



## Clinical trial results:

**A Multicenter, Randomized, Double-Blind, Triple-Dummy, Placebo-Controlled, Parallel Group, Four-Week Study Assessing the Efficacy of Fluticasone Propionate Aqueous Nasal Spray 200mcg QD versus Montelukast 10mg QD in Adolescent and Adult Subjects with Asthma and Seasonal Allergic Rhinitis Who are Receiving ADVAIR™ DISKUS™ 100/50mcg BID or Placebo BID**

### Summary

EudraCT number	2015-004867-35
Trial protocol	Outside EU/EEA
Global end of trial date	16 June 2007

### Results information

Result version number	v1 (current)
This version publication date	25 January 2017
First version publication date	25 January 2017

### Trial information

#### Trial identification

Sponsor protocol code	ADA103578
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
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	28 September 2007
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 June 2007
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of this study are to show that fluticasone propionate/salmeterol combination product 100/50mcg (FSC) BID (available as ADVAIR DISKUS) is superior to montelukast 10mg (MON) QD (available as Singulair) as monotherapy for asthma, and that MON administered concurrently with FSC adds no additional benefit to FSC alone in improving asthma control in a population of subjects with allergic asthma. A secondary objective is to demonstrate that in the presence of FSC, FPANS 200mcg QD (available as FLONASE) was superior to MON for control of rhinitis symptoms in a population of subjects with allergic asthma.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 September 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	United States: 1177
Worldwide total number of subjects	1177
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)	0
Adolescents (12-17 years)	90
Adults (18-64 years)	1053
From 65 to 84 years	34

85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details:

Participants having diagnosed as persistent asthma, for at least three months, who fulfilled eligibility criteria were enrolled for the study. Six hundred sixty (660) subjects were randomly assigned to one of the four double-blind study treatments

### Pre-assignment

Screening details:

Study was conducted at 71 investigational centers in United States. Subjects replaced their current short-acting beta 2-agonist with albuterol to be used as needed throughout the study. After screening, subjects entered a 7-14 day run-in period during which they continued use of their pre-study controller therapy

### 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	Subject, Investigator

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	FSC 100/50mcg (BID)+FPANS (200mcg) QD

Arm description:

Participants received fluticasone propionate/salmeterol (FSC) 100/50microgram (mcg) inhalation powder twice daily (BID) and fluticasone propionate aqueous nasal spray (FPANS) 200mcg once daily (QD) and placebo capsule once daily for four weeks.

Arm type	Experimental
Investigational medicinal product name	Fluticasone propionate/salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

100/50mcg twice a day

Investigational medicinal product name	Fluticasone propionate aqueous nasal spray
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Nasal use

Dosage and administration details:

200mcg once daily

<b>Arm title</b>	FSC 100/50mcg (BID) +MON 10mg (QD)
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Arm description:

Participants received fluticasone propionate/salmeterol 100/50mcg Inhalation powder twice daily, Montelukast (MON) 10mg capsule once daily and vehicle placebo nasal spray once daily for four weeks.

Arm type	Active comparator
Investigational medicinal product name	Fluticasone propionate/salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details: 100/50mcg twice a day	
Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 10mg once daily	
<b>Arm title</b>	FSC 100/50mcg (BID)
Arm description: Participants received fluticasone propionate/salmeterol 100/50mcg Inhalation powder twice daily, vehicle placebo nasal spray once daily and placebo capsule once daily for four weeks.	
Arm type	Experimental
Investigational medicinal product name	Fluticasone propionate/salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use
Dosage and administration details: 100/50mcg twice a day	
<b>Arm title</b>	MON 10mg (QD)
Arm description: Participants received Montelukast 10mg capsule once daily, placebo via dry powder inhaler BID, and vehicle placebo nasal spray QD for four weeks.	
Arm type	Active comparator
Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 10mg once daily	

<b>Number of subjects in period 1<sup>[1]</sup></b>	FSC 100/50mcg (BID)+FPANS (200mcg) QD	FSC 100/50mcg (BID) +MON 10mg (QD)	FSC 100/50mcg (BID)
Started	168	165	157
Completed	139	139	125
Not completed	29	26	32
Consent withdrawn by subject	-	1	-
Physician decision	-	-	1
Adverse event, non-fatal	5	2	3
Other; reasons not specified	7	8	12
Other; Exacerbation	1	1	2
Lost to follow-up	1	2	-
Protocol deviation	6	3	3

Other; Non-compliance	9	9	11
Lack of efficacy	-	-	-

<b>Number of subjects in period 1<sup>[1]</sup></b>	<b>MON 10mg (QD)</b>
Started	170
Completed	134
Not completed	36
Consent withdrawn by subject	4
Physician decision	-
Adverse event, non-fatal	2
Other; reasons not specified	13
Other; Exacerbation	5
Lost to follow-up	-
Protocol deviation	1
Other; Non-compliance	10
Lack of efficacy	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: Although 1177 participants enrolled, a total of 660 subjects comprised the Intent-To-Treat population randomized into the study. Sixty three (63) sites randomized a total of 396 subjects into a Per Protocol population.

## Baseline characteristics

### Reporting groups

Reporting group title	FSC 100/50mcg (BID)+FPANS (200mcg) QD
Reporting group description:	
Participants received fluticasone propionate/salmeterol (FSC) 100/50microgram (mcg) inhalation powder twice daily (BID) and fluticasone propionate aqueous nasal spray (FPANS) 200mcg once daily (QD) and placebo capsule once daily for four weeks.	
Reporting group title	FSC 100/50mcg (BID) +MON 10mg (QD)
Reporting group description:	
Participants received fluticasone propionate/salmeterol 100/50mcg Inhalation powder twice daily, Montelukast (MON) 10mg capsule once daily and vehicle placebo nasal spray once daily for four weeks.	
Reporting group title	FSC 100/50mcg (BID)
Reporting group description:	
Participants received fluticasone propionate/salmeterol 100/50mcg Inhalation powder twice daily, vehicle placebo nasal spray once daily and placebo capsule once daily for four weeks.	
Reporting group title	MON 10mg (QD)
Reporting group description:	
Participants received Montelukast 10mg capsule once daily, placebo via dry powder inhaler BID, and vehicle placebo nasal spray QD for four weeks.	

Reporting group values	FSC 100/50mcg (BID)+FPANS (200mcg) QD	FSC 100/50mcg (BID) +MON 10mg (QD)	FSC 100/50mcg (BID)
Number of subjects	168	165	157
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	36.2 ± 13.12	36.6 ± 12.47	37.4 ± 13.85
Gender categorical Units:			
Female	116	120	108
Male	52	45	49
Race, Customized			
Please note: The unknown category is used to present 1 participant who is missing from the study's demographic table in arm: FSC 100/50mcg (BID)+FPANS (200mcg) QD. There is no further explanation provided about the 1 missing participant data.			
Units: Subjects			
African American/African Heritage	18	19	22
American Indian or Alaska Native	3	3	0
Asian - Central/South Asian Heritage	2	3	1
Asian - East Asian Heritage	1	2	1
Asian - Japanese Heritage	0	2	0
Asian - South East Asian Heritage	1	3	1
Native Hawaiian or other Pacific Islander	1	1	1
White - Arabic/North African Heritage	2	1	0

White - White/Caucasian/European Heritage	137	130	129
White - Mixed Race	1	0	0
Mixed Race	1	1	2
Unknown	1	0	0

Reporting group values	MON 10mg (QD)	Total	
Number of subjects	170	660	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	36.7		
standard deviation	± 13.9	-	
Gender categorical			
Units:			
Female	108	452	
Male	62	208	
Race, Customized			

Please note: The unknown category is used to present 1 participant who is missing from the study's demographic table in arm: FSC 100/50mcg (BID)+FPANS (200mcg) QD. There is no further explanation provided about the 1 missing participant data.

Units: Subjects			
African American/African Heritage	19	78	
American Indian or Alaska Native	3	9	
Asian - Central/South Asian Heritage	2	8	
Asian - East Asian Heritage	0	4	
Asian - Japanese Heritage	0	2	
Asian - South East Asian Heritage	1	6	
Native Hawaiian or other Pacific Islander	1	4	
White - Arabic/North African Heritage	2	5	
White - White/Caucasian/European Heritage	142	538	
White - Mixed Race	0	1	
Mixed Race	0	4	
Unknown	0	1	



## End points

### End points reporting groups

Reporting group title	FSC 100/50mcg (BID)+FPANS (200mcg) QD
Reporting group description: Participants received fluticasone propionate/salmeterol (FSC) 100/50microgram (mcg) inhalation powder twice daily (BID) and fluticasone propionate aqueous nasal spray (FPANS) 200mcg once daily (QD) and placebo capsule once daily for four weeks.	
Reporting group title	FSC 100/50mcg (BID) +MON 10mg (QD)
Reporting group description: Participants received fluticasone propionate/salmeterol 100/50mcg Inhalation powder twice daily, Montelukast (MON) 10mg capsule once daily and vehicle placebo nasal spray once daily for four weeks.	
Reporting group title	FSC 100/50mcg (BID)
Reporting group description: Participants received fluticasone propionate/salmeterol 100/50mcg Inhalation powder twice daily, vehicle placebo nasal spray once daily and placebo capsule once daily for four weeks.	
Reporting group title	MON 10mg (QD)
Reporting group description: Participants received Montelukast 10mg capsule once daily, placebo via dry powder inhaler BID, and vehicle placebo nasal spray QD for four weeks.	

### Primary: Change from baseline in morning peak expiratory flow to assess superiority

End point title	Change from baseline in morning peak expiratory flow to assess superiority
End point description: Peak expiratory flow (PEF) was measured by the participant between clinic visits using the device used for spirometry assessments. Change from baseline is calculated as endpoint value minus baseline value where endpoint was defined as the average of the last (week 4) week's worth of data. Superiority analysis was performed by comparing the values between treatment groups. The Intent-to-Treat (ITT) population was defined as all subjects randomized to double-blind treatment	
End point type	Primary
End point timeframe: Baseline and Week 4	

End point values	FSC 100/50mcg (BID)+FPANS (200mcg) QD	FSC 100/50mcg (BID) +MON 10mg (QD)	FSC 100/50mcg (BID)	MON 10mg (QD)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	165 <sup>[1]</sup>	161 <sup>[2]</sup>	154 <sup>[3]</sup>	162 <sup>[4]</sup>
Units: Liter per minute (L/min)				
geometric mean (standard error)	20.8 (± 3.31)	28.7 (± 3.06)	28.9 (± 3.99)	-2.2 (± 3.5)

Notes:

[1] - Intent-to-treat (ITT) population.

[2] - ITT Population

[3] - ITT Population

[4] - ITT Population

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	MON 10mg (QD) v FSC 100/50mcg (BID)
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	29.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.1
upper limit	39.4
Variability estimate	Standard error of the mean
Dispersion value	4.92

## Primary: Mean change from baseline in morning peak expiratory flow to assess equivalence

End point title	Mean change from baseline in morning peak expiratory flow to assess equivalence
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End point description:

PEF was measured by the participant between clinic visits using the device used for spirometry assessments. Change from baseline is calculated as endpoint value minus baseline value where endpoint was defined as the average of the last (week 4) week's worth of data. Equivalence comparison was significant if Confidence interval falls entirely within (-18, 18) and contains zero. Per protocol (PP) population is defined as analysis can only be restricted to the participants who fulfill the protocol in the terms of the eligibility, interventions, and outcome assessment.

End point type	Primary
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End point timeframe:

Baseline and Week 4

End point values	FSC 100/50mcg (BID)+FPANS (200mcg) QD	FSC 100/50mcg (BID) +MON 10mg (QD)	FSC 100/50mcg (BID)	MON 10mg (QD)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	105 <sup>[5]</sup>	115 <sup>[6]</sup>	78 <sup>[7]</sup>	98 <sup>[8]</sup>
Units: Liter per minute (L/min)				
geometric mean (standard error)	20.8 (± 3.84)	32.4 (± 3.66)	37 (± 6.75)	1.9 (± 4.61)

Notes:

[5] - Per protocol population

[6] - Per protocol population

[7] - Per protocol population

[8] - Per protocol population

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	FSC 100/50mcg (BID) +MON 10mg (QD) v FSC 100/50mcg (BID)
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[9]</sup>
P-value	= 0.006
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	14.2
Variability estimate	Standard error of the mean
Dispersion value	7.02

Notes:

[9] - Equivalence comparison is significant if CI falls entirely within (-18, 18) and contains zero.

### Secondary: Change from baseline in daytime total nasal symptom scores.

End point title	Change from baseline in daytime total nasal symptom scores.
End point description:	Nasal symptoms were evaluated by the subject using 4-point (0 to 3) categorical scale, where 0-none, 1-mild, 2-moderate and 3-severe. The scores of the four component daytime symptoms (nasal congestion, itching, rhinorrhea, and sneezing) were summed to create a Daytime Total Nasal Symptom Score (D-TNSS) for each day. Change from baseline was calculated as Weeks 1-2 values minus baseline value, where values between week 1 and week 2 were averaged for Week 1-2 value. Confidence intervals and p-values are corrected for multiplicity using Hochberg's method.
End point type	Secondary
End point timeframe:	Baseline to Weeks 1-2

End point values	FSC 100/50mcg (BID)+FPANS (200mcg) QD	FSC 100/50mcg (BID) +MON 10mg (QD)	FSC 100/50mcg (BID)	MON 10mg (QD)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	167 <sup>[10]</sup>	162 <sup>[11]</sup>	155 <sup>[12]</sup>	167 <sup>[13]</sup>
Units: Scores				
geometric mean (standard error)	-3.3 (± 0.18)	-2.5 (± 0.16)	-2.3 (± 0.17)	-2.4 (± 0.15)

Notes:

[10] - ITT Population

[11] - ITT Population

[12] - ITT Population

[13] - ITT Population

### Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	FSC 100/50mcg (BID)+FPANS (200mcg) QD v FSC 100/50mcg

	(BID) +MON 10mg (QD)
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	0.22

## Secondary: Change from baseline in night time total nasal symptoms.

End point title	Change from baseline in night time total nasal symptoms. <sup>[14]</sup>
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End point description:

Nasal symptoms were evaluated by the subject using 4-point (0 to 3) categorical scale, where 0-none, 1-mild, 2-moderate and 3-severe. The sum of symptom scores assessing AM nasal congestion upon wakening, difficulty in going to sleep due to nasal symptoms, and night time awakenings due to nasal symptoms. Change from baseline was calculated as Weeks 1-2 values minus baseline value, where values between week 1 and week 2 were averaged for Week 1-2 value. Confidence intervals and p-values are corrected for multiplicity using Hochberg's method.

End point type	Secondary
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End point timeframe:

Baseline to weeks 1-2

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis is presented as available. Statistical analysis is not available for all the baseline period arms.

End point values	FSC 100/50mcg (BID)+FPANS (200mcg) QD	FSC 100/50mcg (BID) +MON 10mg (QD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167 <sup>[15]</sup>	161 <sup>[16]</sup>		
Units: Scores				
geometric mean (standard error)	-2.1 (± 0.13)	-1.8 (± 0.12)		

Notes:

[15] - ITT Population

[16] - ITT Population

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	FSC 100/50mcg (BID)+FPANS (200mcg) QD v FSC 100/50mcg (BID) +MON 10mg (QD)

Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.15

### Secondary: Change from baseline at endpoint in predose AM FEV1

End point title	Change from baseline at endpoint in predose AM FEV1 <sup>[17]</sup>
End point description:	
Forced expiratory volume in one second (FEV1) was evaluated. Change from baseline is calculated as endpoint value minus baseline value where baseline FEV1 was defined as the measure recorded on the morning of Day 1, just prior to randomization and endpoint was defined as the last available on-treatment FEV1 measure. Confidence intervals and p-values are corrected for multiplicity using Hochberg's method.	
End point type	Secondary
End point timeframe:	
Baseline and week 4	

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis is presented as available. Statistical analysis is not available for all the baseline period arms.

End point values	FSC 100/50mcg (BID)	MON 10mg (QD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143 <sup>[18]</sup>	153 <sup>[19]</sup>		
Units: Liter (L)				
geometric mean (standard error)	0.21 (± 0.0277)	0.057 (± 0.026)		

Notes:

[18] - ITT Population

[19] - ITT Population

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	FSC 100/50mcg (BID) v MON 10mg (QD)

Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.131
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.056
upper limit	0.207
Variability estimate	Standard error of the mean
Dispersion value	0.0335

### Secondary: Mean change from baseline in predose morning (AM) FEV1 to assess equivalence

End point title	Mean change from baseline in predose morning (AM) FEV1 to assess equivalence <sup>[20]</sup>
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End point description:

Forced expiratory volume in one second (FEV1) was evaluated. Change from baseline is calculated as endpoint value minus baseline value where baseline FEV1 was defined as the measure recorded on the morning of Day 1, just prior to randomization and endpoint was defined as the last available on-treatment FEV1 measure. Confidence intervals and p-values are corrected for multiplicity using Hochberg's method

End point type	Secondary
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End point timeframe:

Baseline and week 4

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis is presented as available. Statistical analysis is not available for all the baseline period arms.

End point values	FSC 100/50mcg (BID) +MON 10mg (QD)	FSC 100/50mcg (BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113 <sup>[21]</sup>	77 <sup>[22]</sup>		
Units: Liter (L)				
geometric mean (standard error)	0.217 (± 0.0253)	0.219 (± 0.0376)		

Notes:

[21] - Per protocol (PP) population

[22] - PP Population

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	FSC 100/50mcg (BID) +MON 10mg (QD) v FSC 100/50mcg (BID)

Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[23]</sup>
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.156
Variability estimate	Standard error of the mean
Dispersion value	0.0429

Notes:

[23] - Equivalence comparison is significant if CI falls entirely within (-0.2, 0.2) and contains zero.

### Secondary: Change from baseline in the asthma symptom free-days

End point title	Change from baseline in the asthma symptom free-days <sup>[24]</sup>
End point description:	Subject rated overall satisfaction with treatment was analyzed by Percentage of Asthma Symptom-free Days. Change from baseline is calculated as endpoint value minus baseline value, where, Endpoint is defined as the average of the last seven days' worth of data. Confidence intervals and p-values are corrected for multiplicity using Hochberg's method.
End point type	Secondary
End point timeframe:	Baseline and week 4

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis is presented as available. Statistical analysis is not available for all the baseline period arms.

End point values	FSC 100/50mcg (BID)	MON 10mg (QD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 <sup>[25]</sup>	161 <sup>[26]</sup>		
Units: Percentage				
geometric mean (standard error)	32.1 (± 2.99)	13.9 (± 2.43)		

Notes:

[25] - ITT Population

[26] - ITT Population

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	FSC 100/50mcg (BID) v MON 10mg (QD)

Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	18.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.7
upper limit	28.3
Variability estimate	Standard error of the mean
Dispersion value	4.09

## Secondary: Change from baseline in asthma symptom-free days

End point title	Change from baseline in asthma symptom-free days <sup>[27]</sup>
End point description:	Subject rated overall satisfaction with treatment was analyzed by Percentage of Asthma Symptom-free Days. Change from baseline is calculated as endpoint value minus baseline value, where, Endpoint is defined as the average of the last seven days' worth of data. Confidence intervals and p-values are corrected for multiplicity using Hochberg's method.
End point type	Secondary
End point timeframe:	Baseline and Week 4

### Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis is presented as available. Statistical analysis is not available for all the baseline period arms.

End point values	FSC 100/50mcg (BID) +MON 10mg (QD)	FSC 100/50mcg (BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115 <sup>[28]</sup>	78 <sup>[29]</sup>		
Units: Percentage				
geometric mean (standard error)	37.3 (± 3.72)	35.7 (± 4.18)		

### Notes:

[28] - PP Population

[29] - PP Population

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	Equivalence comparison is significant if CI falls entirely within (-15.7, 15.7) and contains zero.
Comparison groups	FSC 100/50mcg (BID) +MON 10mg (QD) v FSC 100/50mcg (BID)



Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.017
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	14.8
Variability estimate	Standard error of the mean
Dispersion value	5.69

### Secondary: Change from baseline in the percentage of albuterol-free-days

End point title	Change from baseline in the percentage of albuterol-free-
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End point description:

Overall satisfaction with treatment was analyzed by percentage of albuterol-free-days (puffs/24hour [hr]). Change from baseline is calculated as endpoint value minus baseline value, where, Endpoint is defined as the average of the last seven days' worth of data. Confidence intervals and p-values are corrected for multiplicity using Hochberg's method.

End point type	Secondary
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End point timeframe:

Baseline and Week 4

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis is presented as available. Statistical analysis is not available for all the baseline period arms.

End point values	FSC 100/50mcg (BID)	MON 10mg (QD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 <sup>[31]</sup>	161 <sup>[32]</sup>		
Units: Percentage				
geometric mean (standard error)	37 (± 3.18)	21.4 (± 2.83)		

Notes:

[31] - ITT Population

[32] - ITT Population

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	FSC 100/50mcg (BID) v MON 10mg (QD)

Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	15.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.5
upper limit	24.1
Variability estimate	Standard error of the mean
Dispersion value	4.22

### Secondary: Change from baseline in percentage of Albuterol-free days .

End point title	Change from baseline in percentage of Albuterol-free days . <sup>[33]</sup>
End point description:	
Overall satisfaction with treatment was analyzed by Percentage of albuterol-free-days (puffs/24hr). Change from baseline is calculated as endpoint value minus baseline value, where, Endpoint is defined as the average of the last seven days' worth of data. Confidence intervals and p-values are corrected for multiplicity using Hochberg's method.	
End point type	Secondary
End point timeframe:	
Baseline and Week 4	

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis is presented as available. Statistical analysis is not available for all the baseline period arms.

End point values	FSC 100/50mcg (BID) +MON 10mg (QD)	FSC 100/50mcg (BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115 <sup>[34]</sup>	78 <sup>[35]</sup>		
Units: Percentage				
geometric mean (standard error)	39.1 (± 3.73)	43.4 (± 4.54)		

Notes:

[34] - PP Population

[35] - PP Population

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	FSC 100/50mcg (BID) +MON 10mg (QD) v FSC 100/50mcg (BID)

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[36]</sup>
P-value	= 0.007
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.8
upper limit	10
Variability estimate	Standard error of the mean
Dispersion value	5.95

Notes:

[36] - Equivalence comparison is significant if CI falls entirely within (-19.5, 19.5) and contains zero.

### Secondary: Subject Rated Overall Satisfaction with Treatment.

End point title	Subject Rated Overall Satisfaction with Treatment.
End point description:	Subject-rated overall satisfaction with treatment (related to percentage of asthma symptom-free days). The satisfaction category ranged from very dissatisfied to very satisfied. The measurement type refers to the number of participants.
End point type	Secondary
End point timeframe:	
At Week 4	

End point values	FSC 100/50mcg (BID)+FPANS (200mcg) QD	FSC 100/50mcg (BID) +MON 10mg (QD)	FSC 100/50mcg (BID)	MON 10mg (QD)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	95	106	71	96
Units: Participants				
number (not applicable)				
Very dissatisfied	0	0	1	6
Dissatisfied	3	4	3	14
Slightly dissatisfied	11	7	12	9
Neutral	12	15	8	16
Slight satisfied	14	19	16	11
Satisfied	29	39	22	33
Very satisfied	26	22	9	7

### Statistical analyses

No statistical analyses for this end point

**Secondary: Change from baseline in evening (PM) peak expiratory flow.**

End point title	Change from baseline in evening (PM) peak expiratory flow. <sup>[37]</sup>
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End point description:

Evening peak expiratory flow (PM PEF) was measured using the device used for spirometry assessments. Change from baseline is calculated as endpoint value minus baseline value where endpoint was defined as the average of the last (week 4) week's worth of data. Superiority analysis was performed by comparing the values between treatment groups.

End point type	Secondary
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End point timeframe:

Baseline and Week 4

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis is presented as available. Statistical analysis is not available for all the baseline period arms.

End point values	FSC 100/50mcg (BID)	MON 10mg (QD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 <sup>[38]</sup>	161 <sup>[39]</sup>		
Units: Liter per minutes				
geometric mean (standard error)	18.3 (± 3.91)	-9.7 (± 3.38)		

Notes:

[38] - ITT Population

[39] - ITT Population

**Statistical analyses**

Statistical analysis title	Statistical Analysis 1
Comparison groups	FSC 100/50mcg (BID) v MON 10mg (QD)
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	25.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.2
upper limit	35.3
Variability estimate	Standard error of the mean
Dispersion value	4.85

**Secondary: Change from Baseline in Asthma Symptom Scores.**

End point title	Change from Baseline in Asthma Symptom Scores. <sup>[40]</sup>
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End point description:

Asthma symptom scores are diary-based asthma measures related to the proportion of asthma symptom-free days. Change from baseline is calculated as endpoint value minus baseline value where

endpoint was defined as the average of the last (week 4) week's worth of data. Superiority analysis was performed by comparing the values between treatment groups.

End point type	Secondary
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End point timeframe:

Baseline and Week 4

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis is presented as available. Statistical analysis is not available for all the baseline period arms.

End point values	FSC 100/50mcg (BID)	MON 10mg (QD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157 <sup>[41]</sup>	170 <sup>[42]</sup>		
Units: Scores				
geometric mean (standard error)	-1.3 (± 0.07)	-1 (± 0.09)		

Notes:

[41] - ITT Population

[42] - ITT Population

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	FSC 100/50mcg (BID) v MON 10mg (QD)
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.346
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.539
upper limit	-0.152
Variability estimate	Standard error of the mean
Dispersion value	0.0985

## Secondary: Mean Change from Baseline in daily albuterol use.

End point title	Mean Change from Baseline in daily albuterol use. <sup>[43]</sup>
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End point description:

Daily albuterol use (puffs/24hr) is a diary-based asthma measures. Change from baseline is calculated as endpoint value minus baseline value where endpoint was defined as the average of the last (week 4) week's worth of data. Superiority analysis was performed by comparing the values between treatment groups.

End point type	Secondary
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End point timeframe:

Baseline to endpoint

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis is presented as available. Statistical analysis is not available for all the baseline period arms.

End point values	FSC 100/50mcg (BID)	MON 10mg (QD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155 <sup>[44]</sup>	161 <sup>[45]</sup>		
Units: Puffs per 24 hours				
geometric mean (standard error)	-1.5 (± 0.14)	-1 (± 0.15)		

Notes:

[44] - ITT Population

[45] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Change from Baseline in Daytime Nasal Congestion Symptom Score.

End point title	Mean Change from Baseline in Daytime Nasal Congestion Symptom Score. <sup>[46]</sup>
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End point description:

Nasal congestion symptom score were evaluated by the subject using 4-point (0 to 3) categorical scale, where 0-none, 1-mild, 2-moderate and 3-severe. Change from baseline is calculated as treatment Week 1-2 value minus baseline value where Week 1-2 was defined as the average of data recorded from Day 2 to Day 15. Superiority analysis was performed by comparing the values between treatment groups.

End point type	Secondary
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End point timeframe:

Baseline to Weeks 1-2

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis is presented as available. Statistical analysis is not available for all the baseline period arms.

End point values	FSC 100/50mcg (BID)+FPANS (200mcg) QD	FSC 100/50mcg (BID) +MON 10mg (QD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168 <sup>[47]</sup>	165 <sup>[48]</sup>		
Units: Score on scale				
geometric mean (standard error)	-0.8 (± 0.05)	-0.6 (± 0.04)		

Notes:

[47] - ITT Population

[48] - ITT Population

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	FSC 100/50mcg (BID)+FPANS (200mcg) QD v FSC 100/50mcg (BID) +MON 10mg (QD)

Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.06

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Serious adverse event (SAE) and non serious adverse event (non-SAE) was analyzed up to 4 week of the study.

Adverse event reporting additional description:

All AE were based on the ITT population. AEs were sorted by system organ class (SOC).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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### Reporting groups

Reporting group title	FSC 100/50mcg (BID)+FPANS (200mcg) QD
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Reporting group description:

Participants received fluticasone propionate/salmeterol (FSC) 100/50microgram (mcg) Inhalation powder twice daily (BID) and fluticasone propionate aqueous nasal spray (FPANS) 200mcg once daily (QD) and placebo capsule once daily for four weeks.

Reporting group title	FSC 100/50mcg (BID) +MON 10mg (QD)
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Reporting group description:

Participants received fluticasone propionate/salmeterol 100/50mcg Inhalation powder twice daily, Montelukast (MON) 10mg capsule once daily and vehicle placebo nasal spray once daily for four weeks.

Reporting group title	FSC 100/50mcg (BID)
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Reporting group description:

Participants received fluticasone propionate/salmeterol 100/50mcg Inhalation powder twice daily, vehicle placebo nasal spray once daily and placebo capsule once daily for four weeks.

Reporting group title	MON 10mg (QD)
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Reporting group description:

Participants received Montelukast 10mg capsule once daily, placebo via dry powder inhaler BID, and vehicle placebo nasal spray QD for four weeks.

Serious adverse events	FSC 100/50mcg (BID)+FPANS (200mcg) QD	FSC 100/50mcg (BID) +MON 10mg (QD)	FSC 100/50mcg (BID)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 168 (0.00%)	0 / 165 (0.00%)	0 / 157 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Pelvic fracture			
subjects affected / exposed	0 / 168 (0.00%)	0 / 165 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	MON 10mg (QD)		
Total subjects affected by serious			



adverse events			
subjects affected / exposed	1 / 170 (0.59%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Pelvic fracture			
subjects affected / exposed	1 / 170 (0.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	FSC 100/50mcg (BID)+FPANS (200mcg) QD	FSC 100/50mcg (BID) +MON 10mg (QD)	FSC 100/50mcg (BID)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 168 (7.74%)	8 / 165 (4.85%)	7 / 157 (4.46%)
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 168 (7.74%)	8 / 165 (4.85%)	7 / 157 (4.46%)
occurrences (all)	15	8	7

<b>Non-serious adverse events</b>	MON 10mg (QD)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 170 (10.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 170 (10.00%)		
occurrences (all)	34		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 July 2005	Replaced all instances of Ventolin Hydrofluoroalkane (HFA) with albuterol/salbutamol. Clarified selection method for best spirometry effort. Included complete rating scale for patient satisfaction with treatment questionnaire.
17 October 2006	Amended Sponsor Contact Information Page. Clarified Statistical Analyses sections.
12 January 2007	Increased number of randomized subjects, revised participating countries, expanded acceptable visit windows, and corrected administrative errors
14 May 2007	Amended Sponsor Contact Information Page, revised asthma therapy footnote to include ADVAIR HFA and Symbicort, and included ciclesonide as allowable prior asthma therapy

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported