.	
Reporting group title	Montelukast 5 mg once daily
Reporting group description:	
During treatment period, participants received montlukast 5 mg chewable tablet once daily plus a placebo for SALM/FP 50/100 mcg DPI BID for 12 weeks.	
Subject analysis set title	SALM/FP 50/100 mcg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
. During treatment period, participants received 1 inhalation of salmeterol/fluticasone propionate (SALM/ FP) 50/100 micrograms (mcg) dry powder inhaler (DPI) twice daily (BID) plus placebo for montelukast 5 milligram (mg) chewable tablet once daily for 12 weeks.	
Subject analysis set title	Montelukast 5 mg once daily
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
During treatment period, participants received montlukast 5 mg chewable tablet once daily plus a placebo for SALM/FP 50/100 mcg DPI BID for 12 weeks.	

Primary: Change from Baseline (Week-1) in mean morning peak expiratory flow rate (PEFR) over Weeks 1 to 12

End point title	Change from Baseline (Week-1) in mean morning peak expiratory flow rate (PEFR) over Weeks 1 to 12
End point description:	
PEFR is defined as the maximum airflow generated during a forced expiration beginning with the lungs fully inflated. PEFR was calculated as the highest value of the three readings recorded in the morning of each day on a diary card for each participant using spirometry. Change from Baseline in PEFR was calculated as the PEFR individual on treatment values time point minus the Baseline value. Baseline is defined as the mean of the non missing daily values over the final seven days of the two-week run-in prior to randomisation.	
End point type	Primary
End point timeframe:	
Baseline and up to Week 12	

End point values	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg	Montelukast 5 mg once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	260[1]	253[2]		
Units: Liter per minute (L/min)				
least squares mean (standard error)	45.8 (± 2.82)	28.7 (± 2.86)		

Notes:

[1] - ITT population

[2] - ITT population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: PEFR (morning) SALM/FP 50/100 mcg vs Montelukast 5 mg once daily	
Comparison groups	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg v Montelukast 5 mg once daily
Number of subjects included in analysis	513
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	17.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.23
upper limit	25.08
Variability estimate	Standard error of the mean
Dispersion value	4.03

Secondary: Change from Baseline in morning pre-dose FEV1 at Week 12 Last observation carried forward (LOCF).

End point title	Change from Baseline in morning pre-dose FEV1 at Week 12 Last observation carried forward (LOCF).
End point description: FEV1 is defined as the volume of air forcefully expelled from lungs in one second. Change from baseline in pre dose FEV1 is the pre dose FEV1 value at a defined time point minus the Baseline (Visit 2) FEV1 value. Adjusted mean FEV1 values were calculated. Data is presented for the participants available at the time of assessment.	
End point type	Secondary
End point timeframe: Baseline and Week 12	

End point values	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg	Montelukast 5 mg once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264[3]	245[4]		
Units: Liters				
least squares mean (standard error)	0.47 (± 0.017)	0.3 (± 0.018)		

Notes:

[3] - ITT population

[4] - ITT population

Statistical analyses

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
FEV1 SALM/FP 50/100 mcg vs Montelukast 5 mg once daily	
Comparison groups	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg v Montelukast 5 mg once daily
Number of subjects included in analysis	509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.21
Variability estimate	Standard error of the mean
Dispersion value	0.025

Secondary: Percent change from Baseline in morning pre dose forced expiratory volume in 1 second (FEV1) at Week 12

End point title	Percent change from Baseline in morning pre dose forced expiratory volume in 1 second (FEV1) at Week 12
End point description:	
FEV1 is the volume of air exhaled in first second of forced spirometry test. Change from baseline in pre-dose FEV1 is the pre dose FEV1 value at a defined time point minus the Baseline (Visit 2) FEV1 value. Adjusted mean FEV1 values were calculated and expressed as percentage change. Data is presented for the participants available at the time of assessment.	
End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg	Montelukast 5 mg once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264[5]	245[6]		
Units: Percent change				
least squares mean (standard error)	33.83 (± 1.22)	22.08 (± 1.267)		

Notes:

[5] - ITT population

[6] - ITT population

Statistical analyses

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
Percent Change FEV1 SALM/FP 50/100 mcg vs Montelukast 5 mg once daily	
Comparison groups	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg v Montelukast 5 mg once daily
Number of subjects included in analysis	509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	11.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.28
upper limit	15.22
Variability estimate	Standard error of the mean
Dispersion value	1.767

Secondary: Change from Baseline in mean evening peak expiratory flow rate (PEFR) over weeks 1 to 12

End point title	Change from Baseline in mean evening peak expiratory flow rate (PEFR) over weeks 1 to 12
End point description:	
PEFR is defined as the maximum airflow generated during a forced expiration beginning with the lungs fully inflated. PEFR was calculated as the highest value of the three readings recorded in evening of each day on diary cards for each participant using spirometry. Change from Baseline in PEFR is the PEFR value at a defined time point minus the Baseline value. Data is presented for participants available at the time of assessment.	
End point type	Secondary
End point timeframe:	
Baseline and up to Week 12	

End point values	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg	Montelukast 5 mg once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261[7]	253[8]		
Units: L/min				
least squares mean (standard error)	46.2 (± 2.84)	27.8 (± 2.89)		

Notes:

[7] - ITT population

[8] - ITT population

Statistical analyses

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
PEFR (evening) SALM/FP 50/100 mcg vs Montelukast 5 mg once daily	
Comparison groups	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg v Montelukast 5 mg once daily
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	18.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.35
upper limit	26.35
Variability estimate	Standard error of the mean
Dispersion value	4.071

Secondary: Number of participants in each category of change in percentage of symptom free 24 hour periods from Baseline toWeeks 1 to 12

End point title	Number of participants in each category of change in percentage of symptom free 24 hour periods from Baseline toWeeks 1 to 12

End point description:

A symptom free 24 hour period is one during which the diary recorded daytime and night time symptom score is zero. Participants were asked to rate the day time asthma symptom scores on a scale of 0 5 (0=no symptoms, 1=symptoms with no discomfort, 2=symptoms with discomfort without affecting daily normal activities, 3=symptoms with discomfort affecting daily normal activities, 4=symptoms with discomfort affecting 2 or more normal daily activities, 5=symptoms with discomfort affecting normal daily activities) and night time asthma symtpoms on a scale of 0 3 (0=no symptoms, 1 3= rating was based on increased awakening during night). The 24 hour period asthma symptom scores were the sum of the daytime and night time symptom scores recorded on diary card. The percentage of symptoms were classified as 0 <25%, 25 <50%, 50 <75%, 75 <100% and 100%.

End point type	Secondary

End point timeframe:

Baseline and up to Week 12

End point values	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg	Montelukast 5 mg once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281[9]	267[10]		
Units: Participants				
Baseline, 0 to <25%	189	176		
Baseline, 25 to <50%	35	59		
Baseline, 50 to <75%	26	14		

Baseline, 75 to <100%	6	2		
Baseline, 100%	7	4		
Weeks 1 to 12, 0 to <25%	34	40		
Weeks 1 to 12, 25 to <50%	20	46		
Weeks 1 to 12, 50 to <75%	57	58		
Weeks 1 to 12, 75 to <100%	128	99		
Weeks 1 to 12, 100%	23	11		

Notes:

[9] - ITT population

[10] - ITT population

Statistical analyses

Statistical analysis title	Statistical analysis 5
Statistical analysis description:	
Symptom free 24 hour periods SALM/FP 50/100 mcg vs Montelukast 5 mg once daily	
Comparison groups	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg v Montelukast 5 mg once daily
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	ANCOVA
Parameter estimate	Odds ratio (OR)
Point estimate	1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	2.82

Secondary: Number of participants in each category of change in percentage of rescue medication free 24 hour periods from Baseline to Weeks 1 to 12

End point title	Number of participants in each category of change in percentage of rescue medication free 24 hour periods from Baseline to Weeks 1 to 12
End point description:	
A rescue medication free 24 hour period is one in which the daytime and night time rescue medication (salbutamol) use recorded in diary cards is zero. The total number of occassions of using rescue medication was calculated. The percentage of rescue medication use was classified as 0 to <25%, 25 to <50%, 50 to <75%, 75 to <100% and 100%.	
End point type	Secondary
End point timeframe:	
Baseline up to Week 12	

End point values	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg	Montelukast 5 mg once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281[11]	267[12]		
Units: Participants				
Baseline, 0 to <25%	187	195		
Baseline, 25 to <50%	54	39		
Baseline, 50 to <75%	12	14		
Baseline, 75 to <100%	4	1		
Baseline, 100%	2	2		
Weeks 1 to 12, 0 to <25%	40	69		
Weeks 1 to 12, 25 to <50%	10	21		
Weeks 1 to 12, 50 to <75%	46	55		
Weeks 1 to 12, 75 to <100%	132	80		
Weeks 1 to 12, 100%	24	15		

Notes:

[11] - ITT population

[12] - ITT population

Statistical analyses

Statistical analysis title	Statistical analysis 6
Statistical analysis description:	
Rescue medication free 24 hour periods SALM/FP 50/100 mcg vs Montelukast 5 mg once daily	
Comparison groups	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg v Montelukast 5 mg once daily
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Odds ratio (OR)
Point estimate	3.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.09
upper limit	5.02

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse events were collected from the start of study treatment to the end of study treatment (up to 12 weeks)

Adverse event reporting additional description:

ITT population

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11

Reporting groups

Reporting group title	Montelukast 5 mg once daily

Reporting group description:

During treatment period, participants received montlukast 5 mg chewable tablet once daily plus a placebo for SALM/FP 50/100 mcg DPI BID for 12 weeks.

Reporting group title	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg

Reporting group description:

. During treatment period, participants received 1 inhalation of salmeterol/fluticasone propionate (SALM/ FP) 50/100 micrograms (mcg) dry powder inhaler (DPI) twice daily (BID) plus placebo for montelukast 5 milligram (mg) chewable tablet once daily for 12 weeks.

Serious adverse events	Montelukast 5 mg once daily	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 267 (0.75%)	0 / 281 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 267 (0.37%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			
subjects affected / exposed	1 / 267 (0.37%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Montelukast 5 mg once daily	Salmeterol/Fluticasone propionate (SALM/FP) 50/100 mcg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	120 / 267 (44.94%)	128 / 281 (45.55%)	
Nervous system disorders			
Headache			
subjects affected / exposed	72 / 267 (26.97%)	66 / 281 (23.49%)	
occurrences (all)	153	123	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	18 / 267 (6.74%)	24 / 281 (8.54%)	
occurrences (all)	22	28	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	13 / 267 (4.87%)	9 / 281 (3.20%)	
occurrences (all)	16	9	
Vomiting			
subjects affected / exposed	12 / 267 (4.49%)	7 / 281 (2.49%)	
occurrences (all)	15	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 267 (5.99%)	13 / 281 (4.63%)	
occurrences (all)	21	18	
Rhinitis allergic			
subjects affected / exposed	10 / 267 (3.75%)	13 / 281 (4.63%)	
occurrences (all)	17	23	
Rhinorrhoea			
subjects affected / exposed	8 / 267 (3.00%)	15 / 281 (5.34%)	
occurrences (all)	10	22	
Pharyngolaryngeal pain			
subjects affected / exposed	6 / 267 (2.25%)	11 / 281 (3.91%)	
occurrences (all)	7	13	
Epistaxis			
subjects affected / exposed	1 / 267 (0.37%)	10 / 281 (3.56%)	
occurrences (all)	1	13	
Infections and infestations			

Pharyngitis			
subjects affected / exposed	17 / 267 (6.37%)	17 / 281 (6.05%)	
occurrences (all)	21	17	
Nasopharyngitis			
subjects affected / exposed	8 / 267 (3.00%)	14 / 281 (4.98%)	
occurrences (all)	8	17	
Sinusitis			
subjects affected / exposed	13 / 267 (4.87%)	9 / 281 (3.20%)	
occurrences (all)	13	9	
Influenza			
subjects affected / exposed	9 / 267 (3.37%)	7 / 281 (2.49%)	
occurrences (all)	15	7	
Tonsillitis			
subjects affected / exposed	9 / 267 (3.37%)	5 / 281 (1.78%)	
occurrences (all)	11	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 February 2005	The study was divided into two phases: I and II. During the study, more subjects had to be recruited. However, the recruitment of subjects could not be achieved prior to the expiry date of the batch of clinical supplies. Therefore, a re-supply was required, which resulted in a second phase of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported