



Clinical trial results:

Randomized, Double-Blind Comparison of Advair 100/50 BID vs Salmeterol BID vs Albuterol QID in subjects with ARG/ARG genotype 12 years of Age and Older with Persistent Asthma on Short-Acting Beta2-Agonists Alone

Summary

EudraCT number	2015-004865-10
Trial protocol	Outside EU/EEA
Global end of trial date	23 January 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	SFA100062
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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	12 April 2007
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 January 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate lung function as assessed by AM PEF

AUC relative to baseline [AUC(bl)] in subjects who have the B16 Arg/Arg genotype compared with that of subjects who have the B16 Gly/Gly genotype over 16 weeks of treatment with FSC DISKUS 100/50mcg BID.

Please note: In the age group population table below, the actual number of adults participants between 18-64 years is 1817. Two participants did not have age information available. Unfortunately, the EU system does not have a way to denote this missing age data, so the 2 participants of unknown age were added to the adult population.

Protection of trial subjects:

Non-applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 October 2004
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	Kenya: 116
Country: Number of subjects enrolled	Peru: 135
Country: Number of subjects enrolled	United States: 1960
Worldwide total number of subjects	2211
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)	329

Adults (18-64 years)	1819
From 65 to 84 years	63
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In the results summary

Arginine is abbreviated as Arg, and Glycine is abbreviated as Gly

Pre-assignment

Screening details:

The study included a screening period(≤ 4 weeks [W]; genotyping of each participant), followed by two 8-W open-label treatment periods (OLTP) (albuterol in OLTP-1; ipratropium bromide [IB] as needed [prn] in OLTP-2) followed by double-blind treatment period of 16 W(fluticasone propionate/salmeterol[FSC] or salmeterol [SM], washout for 2-W (IB prn)

Period 1

Period 1 title	Double-blinded Treatment 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
Arm title	FSC 100/50 microgram (mcg) Arg/Arg

Arm description:

Participants received fixed dose combination of fluticasone propionate/salmeterol (FSC) 100/50 mcg twice daily (BID) for 16 weeks.

Participants with genotype Arg/Arg were enrolled in this arm

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

Dosage and administration details:

100/50 mcg

Arm title	FSC 100/50 mcg Arg/Gly
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Arm description:

Participants received fixed dose combination of FSC

100/50 mcg BID for 16 weeks.

Participants with genotype Arg/Gly were enrolled in this arm

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

Dosage and administration details:

100/50 mcg

Arm title	FSC 100/50 mcg Gly/Gly
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Arm description:

Participants received fixed dose combination of FSC

100/50 mcg BID for 16 weeks.

Participants with genotype Gly/Gly were enrolled in this arm

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

Dosage and administration details:

100/50 mcg

Arm title	SM 50 mcg Arg/Arg
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Arm description:

Participants received salmeterol (SM)

50 mcg twice daily (BID) for 16 weeks.

Participants with genotype Arg/Arg were enrolled in this arm

Arm type	Active comparator
Investigational medicinal product name	Salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

50 mcg

Arm title	SM 50 mcg Arg/Gly
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Arm description:

Participants received SM 50 mcg BID for 16 weeks.

Participants with genotype Arg/Gly were enrolled in this arm

Arm type	Active comparator
Investigational medicinal product name	Salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

50 mcg

Arm title	SM 50 mcg Gly/Gly
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Arm description:

Participants received SM 50 mcg BID for 16 weeks.

Participants with genotype Gly/Gly were enrolled in this arm

Arm type	Active comparator
Investigational medicinal product name	Salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

50 mcg

Number of subjects in period 1 ^[1]	FSC 100/50 microgram (mcg) Arg/Arg	FSC 100/50 mcg Arg/Gly	FSC 100/50 mcg Gly/Gly
Started	89	92	91
Completed	79	84	79
Not completed	10	8	12
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	-	4	6
Adverse event, non-fatal	3	1	1
Exacerbation	1	-	1
Unknown	4	1	-
Lost to follow-up	1	-	3
Sponsor terminated study	-	-	-
Protocol deviation	1	2	1

Number of subjects in period 1 ^[1]	SM 50 mcg Arg/Arg	SM 50 mcg Arg/Gly	SM 50 mcg Gly/Gly
Started	90	90	92
Completed	69	74	76
Not completed	21	16	16
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	6	3	3
Adverse event, non-fatal	1	6	3
Exacerbation	3	-	3
Unknown	2	2	2
Lost to follow-up	4	3	2
Sponsor terminated study	1	-	-
Protocol deviation	4	1	3

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: The worldwide number includes all enrolled participants; baseline information includes ITT population only.

Period 2

Period 2 title	Washout Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	FSC 100/50 mcg Arg/Arg
Arm description: Participants received fixed dose combination of fluticasone propionate/salmeterol (FSC) 100/50 mcg twice daily (BID) for 16 weeks. Participants with genotype Arg/Arg were enrolled in this arm	
Arm type	Experimental
Investigational medicinal product name	Fluticasone propionate/salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details: 100/50 mcg	
Arm title	FSC 100/50 mcg Arg/Gly
Arm description: Participants received fixed dose combination of FSC 100/50 mcg BID for 16 weeks. Participants with genotype Arg/Gly were enrolled in this arm	
Arm type	Experimental
Investigational medicinal product name	Fluticasone propionate/salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details: 100/50 mcg	
Arm title	FSC 100/50 mcg Gly/Gly
Arm description: Participants received fixed dose combination of FSC 100/50 mcg BID for 16 weeks. Participants with genotype Gly/Gly were enrolled in this arm	
Arm type	Experimental
Investigational medicinal product name	Fluticasone propionate/salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details: 100/50 mcg	
Arm title	SM 50 mcg Arg/Arg
Arm description: Participants received salmeterol (SM) 50 mcg twice daily (BID) for 16 weeks. Participants with genotype Arg/Arg were enrolled in this arm	
Arm type	Active comparator
Investigational medicinal product name	Salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details: 50 mcg	
Arm title	SM 50 mcg Arg/Gly

Arm description:

Participants received SM 50 mcg BID for 16 weeks.

Participants with genotype Arg/Gly were enrolled in this arm

Arm type	Active comparator
Investigational medicinal product name	Salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

50 mcg

Arm title	SM 50 mcg Gly/Gly
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Arm description:

Participants received SM 50 mcg BID for 16 weeks.

Participants with genotype Gly/Gly were enrolled in this arm

Arm type	Active comparator
Investigational medicinal product name	Salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

50 mcg

Number of subjects in period 2	FSC 100/50 mcg Arg/Arg	FSC 100/50 mcg Arg/Gly	FSC 100/50 mcg Gly/Gly
Started	79	84	79
Completed	78	82	79
Not completed	1	2	0
Adverse event, non-fatal	-	1	-
Exacerbation	1	-	-
Unknown	-	-	-
Sponsor terminated study	-	-	-
Protocol deviation	-	1	-

Number of subjects in period 2	SM 50 mcg Arg/Arg	SM 50 mcg Arg/Gly	SM 50 mcg Gly/Gly
Started	69	74	76
Completed	68	73	76
Not completed	1	1	0
Adverse event, non-fatal	-	-	-
Exacerbation	-	-	-
Unknown	-	1	-
Sponsor terminated study	1	-	-
Protocol deviation	-	-	-

Baseline characteristics

Reporting groups

Reporting group title	FSC 100/50 microgram (mcg) Arg/Arg
Reporting group description:	
Participants received fixed dose combination of fluticasone propionate/salmeterol (FSC) 100/50 mcg twice daily (BID) for 16 weeks.	
Participants with genotype Arg/Arg were enrolled in this arm	
Reporting group title	FSC 100/50 mcg Arg/Gly
Reporting group description:	
Participants received fixed dose combination of FSC 100/50 mcg BID for 16 weeks.	
Participants with genotype Arg/Gly were enrolled in this arm	
Reporting group title	FSC 100/50 mcg Gly/Gly
Reporting group description:	
Participants received fixed dose combination of FSC 100/50 mcg BID for 16 weeks.	
Participants with genotype Gly/Gly were enrolled in this arm	
Reporting group title	SM 50 mcg Arg/Arg
Reporting group description:	
Participants received salmeterol (SM) 50 mcg twice daily (BID) for 16 weeks.	
Participants with genotype Arg/Arg were enrolled in this arm	
Reporting group title	SM 50 mcg Arg/Gly
Reporting group description:	
Participants received SM 50 mcg BID for 16 weeks.	
Participants with genotype Arg/Gly were enrolled in this arm	
Reporting group title	SM 50 mcg Gly/Gly
Reporting group description:	
Participants received SM 50 mcg BID for 16 weeks.	
Participants with genotype Gly/Gly were enrolled in this arm	

Reporting group values	FSC 100/50 microgram (mcg) Arg/Arg	FSC 100/50 mcg Arg/Gly	FSC 100/50 mcg Gly/Gly
Number of subjects	89	92	91
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	33.8	31	33.3
standard deviation	± 13.31	± 14.4	± 14.33
Gender categorical			
Units:			
Male	27	33	36
Female	62	59	55
Race, Customized			
The "Other" race category below includes Native Hawaiian, Other Pacific Islander, American Indian and Alaska Native.			
Units: Subjects			
Arabic/North African	1	0	0
Black African American	23	16	12

Black African Heritage	6	1	6
East and South East Asian	0	0	0
Japanese	0	1	1
South Asian	0	1	2
White/Caucasian	44	57	59
Other	15	16	11

Reporting group values	SM 50 mcg Arg/Arg	SM 50 mcg Arg/Gly	SM 50 mcg Gly/Gly
Number of subjects	90	90	92
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	30	32.8	35.2
standard deviation	± 12.02	± 14.17	± 16.34
Gender categorical			
Units:			
Male	33	32	41
Female	57	58	51
Race, Customized			
The "Other" race category below includes Native Hawaiian, Other Pacific Islander, American Indian and Alaska Native.			
Units: Subjects			
Arabic/North African	0	0	0
Black African American	18	11	16
Black African Heritage	14	4	3
East and South East Asian	1	3	2
Japanese	0	0	0
South Asian	0	2	0
White/Caucasian	45	54	57
Other	12	16	14

Reporting group values	Total		
Number of subjects	544		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units:			
Male	202		
Female	342		
Race, Customized			
The "Other" race category below includes Native Hawaiian, Other Pacific Islander, American Indian and Alaska Native.			
Units: Subjects			
Arabic/North African	1		
Black African American	96		

Black African Heritage	34		
East and South East Asian	6		
Japanese	2		
South Asian	5		
White/Caucasian	316		
Other	84		

End points

End points reporting groups

Reporting group title	FSC 100/50 microgram (mcg) Arg/Arg
Reporting group description: Participants received fixed dose combination of fluticasone propionate/salmeterol (FSC) 100/50 mcg twice daily (BID) for 16 weeks. Participants with genotype Arg/Arg were enrolled in this arm	
Reporting group title	FSC 100/50 mcg Arg/Gly
Reporting group description: Participants received fixed dose combination of FSC 100/50 mcg BID for 16 weeks. Participants with genotype Arg/Gly were enrolled in this arm	
Reporting group title	FSC 100/50 mcg Gly/Gly
Reporting group description: Participants received fixed dose combination of FSC 100/50 mcg BID for 16 weeks. Participants with genotype Gly/Gly were enrolled in this arm	
Reporting group title	SM 50 mcg Arg/Arg
Reporting group description: Participants received salmeterol (SM) 50 mcg twice daily (BID) for 16 weeks. Participants with genotype Arg/Arg were enrolled in this arm	
Reporting group title	SM 50 mcg Arg/Gly
Reporting group description: Participants received SM 50 mcg BID for 16 weeks. Participants with genotype Arg/Gly were enrolled in this arm	
Reporting group title	SM 50 mcg Gly/Gly
Reporting group description: Participants received SM 50 mcg BID for 16 weeks. Participants with genotype Gly/Gly were enrolled in this arm	
Reporting group title	FSC 100/50 mcg Arg/Arg
Reporting group description: Participants received fixed dose combination of fluticasone propionate/salmeterol (FSC) 100/50 mcg twice daily (BID) for 16 weeks. Participants with genotype Arg/Arg were enrolled in this arm	
Reporting group title	FSC 100/50 mcg Arg/Gly
Reporting group description: Participants received fixed dose combination of FSC 100/50 mcg BID for 16 weeks. Participants with genotype Arg/Gly were enrolled in this arm	
Reporting group title	FSC 100/50 mcg Gly/Gly
Reporting group description: Participants received fixed dose combination of FSC 100/50 mcg BID for 16 weeks. Participants with genotype Gly/Gly were enrolled in this arm	
Reporting group title	SM 50 mcg Arg/Arg
Reporting group description: Participants received salmeterol (SM) 50 mcg twice daily (BID) for 16 weeks. Participants with genotype Arg/Arg were enrolled in this arm	
Reporting group title	SM 50 mcg Arg/Gly
Reporting group description: Participants received SM 50 mcg BID for 16 weeks. Participants with genotype Arg/Gly were enrolled in this arm	
Reporting group title	SM 50 mcg Gly/Gly
Reporting group description: Participants received SM 50 mcg BID for 16 weeks.	

Primary: Mean change from baseline in morning peak expiratory flow (AM/PEF) following the double-blind treatment period.

End point title	Mean change from baseline in morning peak expiratory flow (AM/PEF) following the double-blind treatment period.
End point description:	
AM PEF change from baseline was characterized by the area under the AM PEF curve relative to baseline AUC(bl) over the 16-week double-blind treatment period. Baseline was defined as the average of the AM PEF values recorded on the day of Visit 6 plus the 6 preceding days since AM PEF was measured in the morning (and prior to blinded study drug administration at Randomization [Visit 6]). The PEF measurements were collected via a study-issued Peak Flow Meter. Participants were instructed on proper use of the peak flow meter and on recording the results on the diary card. An analysis of covariance (ANCOVA) model, including terms for genotype, ethnicity stratum and baseline, was used to assess non-inferiority in AM PEF mean change from baseline for the overall 16-week double-blind treatment period. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles).(Overall: Baseline to Week 16).	
End point type	Primary
End point timeframe:	
Baseline and Upto 114 days	

End point values	FSC 100/50 microgram (mcg) Arg/Arg	FSC 100/50 mcg Arg/Gly	FSC 100/50 mcg Gly/Gly	SM 50 mcg Arg/Arg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87 ^[1]	90 ^[2]	91 ^[3]	86 ^[4]
Units: Litre/Minute				
arithmetic mean (standard error)				
Week 1-4 (n=83, 91, 88, 79, 85, 89)	26.9 (± 4.6)	19.2 (± 5.95)	23.5 (± 4.49)	17 (± 3.43)
Week 5-8 (n=80, 88, 84, 75,81, 83)	32.2 (± 5.16)	24.6 (± 6.45)	27.7 (± 5.12)	18.6 (± 4.1)
Week 9-12 (n=76,88,78, 72,76, 79)	37.7 (± 5.48)	26.5 (± 6.79)	27.7 (± 5.41)	22.5 (± 5.91)
Week 13-16 (n=75, 86, 77, 67,73, 75)	38.9 (± 5.66)	27 (± 6.83)	26.4 (± 5.57)	21.7 (± 5.55)
Overall (n=83, 91, 88, 79, 85, 89)	32.6 (± 4.71)	24.9 (± 5.86)	25.9 (± 4.77)	19.4 (± 3.92)

Notes:

[1] - Intent to Treat Population (ITT) (Excluding Investigator 018742)

[2] - Intent to Treat Population (ITT) (Excluding Investigator 018742)

[3] - Intent to Treat Population (ITT) (Excluding Investigator 018742)

[4] - Intent to Treat Population (ITT) (Excluding Investigator 018742)

End point values	SM 50 mcg Arg/Gly	SM 50 mcg Gly/Gly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89 ^[5]	91 ^[6]		
Units: Litre/Minute				
arithmetic mean (standard error)				
Week 1-4 (n=83, 91, 88, 79, 85, 89)	20.6 (± 4.81)	11.8 (± 2.91)		
Week 5-8 (n=80, 88, 84, 75,81, 83)	20.6 (± 5.77)	13.5 (± 3.77)		
Week 9-12 (n=76,88,78, 72,76, 79)	27.8 (± 6.79)	14.8 (± 3.55)		
Week 13-16 (n=75, 86, 77, 67,73, 75)	28 (± 7.27)	12.2 (± 4.04)		
Overall (n=83, 91, 88, 79, 85, 89)	24.6 (± 5.36)	12.4 (± 3.05)		

Notes:

[5] - Intent to Treat Population (ITT) (Excluding Investigator 018742)

[6] - Intent to Treat Population (ITT) (Excluding Investigator 018742)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[7]
P-value	= 0.596
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.1
upper limit	17.5

Notes:

[7] - Estimation Comments: Week 1 to Week 4

Statistical analysis title	Statistical analysis 2
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[8]
P-value	= 0.579
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.1
upper limit	19.8

Notes:

[8] - Estimation Comments: Week 5 to Week 8

Statistical analysis title	Statistical analysis 3
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly

Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[9]
P-value	= 0.214
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	10.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	26.5

Notes:

[9] - Estimation Comments: Week 9 to Week 12

Statistical analysis title	Statistical analysis 4
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[10]
P-value	= 0.165
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	28.3

Notes:

[10] - Estimation Comments: Week 13 to Week 16

Statistical analysis title	Statistical analysis 5
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[11]
P-value	= 0.325
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	21.3

Notes:

[11] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 6
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[12]
P-value	= 0.263
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	21.7

Notes:

[12] - Estimation Comments: Week 1 to Week 4

Statistical analysis title	Statistical analysis 7
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[13]
P-value	= 0.334
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.9
upper limit	23.2

Notes:

[13] - Estimation Comments: Week 5 to Week 8

Statistical analysis title	Statistical analysis 8
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[14]
P-value	= 0.209
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	10.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	27.3

Notes:

[14] - Estimation Comments: Week 9 to Week 12

Statistical analysis title	Statistical analysis 9
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[15]
P-value	= 0.227
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	10.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	27.4

Notes:

[15] - Estimation Comments: Week 13 to Week 16

Statistical analysis title	Statistical analysis 10
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[16]
P-value	= 0.276
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	22.1

Notes:

[16] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 11
Comparison groups	FSC 100/50 mcg Gly/Gly v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[17]
P-value	= 0.541
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	17.6

Notes:

[17] - Estimation Comments: Week 1 to Week 4

Statistical analysis title	Statistical analysis 12
Comparison groups	FSC 100/50 mcg Gly/Gly v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[18]
P-value	= 0.668
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.7
upper limit	18.3

Notes:

[18] - Estimation Comments: Week 5 to Week 8

Statistical analysis title	Statistical analysis 13
Comparison groups	FSC 100/50 mcg Gly/Gly v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[19]
P-value	= 0.965
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.6
upper limit	16.3

Notes:

[19] - Estimation Comments: Week 9 to Week 12

Statistical analysis title	Statistical analysis 14
Comparison groups	FSC 100/50 mcg Gly/Gly v FSC 100/50 mcg Arg/Gly

Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[20]
P-value	= 0.878
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.5
upper limit	15

Notes:

[20] - Estimation Comments: Week 13 to Week 16

Statistical analysis title	Statistical analysis 15
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[21]
P-value	= 0.91
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13
upper limit	14.6

Notes:

[21] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 16
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[22]
P-value	= 0.979
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	10.5

Notes:

[22] - Estimation Comments: Week 1 to Week 4

Statistical analysis title	Statistical analysis 17
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[23]
P-value	= 0.725
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.7
upper limit	15.4

Notes:

[23] - Estimation Comments: Week 5 to Week 8

Statistical analysis title	Statistical analysis 18
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[24]
P-value	= 0.858
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	Other: 17.2 %
sides	2-sided
lower limit	-17.2
upper limit	14.3

Notes:

[24] - Estimation Comments: Week 9 to Week 12

Statistical analysis title	Statistical analysis 19
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[25]
P-value	= 0.761
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.1
upper limit	14

Notes:

[25] - Estimation Comments: Week 13 to Week 16

Statistical analysis title	Statistical analysis 20
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[26]
P-value	= 0.836
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13
upper limit	10.6

Notes:

[26] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 21
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[27]
P-value	= 0.149
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	18.2

Notes:

[27] - Estimation Comments: Week 1 to Week 4

Statistical analysis title	Statistical analysis 22
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[28]
P-value	= 0.21
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	8.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	21

Notes:

[28] - Estimation Comments: Week 5 to Week 8

Statistical analysis title	Statistical analysis 23
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[29]
P-value	= 0.183
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	10.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	25.9

Notes:

[29] - Estimation Comments: Week 9 to Week 12

Statistical analysis title	Statistical analysis 24
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[30]
P-value	= 0.13
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	12.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	28.7

Notes:

[30] - Estimation Comments: Week 13 to Week 16

Statistical analysis title	Statistical analysis 25
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly

Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[31]
P-value	= 0.095
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	9.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	21.4

Notes:

[31] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 26
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[32]
P-value	= 0.131
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	18

Notes:

[32] - Estimation Comments: Week 1 to Week 4

Statistical analysis title	Statistical analysis 27
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[33]
P-value	= 0.357
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	18.3

Notes:

[33] - Estimation Comments: Week 5 to Week 8

Statistical analysis title	Statistical analysis 28
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Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[34]
P-value	= 0.123
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	11.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	27

Notes:

[34] - Estimation Comments: Week 9 to Week 12

Statistical analysis title	Statistical analysis29
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[35]
P-value	= 0.06
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	15.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	30.8

Notes:

[35] - Estimation Comments: Week 13 to Week 16

Statistical analysis title	Statistical analysis 30
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[36]
P-value	= 0.054
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	11.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	22.3

Notes:

[36] - Estimation Comments: Overall

Secondary: Mean change from baseline in the evening peak expiratory flow (PM PEF) following the double-blind treatment period.

End point title	Mean change from baseline in the evening peak expiratory flow (PM PEF) following the double-blind treatment period.
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End point description:

PM PEF change from baseline was characterized by the area under the PM PEF curve relative to baseline AUC(bl) over the 16-week double-blind treatment period. Baseline was defined as the average of the values from the 7 days preceding Visit 6 since these measures were derived from data collected in the evening. . ANCOVA model, including terms for genotype, ethnicity stratum and baseline, was used to assess non-inferiority in PM PEF mean change from baseline for the overall 16-week double-blind treatment period. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles).(Overall: Baseline to Week 16).

End point type	Secondary
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End point timeframe:

Baseline and Upto 114 days

End point values	FSC 100/50 microgram (mcg) Arg/Arg	FSC 100/50 mcg Arg/Gly	FSC 100/50 mcg Gly/Gly	SM 50 mcg Arg/Arg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87 ^[37]	91 ^[38]	90 ^[39]	86 ^[40]
Units: Litre/Minute				
arithmetic mean (standard error)				
Week 1-4 (n=83, 91, 88, 79, 86, 88)	21.7 (± 4.52)	22.7 (± 4.45)	17.1 (± 5.7)	15.8 (± 3.34)
Week 5-8 (n=80, 88, 85, 75,82, 82)	27.9 (± 5.46)	26.8 (± 4.97)	21.6 (± 6.43)	20.3 (± 4.5)
Week 9-12 (n=76,88,78, 72, 77,78)	29.7 (± 5.46)	26.5 (± 5.19)	23.1 (± 6.78)	22.9 (± 5.4)
Week 13-16 (n=75, 86, 77, 69, 74, 75)	31.3 (± 5.65)	25.5 (± 5.14)	24.7 (± 6.56)	21.3 (± 5.1)
Overall n=83, 91, 88, 79,86, 88	26.8 (± 4.75)	25 (± 4.57)	22.4 (± 5.79)	19.3 (± 3.86)

Notes:

[37] - ITT Population (Excluding Investigator 018742)

[38] - ITT Population (Excluding Investigator 018742)

[39] - ITT Population (Excluding Investigator 018742)

[40] - ITT Population (Excluding Investigator 018742)

End point values	SM 50 mcg Arg/Gly	SM 50 mcg Gly/Gly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89 ^[41]	91 ^[42]		
Units: Litre/Minute				
arithmetic mean (standard error)				
Week 1-4 (n=83, 91, 88, 79, 86, 88)	19.7 (± 5.19)	8.7 (± 3.18)		
Week 5-8 (n=80, 88, 85, 75,82, 82)	21.8 (± 5.97)	11.7 (± 3.57)		
Week 9-12 (n=76,88,78, 72, 77,78)	33 (± 7.78)	11.8 (± 3.88)		
Week 13-16 (n=75, 86, 77, 69, 74, 75)	30.6 (± 8.12)	10.7 (± 4.64)		
Overall n=83, 91, 88, 79,86, 88	26.2 (± 5.89)	10.5 (± 3.15)		

Notes:

[41] - ITT Population (Excluding Investigator 018742)

[42] - ITT Population (Excluding Investigator 018742)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[43]
P-value	= 0.943
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.1
upper limit	14.1

Notes:

[43] - Estimation Comments: Week 1 to Week 4

Statistical analysis title	Statistical analysis 3
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[44]
P-value	= 0.621
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.9
upper limit	19.9

Notes:

[44] - Estimation Comments: Week 9 to Week 12

Statistical analysis title	Statistical analysis 2
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[45]
P-value	= 0.811
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.7
upper limit	17.5

Notes:

[45] - Estimation Comments: Week 5 to Week 8

Statistical analysis title	Statistical analysis 4
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[46]
P-value	= 0.463
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.9
upper limit	21.6

Notes:

[46] - Estimation Comments: Week 13 to Week 16

Statistical analysis title	Statistical analysis 6
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[47]
P-value	= 0.667
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.9
upper limit	17

Notes:

[47] - Estimation Comments: overall

Statistical analysis title	Statistical analysis 7
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[48]
P-value	= 0.402
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	19.4

Notes:

[48] - Estimation Comments: Week 1 to Week 4

Statistical analysis title	Statistical analysis 9
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[49]
P-value	= 0.427
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.7
upper limit	22.9

Notes:

[49] - Estimation Comments: Week 9 to Week 12

Statistical analysis title	Statistical analysis 8
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[50]
P-value	= 0.359
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	23

Notes:

[50] - Estimation Comments: Week 5 to Week 8

Statistical analysis title	Statistical analysis 10
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly

Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[51]
P-value	= 0.443
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.9
upper limit	22.5

Notes:

[51] - Estimation Comments: Week 13 to Week 16

Statistical analysis title	Statistical analysis 11
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[52]
P-value	= 0.433
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	19.6

Notes:

[52] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 12
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[53]
P-value	= 0.429
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.9
upper limit	18.5

Notes:

[53] - Estimation Comments: Week 1 to Week 4

Statistical analysis title	Statistical analysis 12
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[54]
P-value	= 0.483
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	20.6

Notes:

[54] - Estimation Comments: Week 5 to Week 8

Statistical analysis title	Statistical analysis 13
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[55]
P-value	= 0.745
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.1
upper limit	18.3

Notes:

[55] - Estimation Comments: Week 9 to Week 12

Statistical analysis title	Statistical analysis 14
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[56]
P-value	= 0.958
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.1
upper limit	15.9

Notes:

[56] - Week 13 to Week 16

Statistical analysis title	Statistical analysis 15
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[57]
P-value	= 0.714
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.1
upper limit	16.1

Notes:

[57] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 16
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[58]
P-value	= 0.957
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.5
upper limit	10.9

Notes:

[58] - Estimation Comments: Week 1 to Week 4

Statistical analysis title	Statistical analysis 17
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[59]
P-value	= 0.741
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.2
upper limit	15.7

Notes:

[59] - Estimation Comments: Week 5 to Week 8

Statistical analysis title	Statistical analysis 19
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[60]
P-value	= 0.586
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.4
upper limit	12.7

Notes:

[60] - Estimation Comments: Week 13 to Week 16

Statistical analysis title	Statistical analysis 18
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[61]
P-value	= 0.479
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.8
upper limit	10.7

Notes:

[61] - Estimation Comments: Week 9 to Week 12

Statistical analysis title	Statistical analysis 20
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[62]
P-value	= 0.648
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.4
upper limit	9.6

Notes:

[62] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 21
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[63]
P-value	= 0.086
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	9.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	20.8

Notes:

[63] - Estimation Comments: Week 1 to Week 4

Statistical analysis title	Statistical analysis 22
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[64]
P-value	= 0.094
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	24.6

Notes:

[64] - Estimation Comments: Week 5 to Week 8

Statistical analysis title	Statistical analysis 24
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Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[65]
P-value	= 0.112
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	31.4

Notes:

[65] - Estimation Comments: Week 13 to Week 16

Statistical analysis title	Statistical analysis 23
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[66]
P-value	= 0.097
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	30.5

Notes:

[66] - Estimation Comments: Week 9 to Week 12

Statistical analysis title	Statistical analysis 25
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[67]
P-value	= 0.062
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	24

Notes:

[67] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 26
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[68]
P-value	= 0.068
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	20.7

Notes:

[68] - Estimation Comments: Week 1 to Week 4

Statistical analysis title	Statistical analysis 27
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[69]
P-value	= 0.165
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	21.9

Notes:

[69] - Estimation Comments: Week 5 to Week 8

Statistical analysis title	Statistical analysis 28
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[70]
P-value	= 0.015
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	20
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.9
upper limit	36.2

Notes:

[70] - Estimation Comments: Week 9 to Week 12

Statistical analysis title	Statistical analysis 29
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[71]
P-value	= 0.028
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	18.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	35.7

Notes:

[71] - Estimation Comments: Week 13 to Week 16

Statistical analysis title	Statistical analysis 30
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[72]
P-value	= 0.017
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	14.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.7
upper limit	26.5

Notes:

[72] - Estimation Comments: Overall

Secondary: Mean forced expiratory volume in one second (FEV1) change from baseline over the 16-week double-blind treatment period

End point title	Mean forced expiratory volume in one second (FEV1) change from baseline over the 16-week double-blind treatment period
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End point description:

FEV1 is the amount of air that is forcefully exhaled in one second of the FVC test. FEV1 was performed on all subjects using the spirometry equipment at each site. It was calculated as the last scheduled measurement of pre-dose FEV1 during the 16-week double-blind treatment period. Baseline was defined as the pre-dose FEV1 measure from Randomization (Visit 6). Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. (Overall: Baseline to Week 16).

End point type	Secondary
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End point timeframe:

Baseline and Upto 114 days

End point values	FSC 100/50 microgram (mcg) Arg/Arg	FSC 100/50 mcg Arg/Gly	FSC 100/50 mcg Gly/Gly	SM 50 mcg Arg/Arg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87 ^[73]	91 ^[74]	90 ^[75]	86 ^[76]
Units: Liter				
arithmetic mean (standard error)				
Visit 7 (Week 4), n=81, 89, 88, 79,84, 84	0.22 (± 0.03)	0.22 (± 0.033)	0.2 (± 0.037)	0.25 (± 0.045)
Visit 8 (Week 8) , n=79, 88, 81,75, 78, 79	0.22 (± 0.031)	0.22 (± 0.034)	0.23 (± 0.032)	0.16 (± 0.032)
Visit 9 (Week 12) , n=78, 84, 79 ,69, 75, 76	0.22 (± 0.031)	0.23 (± 0.038)	0.22 (± 0.035)	0.2 (± 0.038)
Visit 10 (Week 16) , n=77, 83, 79, 66, 73, 75	0.21 (± 0.036)	0.23 (± 0.039)	0.21 (± 0.042)	0.22 (± 0.057)
Endpoint , n=81, 89, 88, 79, 84, 84	0.21 (± 0.034)	0.23 (± 0.038)	0.2 (± 0.038)	0.21 (± 0.049)
Overall , n=81, 89, 88, 79,84, 84	0.22 (± 0.027)	0.22 (± 0.033)	0.21 (± 0.029)	0.21 (± 0.032)

Notes:

[73] - ITT (Excluding Investigator 018742)

[74] - ITT (Excluding Investigator 018742)

[75] - ITT (Excluding Investigator 018742)

[76] - ITT (Excluding Investigator 018742)

End point values	SM 50 mcg Arg/Gly	SM 50 mcg Gly/Gly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89 ^[77]	91 ^[78]		
Units: Liter				
arithmetic mean (standard error)				
Visit 7 (Week 4), n=81, 89, 88, 79,84, 84	0.13 (± 0.035)	0.11 (± 0.032)		
Visit 8 (Week 8) , n=79, 88, 81,75, 78, 79	0.18 (± 0.038)	0.07 (± 0.037)		
Visit 9 (Week 12) , n=78, 84, 79 ,69, 75, 76	0.12 (± 0.035)	0.07 (± 0.031)		
Visit 10 (Week 16) , n=77, 83, 79, 66, 73, 75	0.08 (± 0.035)	0.05 (± 0.033)		
Endpoint , n=81, 89, 88, 79, 84, 84	0.11 (± 0.033)	0.05 (± 0.031)		
Overall , n=81, 89, 88, 79,84, 84	0.13 (± 0.029)	0.08 (± 0.027)		

Notes:

[77] - ITT (Excluding Investigator 018742)

[78] - ITT (Excluding Investigator 018742)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly

Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[79]
P-value	= 0.869
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.1

Notes:

[79] - Estimation Comments: Visit 7 (Week 4)

Statistical analysis title	Statistical analysis 2
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[80]
P-value	= 0.694
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.11

Notes:

[80] - Estimation Comments: Visit 8 (Week 8)

Statistical analysis title	Statistical analysis 3
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[81]
P-value	= 0.925
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.1

Notes:

[81] - Estimation Comments: Visit 9 (Week 12)

Statistical analysis title	Statistical analysis 4
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[82]
P-value	= 0.775
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.09

Notes:

[82] - Estimation Comments: Visit 10 (Week 16)

Statistical analysis title	Statistical analysis 5
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[83]
P-value	= 0.671
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.08

Notes:

[83] - Estimation Comments: Endpoint

Statistical analysis title	Statistical analysis 6
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[84]
P-value	= 0.953
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.09

Notes:

[84] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 7
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[85]
P-value	= 0.484
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.13

Notes:

[85] - Estimation Comments: Visit 7 (Week 4)

Statistical analysis title	Statistical analysis 8
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[86]
P-value	= 0.988
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.09

Notes:

[86] - Estimation Comments: Visit 8 (Week 8)

Statistical analysis title	Statistical analysis 9
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[87]
P-value	= 0.82
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.11

Notes:

[87] - Estimation Comments: Visit 9 (Week 12)

Statistical analysis title	Statistical analysis 10
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[88]
P-value	= 0.883
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.12

Notes:

[88] - Estimation Comments: Visit 10 (Week 16)

Statistical analysis title	Statistical analysis 11
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[89]
P-value	= 0.894
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.11

Notes:

[89] - Estimation Comments: Endpoint

Statistical analysis title	Statistical analysis 12
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly

Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[90]
P-value	= 0.679
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.1

Notes:

[90] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 13
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[91]
P-value	= 0.581
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.12

Notes:

[91] - Estimation Comments: Visit 7 (Week 4)

Statistical analysis title	Statistical analysis 14
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[92]
P-value	= 0.678
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.07

Notes:

[92] - Estimation Comments: Visit 8 (Week 8)

Statistical analysis title	Statistical analysis 15
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Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[93]
P-value	= 0.891
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.1

Notes:

[93] - Estimation Comments: Visit 9 (Week 12)

Statistical analysis title	Statistical analysis 16
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[94]
P-value	= 0.66
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.13

Notes:

[94] - Estimation Comments: Visit 10 (Week 16)

Statistical analysis title	Statistical analysis 17
Comparison groups	FSC 100/50 mcg Gly/Gly v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[95]
P-value	= 0.565
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.13

Notes:

[95] - Estimation Comments: Endpoint

Statistical analysis title	Statistical analysis 18
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[96]
P-value	= 0.714
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.1

Notes:

[96] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 19
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[97]
P-value	= 0.041
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.22

Notes:

[97] - Estimation Comments: Visit 7 (Week 4)

Statistical analysis title	Statistical analysis 20
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[98]
P-value	= 0.736
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.08

Notes:

[98] - Estimation Comments: Visit 8 (Week 8)

Statistical analysis title	Statistical analysis 21
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[99]
P-value	= 0.08
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.19

Notes:

[99] - Estimation Comments: Visit 9 (Week 12)

Statistical analysis title	Statistical analysis 22
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[100]
P-value	= 0.022
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.26

Notes:

[100] - Estimation Comments: Visit 10 (Week 16)

Statistical analysis title	Statistical analysis 23
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[101]
P-value	= 0.055
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.22

Notes:

[101] - Estimation Comments: Endpoint

Statistical analysis title	Statistical analysis 24
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[102]
P-value	= 0.076
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.16

Notes:

[102] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 25
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[103]
P-value	= 0.016
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.23

Notes:

[103] - Estimation Comments: Visit 7 (Week 4)

Statistical analysis title	Statistical analysis 26
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly

Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[104]
P-value	= 0.075
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.19

Notes:

[104] - Estimation Comments: Visit 8 (Week 8)

Statistical analysis title	Statistical analysis 27
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[105]
P-value	= 0.007
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.23

Notes:

[105] - Estimation Comments: Visit 9 (Week 12)

Statistical analysis title	Statistical analysis 28
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[106]
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.3

Notes:

[106] - Estimation Comments: Visit 10 (Week 16)

Statistical analysis title	Statistical analysis 29
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Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[107]
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.27

Notes:

[107] - Estimation Comments: Endpoint

Statistical analysis title	Statistical analysis 30
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[108]
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.21

Notes:

[108] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 31
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[109]
P-value	= 0.712
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.12

Notes:

[109] - Estimation Comments: Visit 7 (Week 4)

Statistical analysis title	Statistical analysis 32
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[110]
P-value	= 0.031
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.21

Notes:

[110] - Estimation Comments: Visit 8 (Week 8)

Statistical analysis title	Statistical analysis 33
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[111]
P-value	= 0.331
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.14

Notes:

[111] - Estimation Comments: Visit 9 (Week 12)

Statistical analysis title	Statistical analysis 34
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[112]
P-value	= 0.517
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.15

Notes:

[112] - Estimation Comments: Visit 10 (Week 16)

Statistical analysis title	Statistical analysis 35
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	equivalence ^[113]
P-value	= 0.311
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.16

Notes:

[113] - Estimation Comments: Endpoint

Statistical analysis title	Statistical analysis 36
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[114]
P-value	= 0.218
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.13

Notes:

[114] - Estimation Comments: Overall

Secondary: Mean change from baseline in percent of symptom-free days

End point title	Mean change from baseline in percent of symptom-free days
End point description:	
A symptom-free day was defined as a day with no symptoms (that is a score of 0, indicated no asthma symptoms during the day or previous night, recorded in the daily diary). Percent of symptom-free days was calculated as the number of symptom-free days divided by the total number of days in the assessment period, multiplied by 100 for each participant. Baseline was defined as the average of the values from the 7 days preceding Visit 6 since these measures were derived from data collected in the evening. P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles) (Overall: Baseline to Week 16).	
End point type	Secondary
End point timeframe:	
Baseline and Upto 114 days	

End point values	FSC 100/50 microgram (mcg) Arg/Arg	FSC 100/50 mcg Arg/Gly	FSC 100/50 mcg Gly/Gly	SM 50 mcg Arg/Arg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87 ^[115]	91 ^[116]	90 ^[117]	86 ^[118]
Units: Days				
arithmetic mean (standard error)				
Weeks 1-4, n=80, 90, 87, 78, 86, 87	9.5 (± 2.91)	12.5 (± 3.13)	16.2 (± 2.99)	7.1 (± 3.09)
Weeks 5-8, n=78, 87, 83, 74,82, 82	9 (± 3.11)	15.1 (± 3.28)	19.5 (± 3.31)	9.8 (± 3.7)
Weeks 9-12, n=74, 87, 78, 71,77, 78	11.6 (± 3.32)	16.6 (± 3.72)	17.4 (± 3.29)	11.5 (± 3.82)
Weeks 13-16, n=73, 84, 76, 68,74, 75	11 (± 3.47)	15.2 (± 4.03)	18.1 (± 3.28)	12.2 (± 4.3)
Overall, n=80, 90, 88, 79,86, 88	9.9 (± 2.83)	14.6 (± 3.19)	18.2 (± 2.88)	9.6 (± 3.21)

Notes:

[115] - ITT Population (Excluding Investigator 018742)

[116] - ITT Population (Excluding Investigator 018742)

[117] - ITT Population (Excluding Investigator 018742)

[118] - ITT Population (Excluding Investigator 018742)

End point values	SM 50 mcg Arg/Gly	SM 50 mcg Gly/Gly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89 ^[119]	91 ^[120]		
Units: Days				
arithmetic mean (standard error)				
Weeks 1-4, n=80, 90, 87, 78, 86, 87	7.7 (± 3.08)	6.7 (± 2.84)		
Weeks 5-8, n=78, 87, 83, 74,82, 82	7.1 (± 3.14)	7.3 (± 3.04)		
Weeks 9-12, n=74, 87, 78, 71,77, 78	8.3 (± 2.71)	9.3 (± 3.03)		
Weeks 13-16, n=73, 84, 76, 68,74, 75	8.3 (± 2.8)	8.2 (± 3.2)		
Overall, n=80, 90, 88, 79,86, 88	9.1 (± 2.69)	8.2 (± 2.69)		

Notes:

[119] - ITT Population (Excluding Investigator 018742)

[120] - ITT Population (Excluding Investigator 018742)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[121]
P-value	= 0.501
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.1
upper limit	5.5

Notes:

[121] - Estimation Comments: Week 1 to 4

Statistical analysis title	Statistical analysis 2
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[122]
P-value	= 0.187
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.7
upper limit	2.9

Notes:

[122] - Estimation Comments: Week 5 to 8

Statistical analysis title	Statistical analysis 3
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[123]
P-value	= 0.383
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.5
upper limit	5.2

Notes:

[123] - Estimation Comments: Week 9 to 12

Statistical analysis title	Statistical analysis 4
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[124]
P-value	= 0.503
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-13
upper limit	6.4

Notes:

[124] - Estimation Comments: Week 13 to 16

Statistical analysis title	Statistical analysis 5
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[125]
P-value	= 0.271
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.6
upper limit	3.6

Notes:

[125] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 6
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[126]
P-value	= 0.144
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.5
upper limit	2.1

Notes:

[126] - Estimation Comments: Week 1 to 4

Statistical analysis title	Statistical analysis 7
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly

Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[127]
P-value	= 0.028
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-9.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.8
upper limit	-1.1

Notes:

[127] - Estimation Comments: Week 5 to 8

Statistical analysis title	Statistical analysis 8
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[128]
P-value	= 0.316
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.3
upper limit	4.6

Notes:

[128] - Estimation Comments: Week 9 to 12

Statistical analysis title	Statistical analysis 9
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[129]
P-value	= 0.208
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.2
upper limit	3.6

Notes:

[129] - Estimation Comments: Week 13 to 16

Statistical analysis title	Statistical analysis 10
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[130]
P-value	= 0.061
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.8
upper limit	0.4

Notes:

[130] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 11
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[131]
P-value	= 0.411
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.4
upper limit	4.7

Notes:

[131] - Estimation Comments: Week 1 to 4

Statistical analysis title	Statistical analysis 12
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[132]
P-value	= 0.354
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.6
upper limit	4.5

Notes:

[132] - Estimation Comments: Week 5 to 8

Statistical analysis title	Statistical analysis 13
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[133]
P-value	= 0.878
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	8.4

Notes:

[133] - Estimation Comments: Week 9 to 12

Statistical analysis title	Statistical analysis 14
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[134]
P-value	= 0.53
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.6
upper limit	6.5

Notes:

[134] - Estimation Comments: Week 13 to 16

Statistical analysis title	Statistical analysis 15
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[135]
P-value	= 0.419
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	4.6

Notes:

[135] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 16
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[136]
P-value	= 0.981
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8
upper limit	7.8

Notes:

[136] - Estimation Comments: Week 1 to Week 4

Statistical analysis title	Statistical analysis 17
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[137]
P-value	= 0.465
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	11.9

Notes:

[137] - Estimation Comments: Week 5 to 8

Statistical analysis title	Statistical analysis 18
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[138]
P-value	= 0.342
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	12.7

Notes:

[138] - Estimation Comments: Week 9 to 12

Statistical analysis title	Statistical analysis 19
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[139]
P-value	= 0.357
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	13.5

Notes:

[139] - Estimation Comments: Week 13 to 16

Statistical analysis title	Statistical analysis 20
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[140]
P-value	= 0.768
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	8.6

Notes:

[140] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 21
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Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[141]
P-value	= 0.774
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	9

Notes:

[141] - Estimation Comments: Week 1 to Week 4

Statistical analysis title	Statistical analysis 22
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[142]
P-value	= 0.432
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	12

Notes:

[142] - Estimation Comments: Week 5 to 8

Statistical analysis title	Statistical analysis 23
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[143]
P-value	= 0.394
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	12.2

Notes:

[143] - Estimation Comments: Week 9 to 12

Statistical analysis title	Statistical analysis 24
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[144]
P-value	= 0.215
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	14.9

Notes:

[144] - Estimation Comments: Week 13 to 16

Statistical analysis title	Statistical analysis 25
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[145]
P-value	= 0.583
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	9.5

Notes:

[145] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 26
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[146]
P-value	= 0.749
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	8.9

Notes:

[146] - Estimation Comments: Week 1 to 4

Statistical analysis title	Statistical analysis 27
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[147]
P-value	= 0.96
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	8.5

Notes:

[147] - Estimation Comments: Week 5 to 8

Statistical analysis title	Statistical analysis 28
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[148]
P-value	= 0.911
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	7.8

Notes:

[148] - Estimation Comments: Week 9 to 12

Statistical analysis title	Statistical analysis 29
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[149]
P-value	= 0.747
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.4
upper limit	10.3

Notes:

[149] - Estimation Comments: Week 13 to 16

Statistical analysis title	Statistical analysis 30
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[150]
P-value	= 0.795
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	8.2

Notes:

[150] - Estimation Comments: Overall

Secondary: Mean change from baseline in supplemental ipratropium use over the 16-week double-blind treatment periods

End point title	Mean change from baseline in supplemental ipratropium use over the 16-week double-blind treatment periods
End point description:	
Supplemental ipratropium use was analyzed as the number of puffs taken per day. Baseline was defined as the average of the values from the 7 days preceding Visit 6 since these measures were derived from data collected in the evening. P-values are from an ANCOVA model with terms for baseline, ethnicity stratum and Arg16Gly genotype. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). (Overall: Baseline to Week 16).	
End point type	Secondary
End point timeframe:	
Baseline and Upto 114 days	

End point values	FSC 100/50 microgram (mcg) Arg/Arg	FSC 100/50 mcg Arg/Gly	FSC 100/50 mcg Gly/Gly	SM 50 mcg Arg/Arg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87 ^[151]	91 ^[152]	90 ^[153]	86 ^[154]
Units: Puffs/Day				
arithmetic mean (standard error)				
Weeks 1-4, n=81, 87, 85, 78, 84, 83	-0.47 (± 0.112)	-0.54 (± 0.109)	-0.6 (± 0.121)	-0.34 (± 0.105)
Weeks 5-8, n=78, 83, 81, 74, 81, 78	-0.47 (± 0.113)	-0.68 (± 0.119)	-0.67 (± 0.131)	-0.31 (± 0.118)

Weeks 9-12, n=73, 84, 75, 71, 76, 74	-0.49 (± 0.124)	-0.69 (± 0.129)	-0.53 (± 0.115)	-0.42 (± 0.119)
Weeks 13-16, n=73, 82, 74, 68, 73, 71	-0.55 (± 0.115)	-0.68 (± 0.129)	-0.47 (± 0.102)	-0.49 (± 0.118)
Overall, n=81, 87, 86, 79, 85, 84	-0.49 (± 0.11)	-0.63 (± 0.113)	-0.6 (± 0.117)	-0.36 (± 0.102)

Notes:

[151] - ITT Population (Excluding Investigator 018742)

[152] - ITT Population (Excluding Investigator 018742)

[153] - ITT Population (Excluding Investigator 018742)

[154] - ITT Population (Excluding Investigator 018742)

End point values	SM 50 mcg Arg/Gly	SM 50 mcg Gly/Gly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89 ^[155]	91 ^[156]		
Units: Puffs/Day				
arithmetic mean (standard error)				
Weeks 1-4, n=81, 87, 85, 78, 84, 83	-0.37 (± 0.122)	-0.33 (± 0.092)		
Weeks 5-8, n=78, 83, 81, 74, 81, 78	-0.38 (± 0.131)	-0.31 (± 0.095)		
Weeks 9-12, n=73, 84, 75, 71, 76, 74	-0.53 (± 0.121)	-0.41 (± 0.09)		
Weeks 13-16, n=73, 82, 74, 68, 73, 71	-0.56 (± 0.132)	-0.42 (± 0.1)		
Overall, n=81, 87, 86, 79, 85, 84	-0.45 (± 0.118)	-0.35 (± 0.083)		

Notes:

[155] - ITT Population (Excluding Investigator 018742)

[156] - ITT Population (Excluding Investigator 018742)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[157]
P-value	= 0.516
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.13

Notes:

[157] - Estimation Comments: Week 1 to 4

Statistical analysis title	Statistical analysis 2
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly

Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[158]
P-value	= 0.702
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.24

Notes:

[158] - Estimation Comments: Week 5 to 8

Statistical analysis title	Statistical analysis 3
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[159]
P-value	= 0.614
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.26

Notes:

[159] - Estimation Comments: Week 9 to 12

Statistical analysis title	Statistical analysis 4
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[160]
P-value	= 0.75
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.18

Notes:

[160] - Estimation Comments: Week 13 to 16

Statistical analysis title	Statistical analysis 5
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Arg/Gly
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[161]
P-value	= 0.926
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.17

Notes:

[161] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 6
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[162]
P-value	= 0.84
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.18

Notes:

[162] - Estimation Comments: Week 1 to 4

Statistical analysis title	Statistical analysis 7
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[163]
P-value	= 0.881
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.22

Notes:

[163] - Estimation Comments: Week 5 to 8

Statistical analysis title	Statistical analysis 8
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[164]
P-value	= 0.545
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.14

Notes:

[164] - Estimation Comments: Week 9 to 12

Statistical analysis title	Statistical analysis 9
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[165]
P-value	= 0.199
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.08

Notes:

[165] - Estimation Comments: Week 13 to 16

Statistical analysis title	Statistical analysis 10
Comparison groups	FSC 100/50 microgram (mcg) Arg/Arg v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[166]
P-value	= 0.637
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.14

Notes:

[166] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 11
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[167]
P-value	= 0.646
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.24

Notes:

[167] - Estimation Comments: Week 1 to 4

Statistical analysis title	Statistical analysis 12
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[168]
P-value	= 0.812
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.17

Notes:

[168] - Estimation Comments: Week 5 to 8

Statistical analysis title	Statistical analysis 13
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly

Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[169]
P-value	= 0.254
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.08

Notes:

[169] - Estimation Comments: Week 9 to 12

Statistical analysis title	Statistical analysis 14
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[170]
P-value	= 0.316
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.1

Notes:

[170] - Estimation Comments: Week 13 to 16

Statistical analysis title	Statistical analysis 15
Comparison groups	FSC 100/50 mcg Arg/Gly v FSC 100/50 mcg Gly/Gly
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[171]
P-value	= 0.697
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.14

Notes:

[171] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 16
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Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[172]
P-value	= 0.607
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.15

Notes:

[172] - Estimation Comments: Week 1 to 4

Statistical analysis title	Statistical analysis 17
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[173]
P-value	= 0.997
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.23

Notes:

[173] - Estimation comments: week 5 to 8

Statistical analysis title	Statistical analysis 18
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[174]
P-value	= 0.799
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.22

Notes:

[174] - Estimation Comments: Week 9 to 12

Statistical analysis title	Statistical analysis 19
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[175]
P-value	= 0.614
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.15

Notes:

[175] - Estimation Comments: Week 13 to 16

Statistical analysis title	Statistical analysis 20
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[176]
P-value	= 0.914
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.17

Notes:

[176] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 21
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[177]
P-value	= 0.573
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.15

Notes:

[177] - Estimation Comments: Week 1 to 4

Statistical analysis title	Statistical analysis 22
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Arg/Gly
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[178]
P-value	= 0.673
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.18

Notes:

[178] - Estimation Comments: Week 5 to 8

Statistical analysis title	Statistical analysis 23
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[179]
P-value	= 0.439
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.12

Notes:

[179] - Estimation Comments: Week 9 to 12

Statistical analysis title	Statistical analysis 24
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[180]
P-value	= 0.087
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.03

Notes:

[180] - Estimation Comments: Week 13 to 16

Statistical analysis title	Statistical analysis 25
Comparison groups	SM 50 mcg Arg/Arg v SM 50 mcg Gly/Gly
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[181]
P-value	= 0.347
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.09

Notes:

[181] - Estimation Comments: Overall

Statistical analysis title	Statistical analysis 26
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[182]
P-value	= 0.959
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.19

Notes:

[182] - Estimation Comments: Week 1 to 4

Statistical analysis title	Statistical analysis 27
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly

Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[183]
P-value	= 0.66
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.17

Notes:

[183] - Estimation Comments: Week 5 to 8

Statistical analysis title	Statistical analysis 28
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[184]
P-value	= 0.291
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.09

Notes:

[184] - Estimation Comments: Week 9 to 12

Statistical analysis title	Statistical analysis 29
Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[185]
P-value	= 0.21
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.07

Notes:

[185] - Estimation Comments: Week 13 to 16

Statistical analysis title	Statistical analysis 30
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Comparison groups	SM 50 mcg Arg/Gly v SM 50 mcg Gly/Gly
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[186]
P-value	= 0.391
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.1

Notes:

[186] - Estimation Comments: Overall

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs were collected from the time the first dose of study medication until the follow up contact (Up to 240 days)

Adverse event reporting additional description:

SAEs and non-serious AEs were collected in members of the Safety Population, comprised of all participants who received at least one dose of study medication.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	9.1
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Reporting groups

Reporting group title	FSC100/50
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Reporting group description:

Reporting group 1 description

Reporting group title	Salmeterol
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Reporting group description:

Reporting group 2 description

Serious adverse events	FSC100/50	Salmeterol	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 272 (0.00%)	2 / 272 (0.74%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Reproductive system and breast disorders			
Ovarian cyst ruptured			
subjects affected / exposed	0 / 272 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 272 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	FSC100/50	Salmeterol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 272 (23.16%)	65 / 272 (23.90%)	
Nervous system disorders			
Headache			
subjects affected / exposed	36 / 272 (13.24%)	30 / 272 (11.03%)	
occurrences (all)	85	70	
Respiratory, thoracic and mediastinal disorders			
Pharyngolaryngeal pain			
subjects affected / exposed	11 / 272 (4.04%)	7 / 272 (2.57%)	
occurrences (all)	13	7	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	21 / 272 (7.72%)	18 / 272 (6.62%)	
occurrences (all)	28	20	
Upper respiratory tract infection			
subjects affected / exposed	8 / 272 (2.94%)	12 / 272 (4.41%)	
occurrences (all)	9	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2004	<ul style="list-style-type: none">• Updated sponsor contact information• Removed the limitation for methacholine challenge testing only on subject ≥ 18 years of age• Added historical PC20 $< 8\text{mg/ml}$ as acceptable• Added exclusion criterion of exercise induced bronchospasm• Modified time intervals for anti-asthma medications• Clarified use of corticosteroids in the Exclusion Criteria• Added an exclusion criterion for peanut and soybean food allergy• Added AM PEF stability limits• Added a requirement to obtain vital signs data during MADR testing• Removed Appendices 5 and 7• Corrected administrative and typographical errors
14 June 2005	<ul style="list-style-type: none">• Clarifications in the Protocol Summary, Open-Label Treatment periods (continuation criteria added at Visit 2)• Study population (number of screened subjects)• Section 5, Inclusion criteria numbers 3, 6, and 7 regarding pregnancy testing, historical reversibility, and pre-study anti-asthma medication use required for participation• Section 5, Exclusion Criteria numbers 4, 5, 6, 9, and 10 regarding exercise induced bronchospasm, prohibited anti-asthma medications, prohibited concurrent medications, respiratory tract infection and antibiotic use• Section 6 Study Assessments, Rescreening (use of historical reversibility), Visit 2 continuation criteria added, premature discontinuation visit (open-label and washout periods), methacholine challenge testing (manual), albuterol and ipratropium bromide use (during open-label, randomization, and washout periods)• Section 7. Dosage and Administration to include the washout period• Section 8. Concomitant Medications, permitted and prohibited medications to agree with Section 5, inclusion and exclusion criteria ENTIAL RM2007/00065/00• Section 9. Subject Completion to include a discontinuation visit and Withdrawal to include screen and open-label, washout failures (data collection)• Section 11. Data Analysis and Statistical Considerations, Other Comparisons of Interest and Sample Size Considerations modified;• Corrections of administrative and reference errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported