



Clinical trial results:

Investigating the mechanism of inhaled corticosteroids associated pneumonia by longitudinal characterisation of the airway microbiome in patients with severe COPD

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2016-000734-21 |
| Trial protocol | GB |
| Global end of trial date | 26 March 2019 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 28 June 2023 |
| First version publication date | 28 June 2023 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 2014RC07 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02972476 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University of Dundee |
| Sponsor organisation address | Ninewells Hospital and Medical School, Dundee, United Kingdom, DD1 9SY |
| Public contact | James Chalmers, University of Dundee, +44 1382 383642, j.chalmers@dundee.ac.uk |
| Scientific contact | James Chalmers, University of Dundee, +44 1382 383642, j.chalmers@dundee.ac.uk |

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 | 31 January 2023 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 March 2019 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs budesonide/formoterol 400/12 mcg on upper airway bacterial load from oropharyngeal swabs.

Protection of trial subjects:

Patients were excluded if they were unable to give informed consent, had a known allergy, intolerance or contraindication to any of the study drugs, or had any unstable co-morbidities (cardiovascular disease, active malignancy) which in the opinion of the investigator would make the patient unsuitable to be enrolled in the study

Background therapy:

During the study it was anticipated that the patient should continue on their usual treatment for COPD, excluding ICS or nasal corticosteroids, LABAs and LAMAs.

Evidence for comparator:

The 4 treatment regime arms are as follows:

1. Budesonide/formoterol 400/12 mcg (Symbicort Turbohaler) 1 inhalation twice daily + Acclidinium Bromide 322 mcg (Eklira Genuair) 1 inhalation twice daily
2. Fluticasone propionate/salmeterol 500/50 mcg (Seretide Accuhaler) 1 inhalation twice daily + Acclidinium Bromide 322 mcg (Eklira Genuair) 1 inhalation twice daily
3. Fluticasone propionate/salmeterol 250/50 mcg (Seretide Accuhaler) 1 inhalation twice daily + Acclidinium Bromide 322 mcg (Eklira Genuair) 1 inhalation twice daily
4. Acclidinium/formoterol combination 340/12 mcg (Duaklir Genuair) 1 inhalation twice daily

The rationale for these doses were that regime 1 and regime 2 are the licensed doses of Symbicort and Seretide in the UK which are commonly used in this patient population. Treatment regime 3 was included as this is commonly used in clinical practice as an equivalent dose to Symbicort and therefore may help to answer whether there is a dose response relationship effecting the airway microbiome. This treatment is licensed in asthma but is not licensed for the treatment of COPD at this lower dose. It is a lower dose of the licensed fluticasone propionate/salmeterol 500/50 which is licensed in COPD and is administered

through the same device. It is equivalent in dose, as measured by BDP, to all other ICS licensed in the treatment of COPD (beclomethasone dipropionate/formoterol fumarate 100/6 2 puff twice daily= 1000BDP, fluticasone furoate + vilanterol trifenate 92/22 1 puff once daily=1000BDP, and Budesonide/formoterol as described above= 800BDP). Treatment regime 4 is included as LABA/LAMA therapy is considered an appropriate alternative to ICS/LABA therapy in emerging clinical guidelines. This also acts as a control population without ICS treatment, thus demonstrating that any changes during the study period are the results of the effect of ICS.

| | |
|---|--------------|
| Actual start date of recruitment | 01 June 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 61 |
| Worldwide total number of subjects | 61 |
| 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) | 0 |
| Adults (18-64 years) | 23 |
| From 65 to 84 years | 37 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at 6 NHS sites in the UK (NHS Tayside, NHS Lothian, NHS Lanarkshire, NHS Fife, NHS Blackpool, NHS Greater Glasgow and Clyde)

Pre-assignment

Screening details:

158 patients screened. Screen failures-asthma (1), antibiotics or oral steroids in previous 28 days (2), dental infection (1), <10 pack year history (1), FEV1/FVC >0.7 (8), did not meet GOLD criteria (22), could not perform spirometry (1). 122 patients started 4-week wash-out (withdrawal COPD exacerbations (45), other (16). 61 subjects randomised

Period 1

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

Blinding implementation details:

Open label

Arms

| | |
|------------------------------|-----------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Symbicort 400/12 & Eklira Genuair |

Arm description:

Budesonide 400mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months
Budesonide & formoterol fumarate and Acclidinium bromide

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Budesonide & formoterol fumarate and Acclidinium bromide |
| Investigational medicinal product code | |
| Other name | Symbicort 400/12 & Eklira Genuair |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Budesonide 400mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months

| | |
|------------------|----------------------------------|
| Arm title | Seretide 500/50 & Eklira Genuair |
|------------------|----------------------------------|

Arm description:

Fluticasone propionate 500mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months
Fluticasone 500 & salmeterol and Acclidinium bromide

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Fluticasone 500 & salmeterol and Acclidinium bromide |
| Investigational medicinal product code | |
| Other name | Seretide 500/50 & Eklira Genuair |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Fluticasone propionate 500mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Acclidinium

| | |
|--|--|
| Arm title | Seretide 250/50 & Eklira Genuair |
| Arm description: Fluticasone propionate 250mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Fluticasone 250 & salmeterol and Acclidinium bromide | |
| Arm type | Active comparator |
| Investigational medicinal product name | Fluticasone 250 & salmeterol and Acclidinium bromide |
| Investigational medicinal product code | |
| Other name | Seretide 250/50 & Eklira Genuair |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

1 inhalation twice daily, inhalation powder for 3 months

| | |
|---|---|
| Arm title | Duaklir Genuair |
| Arm description: Acclidinium bromide 340mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder for 3 months Acclidinium bromide & formoterol fumarate | |
| Arm type | Active comparator |
| Investigational medicinal product name | Acclidinium bromide & formoterol fumarate |
| Investigational medicinal product code | |
| Other name | Duaklir Genuair |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Acclidinium bromide 340mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder for 3 months

| Number of subjects in period 1 | Symbicort 400/12 & Eklira Genuair | Seretide 500/50 & Eklira Genuair | Seretide 250/50 & Eklira Genuair |
|---------------------------------------|-----------------------------------|----------------------------------|----------------------------------|
| Started | 18 | 13 | 15 |
| Completed | 16 | 13 | 14 |
| Not completed | 2 | 0 | 1 |
| Consent withdrawn by subject | 1 | - | 1 |
| Adverse event, non-fatal | 1 | - | - |

| Number of subjects in period 1 | Duaklir Genuair |
|---------------------------------------|-----------------|
| Started | 15 |
| Completed | 14 |
| Not completed | 1 |
| Consent withdrawn by subject | 1 |

| | |
|--------------------------|---|
| Adverse event, non-fatal | - |
|--------------------------|---|

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------|
| Reporting group title | Overall trial |
| Reporting group description: - | |

| Reporting group values | Overall trial | Total | |
|--|---------------|-------|--|
| Number of subjects | 61 | 61 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 0 | |
| Newborns (0-27 days) | | 0 | |
| Infants and toddlers (28 days-23 months) | | 0 | |
| Children (2-11 years) | | 0 | |
| Adolescents (12-17 years) | | 0 | |
| Adults (18-64 years) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous | | | |
| Age (years) | | | |
| Units: years | | | |
| arithmetic mean | 66.9 | | |
| standard deviation | ± 7.8 | - | |
| Gender categorical | | | |
| Gender | | | |
| Units: Subjects | | | |
| Female | 28 | 28 | |
| Male | 33 | 33 | |
| Smoking status | | | |
| Smoking status at enrolment | | | |
| Units: Subjects | | | |
| Ex-smoker | 37 | 37 | |
| Current smoker | 24 | 24 | |
| Blood eosinophil count at baseline | | | |
| Units: Subjects | | | |
| <150 | 21 | 21 | |
| 150-299 | 28 | 28 | |
| ≥300 | 12 | 12 | |
| GOLD classification | | | |
| Units: Subjects | | | |
| GOLD B | 8 | 8 | |
| GOLD C | 1 | 1 | |
| GOLD D | 52 | 52 | |
| Pack years | | | |
| Smoking pack years | | | |
| Units: Years | | | |

| | | | |
|---|----------------|---|--|
| arithmetic mean standard deviation | 44.4 ± 21.5 | - | |
| BMI Units: kg/m ² arithmetic mean standard deviation | 28.9 ± 6.9 | - | |
| MRC Dyspnoea Score Units: MRC Dyspnoea Score arithmetic mean standard deviation | 3.3 ± 1.0 | - | |
| CAT Score | | | |
| COPD Assessment Test | | | |
| Units: CAT Score arithmetic mean standard deviation | 21.5 ± 7.2 | - | |
| FEV1 (L) Units: litre(s) arithmetic mean standard deviation | 1.32 ± 0.61 | - | |
| FEV1 (%) Units: percent arithmetic mean standard deviation | 53.0 ± 25.5 | - | |
| FVC (L) Units: litre(s) arithmetic mean standard deviation | 2.74 ± 0.94 | - | |
| FVC (%) Units: percent arithmetic mean standard deviation | 88.9 ± 28.7 | - | |
| FEV1/FEVC ratio Units: percent arithmetic mean standard deviation | 46.6 ± 16.1 | - | |
| FEF 25-75% Units: percent arithmetic mean standard deviation | 20.8 ± 15.3 | - | |
| Oxygen saturation at rest Units: percent arithmetic mean standard deviation | 95 ± 2.4 | - | |
| Number of exacerbations in the last year Units: exacerbations arithmetic mean standard deviation | 2.2 ± 1.5 | - | |

Subject analysis sets

| | |
|--|-----------------------------------|
| Subject analysis set title | Arm 1: BF400 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Budesonide & formoterol fumarate and Acclidinium bromide | |
| Subject analysis set title | Arm 2: FS500 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Fluticasone 500 & salmeterol and Acclidinium bromide | |
| Subject analysis set title | Arm 3: FS250 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Fluticasone 250 & salmeterol and Acclidinium bromide | |
| Subject analysis set title | Arm 4: AF |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Acclidinium bromide & formoterol fumarate | |
| Subject analysis set title | Pooled Fluticasone propionate ICS |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Pooled Arms 2 and Arm 3 Fluticasone propionate 250mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Fluticasone 250 & salmeterol and Acclidinium bromide Fluticasone propionate 500mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Fluticasone 500 & salmeterol and Acclidinium bromide | |
| Subject analysis set title | Pooled ICS |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Pooled ICS treatments: Budesonide 400mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months. Budesonide & formoterol fumarate and Acclidinium bromide Fluticasone propionate 500mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months. Fluticasone 500 & salmeterol and Acclidinium bromide Fluticasone propionate 250mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months. Fluticasone 250 & salmeterol and Acclidinium bromide | |

| Reporting group values | Arm 1: BF400 | Arm 2: FS500 | Arm 3: FS250 |
|--|--------------|--------------|--------------|
| Number of subjects | 18 | 13 | 15 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) | | | |

| | | | |
|---------------------------------------|--------|--------|--------|
| From 65-84 years 85 years and over | | | |
| | | | |
| Age continuous | | | |
| Age (years) | | | |
| Units: years | | | |
| arithmetic mean | 68.8 | 67.4 | 65.1 |
| standard deviation | ± 8.4 | ± 10.2 | ± 5.3 |
| Gender categorical | | | |
| Gender | | | |
| Units: Subjects | | | |
| Female | 6 | 9 | 5 |
| Male | 12 | 4 | 10 |
| Smoking status | | | |
| Smoking status at enrolment | | | |
| Units: Subjects | | | |
| Ex-smoker | 10 | 8 | 8 |
| Current smoker | 8 | 5 | 7 |
| Blood eosinophil count at baseline | | | |
| Units: Subjects | | | |
| <150 | 4 | 4 | 5 |
| 150-299 | 9 | 7 | 7 |
| >=300 | 5 | 2 | 3 |
| GOLD classification | | | |
| Units: Subjects | | | |
| GOLD B | 1 | 1 | 2 |
| GOLD C | 0 | 1 | 0 |
| GOLD D | 17 | 11 | 13 |
| Pack years | | | |
| Smoking pack years | | | |
| Units: Years | | | |
| arithmetic mean | 46.1 | 49.4 | 39.7 |
| standard deviation | ± 20.3 | ± 26.9 | ± 12.9 |
| BMI | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 26.4 | 28.5 | 29.8 |
| standard deviation | ± 6.0 | ± 7.8 | ± 8.7 |
| MRC Dyspnoea Score | | | |
| Units: MRC Dyspnoea Score | | | |
| arithmetic mean | .71 | 3.4 | 2.9 |
| standard deviation | ± 1.0 | ± 0.8 | ± 1.0 |
| CAT Score | | | |
| COPD Assessment Test | | | |
| Units: CAT Score | | | |
| arithmetic mean | 21.1 | 21.6 | 23.0 |
| standard deviation | ± 7.2 | ± 10.1 | ± 6.5 |
| FEV1 (L) | | | |
| Units: litre(s) | | | |
| arithmetic mean | 1.49 | 1.21 | 1.45 |
| standard deviation | ± 0.67 | ± 0.55 | ± 0.58 |
| FEV1 (%) | | | |

| | | | |
|---|----------------|----------------|----------------|
| Units: percent arithmetic mean standard deviation | 58.9 ± 24.7 | 57.6 ± 33.6 | 54.3 ± 20.0 |
| FVC (L) Units: litre(s) arithmetic mean standard deviation | 2.72 ± 0.95 | 2.68 ± 1.1 | 3.10 ± 0.87 |
| FVC (%) Units: percent arithmetic mean standard deviation | 86.5 ± 32.2 | 98.6 ± 39.3 | 91.9 ± 19.2 |
| FEV1/FEVC ratio Units: percent arithmetic mean standard deviation | 51.5 ± 18.1 | 43.3 ± 20.4 | 46.6 ± 10.6 |
| FEF 25-75% Units: percent arithmetic mean standard deviation | 23.2 ± 14.3 | 17.5 ± 13.7 | 22.6 ± 2.08 |
| Oxygen saturation at rest Units: percent arithmetic mean standard deviation | 94.2 ± 3.4 | 95.8 ± 2.4 | 95.1 ± 1.5 |
| Number of exacerbations in the last year Units: exacerbations arithmetic mean standard deviation | 2.89 ± 1.8 | 2.28 ± 1.3 | 20.8 ± 1.3 |

| Reporting group values | Arm 4: AF | Pooled Fluticasone propionate ICS | Pooled ICS |
|---|---------------|-----------------------------------|------------|
| Number of subjects | 15 | 25 | 40 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous | | | |
| Age (years) | | | |
| Units: years arithmetic mean standard deviation | 66.0 ± 6.8 | ± | ± |
| Gender categorical | | | |
| Gender | | | |
| Units: Subjects | | | |

| | | | |
|--------|---|--|--|
| Female | 8 | | |
| Male | 7 | | |

| | | | |
|------------------------------------|--------|---|---|
| Smoking status | | | |
| Smoking status at enrolment | | | |
| Units: Subjects | | | |
| Ex-smoker | 11 | | |
| Current smoker | 4 | | |
| Blood eosinophil count at baseline | | | |
| Units: Subjects | | | |
| <150 | 8 | | |
| 150-299 | 5 | | |
| >=300 | 2 | | |
| GOLD classification | | | |
| Units: Subjects | | | |
| GOLD B | 4 | | |
| GOLD C | 0 | | |
| GOLD D | 11 | | |
| Pack years | | | |
| Smoking pack years | | | |
| Units: Years | | | |
| arithmetic mean | 42.9 | | |
| standard deviation | ± 25.3 | ± | ± |
| BMI | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 28.7 | | |
| standard deviation | ± 4.5 | ± | ± |
| MRC Dyspnoea Score | | | |
| Units: MRC Dyspnoea Score | | | |
| arithmetic mean | 3.1 | | |
| standard deviation | ± 1.1 | ± | ± |
| CAT Score | | | |
| COPD Assessment Test | | | |
| Units: CAT Score | | | |
| arithmetic mean | 20.3 | | |
| standard deviation | ± 4.9 | ± | ± |
| FEV1 (L) | | | |
| Units: litre(s) | | | |
| arithmetic mean | 1.08 | | |
| standard deviation | ± 0.57 | ± | ± |
| FEV1 (%) | | | |
| Units: percent | | | |
| arithmetic mean | 40.4 | | |
| standard deviation | ± 21.0 | ± | ± |
| FVC (L) | | | |
| Units: litre(s) | | | |
| arithmetic mean | 2.45 | | |
| standard deviation | ± 0.83 | ± | ± |
| FVC (%) | | | |
| Units: percent | | | |
| arithmetic mean | 80.5 | | |

| | | | |
|--|--------|---|---|
| standard deviation | ± 20.2 | ± | ± |
| FEV1/FEVC ratio | | | |
| Units: percent | | | |
| arithmetic mean | 43.5 | | |
| standard deviation | ± 14.1 | ± | ± |
| FEF 25-75% | | | |
| Units: percent | | | |
| arithmetic mean | 18.9 | | |
| standard deviation | ± 2.40 | ± | ± |
| Oxygen saturation at rest | | | |
| Units: percent | | | |
| arithmetic mean | 94.3 | | |
| standard deviation | ± 2.9 | ± | ± |
| Number of exacerbations in the last year | | | |
| Units: exacerbations | | | |
| arithmetic mean | 2.40 | | |
| standard deviation | ± 2.0 | ± | ± |

End points

End points reporting groups

| | |
|--|-----------------------------------|
| Reporting group title | Symbicort 400/12 & Eklira Genuair |
| Reporting group description: Budesonide 400mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Budesonide & formoterol fumarate and Acclidinium bromide | |
| Reporting group title | Seretide 500/50 & Eklira Genuair |
| Reporting group description: Fluticasone propionate 500mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Fluticasone 500 & salmeterol and Acclidinium bromide | |
| Reporting group title | Seretide 250/50 & Eklira Genuair |
| Reporting group description: Fluticasone propionate 250mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Fluticasone 250 & salmeterol and Acclidinium bromide | |
| Reporting group title | Duaklir Genuair |
| Reporting group description: Acclidinium bromide 340mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder for 3 months Acclidinium bromide & formoterol fumarate | |
| Subject analysis set title | Arm 1: BF400 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Budesonide & formoterol fumarate and Acclidinium bromide | |
| Subject analysis set title | Arm 2: FS500 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Fluticasone 500 & salmeterol and Acclidinium bromide | |
| Subject analysis set title | Arm 3: FS250 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Fluticasone 250 & salmeterol and Acclidinium bromide | |
| Subject analysis set title | Arm 4: AF |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Acclidinium bromide & formoterol fumarate | |
| Subject analysis set title | Pooled Fluticasone propionate ICS |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Pooled Arms 2 and Arm 3 Fluticasone propionate 250mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Fluticasone 250 & salmeterol and Acclidinium bromide Fluticasone propionate 500mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Fluticasone 500 & salmeterol and Acclidinium bromide | |
| Subject analysis set title | Pooled ICS |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Pooled ICS treatments: Budesonide 400mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months. Budesonide & formoterol fumarate and Acclidinium bromide Fluticasone propionate 500mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months. Fluticasone 500 & salmeterol and Acclidinium bromide Fluticasone propionate 250mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Acclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months. Fluticasone 250 & salmeterol and Acclidinium bromide

Primary: Change in Bacterial Load of Total Respiratory Pathogens in Oropharyngeal Samples FS500 vs BF400

| | |
|-----------------|---|
| End point title | Change in Bacterial Load of Total Respiratory Pathogens in Oropharyngeal Samples FS500 vs BF400 |
|-----------------|---|

End point description:

To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs budesonide/formoterol 400/12 mcg on upper airway bacterial load from oropharyngeal swabs.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Month 1 to month 3

| End point values | Arm 1: BF400 | Arm 2: FS500 | | |
|---|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 16 | 12 | | |
| Units: cfu/g equivalents | | | | |
| arithmetic mean (confidence interval 95%) | 8.88 (8.46 to 9.30) | 8.89 (8.34 to 9.44) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Change in Bacterial Load FS500 vs BF400 |
|-----------------------------------|---|

Statistical analysis description:

Change in Bacterial Load of Total Respiratory Pathogens in Oropharyngeal Samples FS500 vs BF400

| | |
|---|--------------------------------|
| Comparison groups | Arm 1: BF400 v Arm 2: FS500 |
| Number of subjects included in analysis | 28 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5666 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.26 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.648 |
| upper limit | 1.176 |

Secondary: Change in Bacterial Load of Total Respiratory Pathogens in Sputum Samples FS500 vs BF400

| | |
|---|--|
| End point title | Change in Bacterial Load of Total Respiratory Pathogens in Sputum Samples FS500 vs BF400 |
| End point description: To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs budesonide/formoterol 400/12 mcg on lower airway bacterial load from sputum | |
| End point type | Secondary |
| End point timeframe: Month 1 to month 3 | |

| End point values | Arm 1: BF400 | Arm 2: FS500 | | |
|---|------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 11 | | |
| Units: cfu/g equivalent units | | | | |
| arithmetic mean (confidence interval 95%) | 9.87 (9.447 to 10.300) | 10.44 (10.049 to 10.822) | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Change in Sput BL BF400 vs FS500 |
| Statistical analysis description: Change in Bacterial Load of Total Respiratory Pathogens in Sputum Samples FS500 vs BF400 | |
| Comparison groups | Arm 1: BF400 v Arm 2: FS500 |
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.00037 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.867 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.292 |
| upper limit | 1.442 |

Secondary: Change in Bacterial Load of Total Respiratory Pathogens in Nasopharyngeal Samples FS500 vs BF400

| | |
|--|--|
| End point title | Change in Bacterial Load of Total Respiratory Pathogens in Nasopharyngeal Samples FS500 vs BF400 |
| End point description: To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs budesonide/formoterol 400/12 mcg on bacterial load from nasopharyngeal swabs | |
| End point type | Secondary |
| End point timeframe: Month 1 to month 3 | |

| | | | | |
|---|-----------------------|----------------------|--|--|
| End point values | Arm 1: BF400 | Arm 2: FS500 | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 16 | 13 | | |
| Units: CFU/g equivalent units | | | | |
| arithmetic mean (confidence interval 95%) | 6.96 (6.556 to 7.361) | 6.9 (6.461 to 7.339) | | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Change in NP BL BF400 vs FS500 |
| Statistical analysis description: Change in Bacterial Load of Total Respiratory Pathogens in Nasopharyngeal Samples FS500 vs BF400 | |
| Comparison groups | Arm 1: BF400 v Arm 2: FS500 |
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5793 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.222 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.016 |
| upper limit | 0.572 |

Secondary: Change in the Microbiome by Alpha-diversity in Sputum Samples FS500 vs BF400

| | |
|-----------------|--|
| End point title | Change in the Microbiome by Alpha-diversity in Sputum Samples FS500 vs BF400 |
|-----------------|--|

| | |
|---|-----------|
| End point description: | |
| Treatment period, month 1 to month 3 | |
| End point type | Secondary |
| End point timeframe: | |
| To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs budesonide/formoterol 400/12 mcg on the microbiome by alpha-diversity from sputum | |

| End point values | Arm 1: BF400 | Arm 2: FS500 | | |
|---|-----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 11 | | |
| Units: Shannon Weiner diversity index | | | | |
| arithmetic mean (confidence interval 95%) | 1.62 (1.288 to 1.954) | 1.58 (1.389 to 1.772) | | |

Statistical analyses

| Statistical analysis title | Change in SWDI FS500 vs BF400 |
|--|--------------------------------|
| Statistical analysis description: | |
| Change in the Microbiome by Alpha-diversity in Sputum Samples FS500 vs BF400 | |
| Comparison groups | Arm 2: FS500 v Arm 1: BF400 |
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7904 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.055 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.463 |
| upper limit | 0.353 |

Secondary: Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS500 vs BF400

| | |
|---|--|
| End point title | Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS500 vs BF400 |
| End point description: | |
| To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs budesonide/formoterol 400/12 mcg on the microbiome by alpha-diversity from nasopharyngeal swabs | |
| End point type | Secondary |
| End point timeframe: | |
| Treatment period, month 1 to 3 | |

| | | | | |
|---|-----------------------|-----------------------|--|--|
| End point values | Arm 1: BF400 | Arm 2: FS500 | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 16 | 13 | | |
| Units: Shannon Weiner diversity index | | | | |
| arithmetic mean (confidence interval 95%) | 1.46 (1.166 to 1.751) | 1.18 (0.789 to 1.563) | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Change in SWDI NP FS500 vs BF400 |
| Statistical analysis description: Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS500 vs BF400 | |
| Comparison groups | Arm 1: BF400 v Arm 2: FS500 |
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.324 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.231 |
| upper limit | 0.692 |

Secondary: Change in Total Bacterial Load FS250 vs BF400 in Sputum

| | |
|---|---|
| End point title | Change in Total Bacterial Load FS250 vs BF400 in Sputum |
| End point description: To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 250/50 mcg vs budesonide/formoterol 400/12 mcg on lower airway bacterial load from sputum | |
| End point type | Secondary |
| End point timeframe: Treatment period, months 1 to 3 | |

| End point values | Arm 1: BF400 | Arm 3: FS250 | | |
|---|------------------------|-------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 14 | | |
| Units: CFU/g equivalent units | | | | |
| arithmetic mean (confidence interval 95%) | 9.87 (9.447 to 10.300) | 10.35 (9.897 to 10.798) | | |

Statistical analyses

| Statistical analysis title | Change in BL Sput FS250 vs BF400 |
|--|----------------------------------|
| Statistical analysis description: Change in Total Bacterial Load FS250 vs BF400 in Sputum | |
| Comparison groups | Arm 1: BF400 v Arm 3: FS250 |
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3635 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.286 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.337 |
| upper limit | 0.909 |

Secondary: Change in Total Bacterial Load FS250 vs BF400 in Oropharyngeal Samples

| End point title | Change in Total Bacterial Load FS250 vs BF400 in Oropharyngeal Samples |
|--|--|
| End point description: To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 250/50 mcg vs budesonide/formoterol 400/12 mcg on lower airway bacterial load from oropharyngeal samples | |
| End point type | Secondary |
| End point timeframe: Treatment period, months 1 to 3 | |

| End point values | Arm 1: BF400 | Arm 3: FS250 | | |
|---|-----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 16 | 14 | | |
| Units: CFU/g equivalent units | | | | |
| arithmetic mean (confidence interval 95%) | 8.88 (8.462 to 9.298) | 8.08 (7.529 to 8.636) | | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Change in BL OP FS250 vs BF400 |
| Statistical analysis description: Change in Total Bacterial Load FS250 vs BF400 in Oropharyngeal Samples | |
| Comparison groups | Arm 1: BF400 v Arm 3: FS250 |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1007 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.863 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.897 |
| upper limit | 0.171 |

Secondary: Change in Total Bacterial Load FS250 vs BF400 in Nasopharyngeal Samples

| | |
|---|---|
| End point title | Change in Total Bacterial Load FS250 vs BF400 in Nasopharyngeal Samples |
| End point description: To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 250/50 mcg vs budesonide/formoterol 400/12 mcg on lower airway bacterial load from nasopharyngeal samples | |
| End point type | Secondary |
| End point timeframe: Treatment period, months 1 to 3 | |

| | | | | |
|---|-----------------------|-----------------------|--|--|
| End point values | Arm 1: BF400 | Arm 3: FS250 | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 16 | 14 | | |
| Units: CFU/g equivalent units | | | | |
| arithmetic mean (confidence interval 95%) | 6.96 (6.556 to 7.361) | 6.89 (6.306 to 7.479) | | |

Statistical analyses

| | |
|--|--------------------------------|
| Statistical analysis title | Change in BL NP FS250 vs BF400 |
| Statistical analysis description: Change in Total Bacterial Load FS250 vs BF400 in Nasopharyngeal Samples | |
| Comparison groups | Arm 1: BF400 v Arm 3: FS250 |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8345 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.122 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.032 |
| upper limit | 1.276 |

Secondary: Change in the Microbiome by Alpha-diversity in Sputum Samples FS250 vs BF400

| | |
|---|--|
| End point title | Change in the Microbiome by Alpha-diversity in Sputum Samples FS250 vs BF400 |
| End point description: To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 250/50 mcg vs budesonide/ formoterol 400/12 mcg on the microbiome by alpha-diversity from sputum | |
| End point type | Secondary |
| End point timeframe: Treatment period, months 1 to 3 | |

| | | | | |
|---|-----------------------|-----------------------|--|--|
| End point values | Arm 1: BF400 | Arm 3: FS250 | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 14 | | |
| Units: Shannon Weiner diversity index | | | | |
| arithmetic mean (confidence interval 95%) | 1.62 (1.288 to 1.954) | 1.56 (1.298 to 1.831) | | |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Change in SWD Sputum FS250 vs BF400 |
| Statistical analysis description: Change in the Microbiome by Alpha-diversity in Sputum Samples FS250 vs BF400 | |
| Comparison groups | Arm 1: BF400 v Arm 3: FS250 |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8015 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.052 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.466 |
| upper limit | 0.361 |

Secondary: Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS250 vs BF400

| | |
|---------------------------------|--|
| End point title | Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS250 vs BF400 |
| End point description: | To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 250/50 mcg vs budesonide/formoterol 400/12 mcg on the microbiome by alpha-diversity from oropharyngeal samples |
| End point type | Secondary |
| End point timeframe: | |
| Treatment period, months 1 to 3 | |

| | | | | |
|---|-----------------------|----------------------|--|--|
| End point values | Arm 1: BF400 | Arm 3: FS250 | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 16 | 14 | | |
| Units: Shannon Weiner Diversity Index | | | | |
| arithmetic mean (confidence interval 95%) | 1.69 (1.413 to 1.975) | 1.28 (0.9 to 1.662) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change in SWDI OP FS250 vs BF400 |
| Statistical analysis description: | Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS250 vs BF400 |
| Comparison groups | Arm 1: BF400 v Arm 3: FS250 |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.015 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.51 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.825 |
| upper limit | -0.194 |

Secondary: Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS250 vs BF400

| | |
|---|--|
| End point title | Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS250 vs BF400 |
| End point description: To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 250/50 mcg vs budesonide/formoterol 400/12 mcg on the microbiome by alpha-diversity from nasopharyngeal samples | |
| End point type | Secondary |
| End point timeframe: Treatment period, months 1 to 3 | |

| End point values | Arm 1: BF400 | Arm 3: FS250 | | |
|---|-----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 16 | 14 | | |
| Units: Shannon Weiner diversity index | | | | |
| arithmetic mean (confidence interval 95%) | 1.46 (1.166 to 1.751) | 1.33 (0.962 to 1.701) | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Change in SWDI NP FS250 vs BF400 |
| Statistical analysis description: Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS250 vs BF400 | |
| Comparison groups | Arm 1: BF400 v Arm 3: FS250 |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.913 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.026 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.506 |
| upper limit | 0.453 |

Secondary: Change in the Microbiome by Alpha-diversity in Sputum Samples FS ICS vs LABA/LAMA

| | |
|-----------------|---|
| End point title | Change in the Microbiome by Alpha-diversity in Sputum Samples FS ICS vs LABA/LAMA |
|-----------------|---|

End point description:

To compare the effects on the lower airway microbiome in sputum of inhaled corticosteroids fluticasone propionate compared to a dual bronchodilator-based regime without ICS

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Treatment period, months 1 to 3

| End point values | Arm 4: AF | Pooled Fluticasone propionate ICS | | |
|---|-----------------------|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 25 | | |
| Units: Shannon Weiner diversity index | | | | |
| arithmetic mean (confidence interval 95%) | 1.27 (0.897 to 1.650) | 1.57 (1.412 to 1.731) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Change in alpha-diversity in sput FS ICS vs LB/LM |
|-----------------------------------|---|

Statistical analysis description:

Change in the Microbiome by Alpha-diversity in Sputum Samples FS ICS vs LABA/LAMA

| | |
|-------------------|---|
| Comparison groups | Arm 4: AF v Pooled Fluticasone propionate ICS |
|-------------------|---|

| | |
|---|----|
| Number of subjects included in analysis | 39 |
|---|----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

| | |
|---------|----------|
| P-value | = 0.7553 |
|---------|----------|

| | |
|--------|-----------------------|
| Method | Mixed models analysis |
|--------|-----------------------|

| | |
|--------------------|--------------------------------|
| Parameter estimate | Mean difference (final values) |
|--------------------|--------------------------------|

| | |
|----------------|--------|
| Point estimate | -0.047 |
|----------------|--------|

Confidence interval

| | |
|-------|------|
| level | 95 % |
|-------|------|

| | |
|-------|---------|
| sides | 2-sided |
|-------|---------|

| | |
|-------------|--------|
| lower limit | -0.342 |
|-------------|--------|

| | |
|-------------|-------|
| upper limit | 0.249 |
|-------------|-------|

Secondary: Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS ICS vs LABA/LAMA

| | |
|---|--|
| End point title | Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS ICS vs LABA/LAMA |
| End point description: To compare the effects on the upper airway microbiome in oropharyngeal samples of inhaled corticosteroids fluticasone propionate compared to a dual bronchodilator-based regime without ICS | |
| End point type | Secondary |
| End point timeframe: Treatment period, months 1-3 | |

| End point values | Arm 4: AF | Pooled Fluticasone propionate ICS | | |
|---|-----------------------|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 13 | 26 | | |
| Units: Shannon Weiner diversity index | | | | |
| arithmetic mean (confidence interval 95%) | 1.32 (1.032 to 1.604) | 1.43 (1.207 to 1.646) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change in microbiome OP FS ICS vs LABA/LAMA |
| Statistical analysis description: Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS ICS vs LABA/LAMA | |
| Comparison groups | Pooled Fluticasone propionate ICS v Arm 4: AF |
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5283 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.109 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.45 |
| upper limit | 0.232 |

Secondary: Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS ICS vs LABA/LAMA

| | |
|--|---|
| End point title | Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS ICS vs LABA/LAMA |
| End point description: To compare the effects on the upper airway microbiome in nasopharyngeal samples of inhaled corticosteroids fluticasone propionate compared to a dual bronchodilator-based regime without ICS | |
| End point type | Secondary |

End point timeframe:

Treatment period, months 1-3

| End point values | Arm 4: AF | Pooled Fluticasone propionate ICS | | |
|---|-----------------------|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 27 | | |
| Units: Shannon Weiner diversity index | | | | |
| arithmetic mean (confidence interval 95%) | 1.47 (1.174 to 1.766) | 1.26 (1.006 to 1.507) | | |

Statistical analyses

| Statistical analysis title | Change in microbiome NP FS ICS vs LABA/LAMA |
|---|---|
| Comparison groups | Arm 4: AF v Pooled Fluticasone propionate ICS |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8247 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.108 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.859 |
| upper limit | 1.075 |

Secondary: Change in the Microbiome by Alpha-diversity in Sputum Samples BF ICS vs LABA/LAMA

| | |
|---------------------------------|--|
| End point title | Change in the Microbiome by Alpha-diversity in Sputum Samples BF ICS vs LABA/LAMA |
| End point description: | To compare the effects on the lower airway microbiome in sputum of inhaled corticosteroids budesonide compared to a dual bronchodilator-based regime without ICS |
| End point type | Secondary |
| End point timeframe: | |
| Treatment period, months 1 to 3 | |

| End point values | Arm 1: BF400 | Arm 4: AF | | |
|---|-----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 14 | | |
| Units: Shannon Weiner diversity index | | | | |
| arithmetic mean (confidence interval 95%) | 1.62 (1.288 to 1.954) | 1.27 (0.897 to 1.650) | | |

Statistical analyses

| Statistical analysis title | Change in microbiome Sput BF vs LABA/LAMA |
|---|---|
| Comparison groups | Arm 1: BF400 v Arm 4: AF |
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9556 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.141 |
| upper limit | 1.079 |

Secondary: Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples BF ICS vs LABA/LAMA

| | |
|---|--|
| End point title | Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples BF ICS vs LABA/LAMA |
| End point description: | |
| To compare the effects on the upper airway microbiome in oropharyngeal swabs of inhaled corticosteroids budesonide compared to a dual bronchodilator-based regime without ICS | |
| End point type | Secondary |
| End point timeframe: | |
| Treatment period, months 1 to 3 | |

| End point values | Arm 1: BF400 | Arm 4: AF | | |
|---|-----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 16 | 13 | | |
| Units: Shannon Weiner diversity index | | | | |
| arithmetic mean (confidence interval 95%) | 1.69 (1.413 to 1.975) | 1.32 (1.032 to 1.604) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change in microbiome OP BF vs LABA/LAMA |
| Comparison groups | Arm 1: BF400 v Arm 4: AF |
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1264 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.257 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.587 |
| upper limit | 0.074 |

Secondary: Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples BF ICS vs LABA/LAMA

| | |
|--|---|
| End point title | Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples BF ICS vs LABA/LAMA |
| End point description: | |
| To compare the effects on the upper airway microbiome in nasopharyngeal swabs of inhaled corticosteroids budesonide compared to a dual bronchodilator-based regime without ICS | |
| End point type | Secondary |
| End point timeframe: | |
| Treatment period, months 1 to 3 | |

| | | | | |
|---|-----------------------|-----------------------|--|--|
| End point values | Arm 1: BF400 | Arm 4: AF | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 16 | 14 | | |
| Units: Shannon Weiner diversity index | | | | |
| arithmetic mean (confidence interval 95%) | 1.46 (1.166 to 1.751) | 1.47 (1.174 to 1.766) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Change in microbiome NP BF vs LABA/LAMA |
| Comparison groups | Arm 1: BF400 v Arm 4: AF |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9367 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.028 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.724 |
| upper limit | 0.668 |

Secondary: Change in Total Bacterial Load FS500 vs FS250 in Sputum Samples

| | |
|---|---|
| End point title | Change in Total Bacterial Load FS500 vs FS250 in Sputum Samples |
| End point description: | |
| To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs fluticasone propionate/salmeterol 250/50 mcg on lower airway bacterial load in sputum samples | |
| End point type | Secondary |
| End point timeframe: | |
| Treatment period, months 1 to 3 | |

| End point values | Arm 2: FS500 | Arm 3: FS250 | | |
|---|--------------------------|-------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 11 | 14 | | |
| Units: CFU/g equivalent units | | | | |
| arithmetic mean (confidence interval 95%) | 10.44 (10.049 to 10.822) | 10.35 (9.897 to 10.798) | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Change in BL Sput FS500 vs FS250 |
| Comparison groups | Arm 3: FS250 v Arm 2: FS500 |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0712 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.626 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.307 |
| upper limit | 0.055 |

Secondary: Change in Total Bacterial Load FS500 vs FS250 in Oropharyngeal Swab Samples

| | |
|---|---|
| End point title | Change in Total Bacterial Load FS500 vs FS250 in Oropharyngeal Swab Samples |
| End point description: To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs fluticasone propionate/salmeterol 250/50 mcg on upper airway in oropharyngeal samples | |
| End point type | Secondary |
| End point timeframe: Treatment period, months 1 to 3 | |

| End point values | Arm 2: FS500 | Arm 3: FS250 | | |
|---|-----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 14 | | |
| Units: CFU/g equivalent units | | | | |
| arithmetic mean (confidence interval 95%) | 8.89 (8.337 to 9.438) | 8.08 (7.529 to 8.636) | | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Change in BL OP FS500 vs FS250 |
| Comparison groups | Arm 2: FS500 v Arm 3: FS250 |
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1279 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.114 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.556 |
| upper limit | 0.328 |

Secondary: Change in Total Bacterial Load FS500 vs FS250 in Nasopharyngeal Swab Samples

| | |
|--|--|
| End point title | Change in Total Bacterial Load FS500 vs FS250 in Nasopharyngeal Swab Samples |
| End point description: To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs fluticasone propionate/salmeterol 250/50 mcg on upper airway in nasopharyngeal samples | |
| End point type | Secondary |
| End point timeframe: Treatment period, months 1 to 3 | |

| End point values | Arm 2: FS500 | Arm 3: FS250 | | |
|---|----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 13 | 14 | | |
| Units: CFU/g equivalent units | | | | |
| arithmetic mean (confidence interval 95%) | 6.9 (6.461 to 7.339) | 6.89 (6.306 to 7.479) | | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Change in BL NP FS250 vs BF400 |
| Comparison groups | Arm 2: FS500 v Arm 3: FS250 |
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7561 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.335 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.807 |
| upper limit | 2.477 |

Secondary: Change in the Microbiome by Alpha-diversity in Sputum Samples FS500 vs FS250

| | |
|---|--|
| End point title | Change in the Microbiome by Alpha-diversity in Sputum Samples FS500 vs FS250 |
| End point description: To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs fluticasone propionate/salmeterol 250/50 mcg on the microbiome by alpha-diversity from sputum | |
| End point type | Secondary |

End point timeframe:

Treatment period, months 1 to 3

| | | | | |
|---|-----------------------|-----------------------|--|--|
| End point values | Arm 2: FS500 | Arm 3: FS250 | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 11 | 14 | | |
| Units: Shannon Weiner diversity index | | | | |
| arithmetic mean (confidence interval 95%) | 1.58 (1.389 to 1.772) | 1.56 (1.298 to 1.831) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Change in microbiome Sput FS500 vs FS250 |
| Comparison groups | Arm 2: FS500 v Arm 3: FS250 |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8517 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.341 |
| upper limit | 0.282 |

Secondary: Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS500 vs FS250

| | |
|--|---|
| End point title | Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS500 vs FS250 |
| End point description: | |
| To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs fluticasone propionate/salmeterol 250/50 mcg on the microbiome by alpha-diversity from oropharyngeal samples | |
| End point type | Secondary |
| End point timeframe: | |
| Treatment period, months 1 to 3 | |

| End point values | Arm 2: FS500 | Arm 3: FS250 | | |
|---|----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 14 | | |
| Units: Shannon Weiner diversity index | | | | |
| arithmetic mean (confidence interval 95%) | 1.6 (1.398 to 1.794) | 1.28 (0.900 to 1.662) | | |

Statistical analyses

| Statistical analysis title | Change in alpha-diversity in OP FS500 vs FS250 |
|--|--|
| Statistical analysis description: Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS500 vs FS250 | |
| Comparison groups | Arm 2: FS500 v Arm 3: FS250 |
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0688 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.333 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.693 |
| upper limit | 0.026 |

Secondary: Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS500 vs FS250

| End point title | Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS500 vs FS250 |
|---|--|
| End point description: To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs fluticasone propionate/salmeterol 250/50 mcg on the microbiome by alpha-diversity from nasopharyngeal samples | |
| End point type | Secondary |
| End point timeframe: Treatment period, months 1 to 3 | |

| End point values | Arm 2: FS500 | Arm 3: FS250 | | |
|---|-----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 13 | 14 | | |
| Units: Shannon Weiner diversity index | | | | |
| arithmetic mean (confidence interval 95%) | 1.18 (0.789 to 1.563) | 1.33 (0.962 to 1.701) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Change in alpha-diversity in NP FS500 vs FS250 |
| Comparison groups | Arm 2: FS500 v Arm 3: FS250 |
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3262 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.755 |
| upper limit | 0.254 |

Secondary: Change in Total Bacterial Load in Pooled ICS vs LABA/LAMA in Sputum Samples

| | |
|---|---|
| End point title | Change in Total Bacterial Load in Pooled ICS vs LABA/LAMA in Sputum Samples |
| End point description: | |
| To determine the combined impact of inhaled corticosteroids on bacterial load in upper and lower airway using sputum samples compared to dual bronchodilator regime | |
| End point type | Secondary |
| End point timeframe: | |
| Treatment period, months 1 to 3 | |

| | | | | |
|---|------------------------|-------------------------|--|--|
| End point values | Arm 4: AF | Pooled ICS | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 40 | | |
| Units: CFU/g equivalent units | | | | |
| arithmetic mean (confidence interval 95%) | 9.73 (9.352 to 10.116) | 10.19 (9.953 to 10.434) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Change in BL Sput All ICS vs LABA/LAMA |
| Comparison groups | Pooled ICS v Arm 4: AF |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1455 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.424 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.148 |
| upper limit | 0.996 |

Secondary: Change in Total Bacterial Load in Pooled ICS vs LABA/LAMA in Oropharyngeal Swab Samples

| | |
|---------------------------------|---|
| End point title | Change in Total Bacterial Load in Pooled ICS vs LABA/LAMA in Oropharyngeal Swab Samples |
| End point description: | To determine the combined impact of inhaled corticosteroids on bacterial load in upper and lower airway using oropharyngeal swab samples compared to dual bronchodilator regime |
| End point type | Secondary |
| End point timeframe: | |
| Treatment period, months 1 to 3 | |

| | | | | |
|---|-----------------------|-----------------------|--|--|
| End point values | Arm 4: AF | Pooled ICS | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 13 | 42 | | |
| Units: CFU/g equivalent units | | | | |
| arithmetic mean (confidence interval 95%) | 8.53 (7.762 to 9.294) | 8.62 (8.327 to 8.906) | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | Change in BL OP All ICS vs LABA/LAMA |
| Comparison groups | Arm 4: AF v Pooled ICS |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.607 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.205 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.581 |
| upper limit | 0.991 |

Secondary: Change in Total Bacterial Load in Pooled ICS vs LABA/LAMA in Nasopharyngeal Swab Samples

| | |
|--|--|
| End point title | Change in Total Bacterial Load in Pooled ICS vs LABA/LAMA in Nasopharyngeal Swab Samples |
| End point description: To determine the combined impact of inhaled corticosteroids on bacterial load in upper and lower airway using nasopharyngeal swab samples compared to dual bronchodilator regime | |
| End point type | Secondary |
| End point timeframe: Treatment period, months 1 to 3 | |

| End point values | Arm 4: AF | Pooled ICS | | |
|---|-----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 43 | | |
| Units: CFU/g equivalent units | | | | |
| arithmetic mean (confidence interval 95%) | 7.27 (6.695 to 7.836) | 6.92 (6.667 to 7.172) | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | Change in BL NP All ICS vs LABA/LAMA |
| Comparison groups | Arm 4: AF v Pooled ICS |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.463 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.359 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.322 |
| upper limit | 0.605 |

Secondary: Change in Microbiome by Alpha-diversity in Pooled ICS vs LABA/LAMA in Sputum Samples

| | |
|---|--|
| End point title | Change in Microbiome by Alpha-diversity in Pooled ICS vs LABA/LAMA in Sputum Samples |
| End point description: To determine the effects of inhaled corticosteroids vs LABA/LAMA on the microbiome by alpha-diversity in sputum samples | |
| End point type | Secondary |
| End point timeframe: Treatment period, months 1-3 | |

| End point values | Arm 4: AF | Pooled ICS | | |
|---|-----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 40 | | |
| Units: Shannon Weiner diversity index | | | | |
| arithmetic mean (confidence interval 95%) | 1.27 (0.897 to 1.650) | 1.59 (1.439 to 1.741) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change in alpha-diversity Sput All ICS vs LB/LM |
| Comparison groups | Arm 4: AF v Pooled ICS |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8915 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.022 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.338 |
| upper limit | 0.294 |

Secondary: Change in Microbiome by Alpha-diversity in Pooled ICS vs LABA/LAMA in Oropharyngeal Swab Samples

| | |
|---|--|
| End point title | Change in Microbiome by Alpha-diversity in Pooled ICS vs LABA/LAMA in Oropharyngeal Swab Samples |
| End point description: To determine the effects of inhaled corticosteroids vs LABA/LAMA on the microbiome by alpha-diversity in oropharyngeal swab samples | |
| End point type | Secondary |

End point timeframe:

Treatment period, months 1 to 3

| End point values | Arm 4: AF | Pooled ICS | | |
|---|-----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 13 | 42 | | |
| Units: Shannon Weiner diversity index | | | | |
| arithmetic mean (confidence interval 95%) | 1.32 (1.032 to 1.604) | 1.53 (1.358 to 1.699) | | |

Statistical analyses

| Statistical analysis title | Change in alpha-diversity in OP ICS vs LABA/LAMA |
|---|--|
| Comparison groups | Arm 4: AF v Pooled ICS |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.846 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.273 |
| upper limit | 0.332 |

Secondary: Change in Microbiome by Alpha-diversity in Pooled ICS vs LABA/LAMA in Nasopharyngeal Swab Samples

| | |
|-----------------|---|
| End point title | Change in Microbiome by Alpha-diversity in Pooled ICS vs LABA/LAMA in Nasopharyngeal Swab Samples |
|-----------------|---|

End point description:

To determine the effects of inhaled corticosteroids vs LABA/LAMA on the microbiome by alpha-diversity in nasopharyngeal swab samples

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Treatment period, months 1 to 3

| End point values | Arm 4: AF | Pooled ICS | | |
|---|-----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 43 | | |
| Units: Shannon weiner diversity index | | | | |
| arithmetic mean (confidence interval 95%) | 1.47 (1.174 to 1.766) | 1.33 (1.146 to 1.518) | | |

Statistical analyses

| Statistical analysis title | Change in alpha-diversity NP All ICS vs LABA/LAMA |
|---|---|
| Comparison groups | Arm 4: AF v Pooled ICS |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.798 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.073 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.487 |
| upper limit | 0.632 |

Secondary: Change in Airway MPO for ICS vs LABA/LAMA in Sputum Samples

| | |
|---------------------------------|---|
| End point title | Change in Airway MPO for ICS vs LABA/LAMA in Sputum Samples |
| End point description: | To evaluate the impact of inhaled corticosteroids on airway myeloperoxidase compared to LABA/LAMA |
| End point type | Secondary |
| End point timeframe: | |
| Treatment period, months 1 to 3 | |

| End point values | Arm 4: AF | Pooled ICS | | |
|---|-----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 38 | | |
| Units: Units/mL | | | | |
| arithmetic mean (confidence interval 95%) | 0.53 (0.078 to 0.988) | 0.49 (0.291 to 0.695) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change in Sput MPO for ICS vs LABA/LAMA |
| Comparison groups | Arm 4: AF v Pooled ICS |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0376 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.034 |
| upper limit | 1.105 |

Secondary: Change in Airway Neutrophil Elastase for ICS vs LABA/LAMA in Sputum Samples

| | |
|---------------------------------|---|
| End point title | Change in Airway Neutrophil Elastase for ICS vs LABA/LAMA in Sputum Samples |
| End point description: | To evaluate the impact of inhaled corticosteroids on airway neutrophil elastase compared to LABA/LAMA |
| End point type | Secondary |
| End point timeframe: | |
| Treatment period. months 1 to 3 | |

| | | | | |
|---|------------------------|------------------------|--|--|
| End point values | Arm 4: AF | Pooled ICS | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 38 | | |
| Units: Units/mL | | | | |
| arithmetic mean (confidence interval 95%) | 0.03 (-0.017 to 0.081) | 0.70 (-0.565 to 1.973) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Change in Sput NE for ICS vs LABA/LAMA |
| Comparison groups | Arm 4: AF v Pooled ICS |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.897 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.307 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.84 |
| upper limit | 3.454 |

Secondary: Change in Resistin for ICS vs LABA/LAMA in Whole Blood

| | |
|---|--|
| End point title | Change in Resistin for ICS vs LABA/LAMA in Whole Blood |
| End point description: To evaluate the impact of inhaled corticosteroids on blood resistin compared to LABA/LAMA | |
| End point type | Secondary |
| End point timeframe: Treatment period, months 1 to 3 | |

| End point values | Arm 4: AF | Pooled ICS | | |
|---|--------------------------|------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 43 | | |
| Units: ng/mL | | | | |
| arithmetic mean (confidence interval 95%) | 15.08 (11.914 to 18.228) | 151.07 (-113.935 to 416.074) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change in blood resistin ICS vs LABA/LAMA |
| Comparison groups | Arm 4: AF v Pooled ICS |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3686 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.261 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.316 |
| upper limit | 0.837 |

Secondary: Change in Airway Resistin for ICS vs LABA/LAMA in Sputum Samples

| | |
|-----------------|--|
| End point title | Change in Airway Resistin for ICS vs LABA/LAMA in Sputum Samples |
|-----------------|--|

| | |
|--|-----------|
| End point description: | |
| To evaluate the impact of inhaled corticosteroids on airway resistin compared to LABA/LAMA | |
| End point type | Secondary |
| End point timeframe: | |
| Treatment period, months 1 to 3 | |

| End point values | Arm 4: AF | Pooled ICS | | |
|---|----------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 38 | | |
| Units: ng/mL | | | | |
| arithmetic mean (confidence interval 95%) | 132.83 (17.362 to 248.295) | 96.53 (30.625 to 162.426) | | |

Statistical analyses

| Statistical analysis title | Change in sput Resistin ICS vs LABA/LAMA |
|---|--|
| Comparison groups | Arm 4: AF v Pooled ICS |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8979 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.064 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.941 |
| upper limit | 1.07 |

Secondary: Change in Airway IL-8 for ICS vs LABA/LAMA in Sputum Samples

| | |
|--|--|
| End point title | Change in Airway IL-8 for ICS vs LABA/LAMA in Sputum Samples |
| End point description: | |
| To evaluate the impact of inhaled corticosteroids on airway IL-8 compared to LABA/LAMA | |
| End point type | Secondary |
| End point timeframe: | |
| Treatment window, months 1 to 3 | |

| End point values | Arm 4: AF | Pooled ICS | | |
|---|-----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 38 | | |
| Units: ng/mL | | | | |
| arithmetic mean (confidence interval 95%) | 1.20 (0.227 to 2.170) | 1.27 (0.572 to 1.977) | | |

Statistical analyses

| Statistical analysis title | Change in sput IL8 ICS vs LABA/LAMA |
|---|-------------------------------------|
| Comparison groups | Arm 4: AF v Pooled ICS |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1098 |
| Method | Mixed models analysis |
| Parameter estimate | Median difference (final values) |
| Point estimate | -1.024 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.287 |
| upper limit | 0.24 |

Secondary: Change in Airway IL1-beta for ICS vs LABA/LAMA in Sputum Samples

| | |
|------------------------|--|
| End point title | Change in Airway IL1-beta for ICS vs LABA/LAMA in Sputum Samples |
| End point description: | To evaluate the impact of inhaled corticosteroids on airway IL1-beta compared to LABA/LAMA |
| End point type | Secondary |
| End point timeframe: | Treatment period, months 1 to 3 |

| End point values | Arm 4: AF | Pooled ICS | | |
|---|-------------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 38 | | |
| Units: ug/mL | | | | |
| arithmetic mean (confidence interval 95%) | 9.57 (-8.659 to 27.803) | 5.86 (2.641 to 9.072) | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | Change in sput IL1b ICS vs LABA/LAMA |
| Comparison groups | Arm 4: AF v Pooled ICS |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3261 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.752 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.776 |
| upper limit | 2.28 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from screening to end of study

Adverse event reporting additional description:

Adverse events were assessed systematically, and defined using MedDRA dictionary

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 24 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Symbicort 400/12 & Eklira Genuair |
|-----------------------|-----------------------------------|

Reporting group description:

Budesonide 400mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder and Acridinium

bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months

Budesonide & formoterol fumarate and Acridinium bromide

| | |
|-----------------------|----------------------------------|
| Reporting group title | Seretide 500/50 & Eklira Genuair |
|-----------------------|----------------------------------|

Reporting group description:

Fluticasone propionate 500mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Acridinium

bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months

Fluticasone 500 & salmeterol and Acridinium bromide

| | |
|-----------------------|----------------------------------|
| Reporting group title | Seretide 250/50 & Eklira Genuair |
|-----------------------|----------------------------------|

Reporting group description:

Fluticasone propionate 250mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Acridinium

bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months

Fluticasone 250 & salmeterol and Acridinium bromide

| | |
|-----------------------|-----------------|
| Reporting group title | Duaklir Genuair |
|-----------------------|-----------------|

Reporting group description:

Acridinium bromide 340mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder for 3 months

Acridinium bromide & formoterol fumarate

| Serious adverse events | Symbicort 400/12 & Eklira Genuair | Seretide 500/50 & Eklira Genuair | Seretide 250/50 & Eklira Genuair |
|--|-----------------------------------|----------------------------------|----------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | 0 / 13 (0.00%) | 0 / 15 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Facial injury | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 0 / 13 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 13 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | 0 / 13 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|--|--|
| Serious adverse events | Duaklir Genuair | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| General disorders and administration site conditions | | | |
| Facial injury | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Symbicort 400/12 & Eklira Genuair | Seretide 500/50 & Eklira Genuair | Seretide 250/50 & Eklira Genuair |
|---|-----------------------------------|----------------------------------|----------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 18 (72.22%) | 13 / 13 (100.00%) | 12 / 15 (80.00%) |
| Investigations | | | |
| Investigations | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 0 / 13 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Cardiac disorders | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 0 / 13 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 13 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Neurological symptom | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 2 / 13 (15.38%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| General disorders and administration site conditions | | | |
| Oral and laryngeal symptoms | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | 2 / 13 (15.38%) | 4 / 15 (26.67%) |
| occurrences (all) | 2 | 2 | 7 |
| Other | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 2 / 13 (15.38%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 2 | 1 |
| Immune system disorders | | | |
| Allergy | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 1 / 13 (7.69%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 13 (7.69%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 8 / 18 (44.44%) | 4 / 13 (30.77%) | 4 / 15 (26.67%) |
| occurrences (all) | 9 | 4 | 4 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | 1 / 13 (7.69%) | 4 / 15 (26.67%) |
| occurrences (all) | 4 | 1 | 5 |
| Cough | | | |
| subjects affected / exposed | 5 / 18 (27.78%) | 0 / 13 (0.00%) | 2 / 15 (13.33%) |
| occurrences (all) | 6 | 0 | 2 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | 0 / 13 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 2 | 0 | 1 |
| Sputum increased | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 0 / 13 (0.00%) | 0 / 15 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 18 (22.22%) | 1 / 13 (7.69%) | 1 / 15 (6.67%) |
| occurrences (all) | 4 | 1 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Skin disorder | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 1 / 13 (7.69%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal and connective tissue disorders | | | |
| subjects affected / exposed | 4 / 18 (22.22%) | 4 / 13 (30.77%) | 3 / 15 (20.00%) |
| occurrences (all) | 4 | 5 | 3 |
| Infections and infestations | | | |
| General infections | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 4 / 13 (30.77%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |

| | | | |
|---|------------------|--|--|
| Non-serious adverse events | Duaklir Genuair | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 14 / 15 (93.33%) | | |
| Investigations | | | |
| Investigations | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | | |
| occurrences (all) | 2 | | |
| Cardiac disorders | | | |

| | | | |
|---|----------------------|--|--|
| Cardiac disorders subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Neurological symptom subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| General disorders and administration site conditions Oral and laryngeal symptoms subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | | |
| Other subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | | |
| Immune system disorders Allergy subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | | |
| Gastrointestinal disorders Gastrointestinal disorder subjects affected / exposed occurrences (all) | 3 / 15 (20.00%) 3 | | |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 7 / 15 (46.67%) 7 | | |
| Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) | 5 / 15 (33.33%) 8 | | |
| Cough subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Lower respiratory tract infection | | | |

| | | | |
|--|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 15 (13.33%) 2 | | |
| Sputum increased subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 15 (13.33%) 3 | | |
| Skin and subcutaneous tissue disorders Skin disorder subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | | |
| Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all) | 2 / 15 (13.33%) 3 | | |
| Infections and infestations General infections subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported