



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 |
|-----------------------|-----------|

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 |
|------------------|------------------------|

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 |
|------------------|-------------------|

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 |
|------------------------------|-----|

| | |
|---|-----------------------------------|
| 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 |
|------------------|-------------------|

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 standard deviation | 33.8 ± 13.31 | 31 ± 14.4 | 33.3 ± 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 |
|-----------------------------------|-------------------------|

| | |
|---|---------------------------------------|
| 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. |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------------------------|-------------------------|

| | |
|---|---------------------------------------|
| 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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------------------------|-------------------------|

| | |
|---|---|
| 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 |
|-----------------------------------|-------------------------|

| | |
|---|---------------------------------------|
| 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: | |
| <p>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).</p> | |
| 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 |
|-----------------------------------|-------------------------|

| | |
|---|---------------------------------------|
| 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 |
|-----------------------------------|-------------------------|

| | |
|---|---------------------------------------|
| 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 |
|-----------------------------------|-------------------------|

| | |
|---|---------------------------------------|
| 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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|-----|
| Dictionary version | 9.1 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | FSC100/50 |
|-----------------------|-----------|

Reporting group description:

Reporting group 1 description

| | |
|-----------------------|------------|
| Reporting group title | Salmeterol |
|-----------------------|------------|

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