

**Clinical trial results:**

Randomized, double-blind, double-dummy, active-controlled, 4 period complete cross-over study to compare the effect on lung function of 6 weeks once daily treatment with orally inhaled Tiotropium+Olodaterol fixed dose combination delivered by the Respimat® inhaler vs. 6 weeks twice daily treatment with Fluticasone Propionate+Salmeterol fixed dose combination delivered by the Accuhaler® in patients with Chronic Obstructive Pulmonary Disease (COPD). [ENERGITO™]

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2013-000808-41 |
| Trial protocol | ES NL CZ BE DK SE HU DE |
| Global end of trial date | 04 February 2015 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 16 September 2016 |
| First version publication date | 01 July 2016 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set One value for endpoint "FEV1 AUC (12–24h) Change from Patient Baseline after 6 Weeks of Treatment" needs correction |

Trial information**Trial identification**

| | |
|-----------------------|---------|
| Sponsor protocol code | 1237.11 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01969721 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, 55216 |
| Public contact | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |

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 | 20 March 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 14 January 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 February 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The objective of the trial is to compare the lung function profile of once daily treatment with Tiotropium+Olodaterol (Tio+Olo) Fixed Dose Combination (FDC) [2.5/5µg and 5/5µg] delivered by the Respimat® with the lung function profile of twice daily treatment with Fluticasone propionate+Salmeterol (F+S) FDC [250/50µg and 500/50µg] delivered by the Accuhaler® after 6 weeks of treatment in patients with COPD.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator:

Placebo matching Tiotropium + Olodaterol inhalation solution via Respimat® inhaler inhaled orally. Fluticasone+Salmeterol FDC (inhalation powder) via Accuhaler® inhaled orally as 250 µg/50 µg or 500 µg/50 µg per inhalation, twice daily. Placebo matching Fluticasone+Salmeterol inhalation powder via Accuhaler® inhaled orally.

| | |
|---|-----------------|
| Actual start date of recruitment | 29 October 2013 |
| 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 | Belgium: 16 |
| Country: Number of subjects enrolled | Czech Republic: 39 |
| Country: Number of subjects enrolled | Germany: 54 |
| Country: Number of subjects enrolled | Denmark: 23 |
| Country: Number of subjects enrolled | Spain: 23 |
| Country: Number of subjects enrolled | Hungary: 36 |
| Country: Number of subjects enrolled | Netherlands: 78 |
| Country: Number of subjects enrolled | Sweden: 19 |
| Worldwide total number of subjects | 288 |
| EEA total number of subjects | 288 |

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) | 159 |
| From 65 to 84 years | 129 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This was a randomized, double-blind, double-dummy, active-controlled, 4-treatment, 4-period, complete cross-over design. The treatments were A: T+O 2.5/5; B: T+O 5/5; C: F+S 250/50; D: F+S 500/50. ABCD, BDAC, CADB, and DCBA were four treatment sequences.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in trial. Subjects attended specialist sites to ensure that they met all implemented inclusion/exclusion criteria. Subjects were not randomised to trial drug if any of the specific entry criteria was violated. In this study, 288 subjects were enrolled.

Period 1

| | |
|------------------------------|-------------------------------------|
| Period 1 title | Overall trial by sequence |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Data analyst |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | T+O 2.5/5 / T+O 5/5 / F+S 250/50 / F+S 500/50 |

Arm description:

Tiotropium+Olodaterol (T+O) FDC (2.5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching Fluticasone propionate+Salmeterol (F+S) FDC inhalation powder via Accuhaler® twice daily in period 1, followed with T+O FDC (5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 2, followed with F+S FDC (250 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 3, then followed with F+S FDC (500 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 4. Each treatment period was 6 weeks (wks) and washing-out period 3 wks. Treatment sequence was 33 wks including 4 treatment periods and 3 washing-out periods.

| | |
|--|---|
| Arm type | Treatment sequence |
| Investigational medicinal product name | Tiotropium 2.5 µg / Olodaterol 5 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Tiotropium+Olodaterol (2.5/5 µg) FDC inhalation solution was administered via the Respimat® inhaler once daily.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Tiotropium 5 µg / Olodaterol 5 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Tiotropium+Olodaterol (5/5 µg) FDC inhalation solution was administered via the Respimat® inhaler once daily.

| | |
|--|--|
| Investigational medicinal product name | Fluticasone propionate 250 µg / Salmeterol 50 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |

| | |
|--|--|
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Fluticasone propionate+Salmeterol (250/50 µg) FDC inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. | |
| Investigational medicinal product name | Fluticasone propionate 500 µg / Salmeterol 50 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Fluticasone propionate+Salmeterol (500/50 µg) FDC inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. | |
| Investigational medicinal product name | Placebo matching Tiotropium / Olodaterol_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Tiotropium+Olodaterol placebo inhalation solution was administered via the Respimat® inhaler once daily. | |
| Investigational medicinal product name | Placebo matching Fluticasone propionate / Salmeterol_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Fluticasone propionate+Salmeterol placebo inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. | |
| Arm title | T+O 5/5 / F+S 500/50 / T+O 2.5/5 / F+S 250/50 |
| Arm description: | |
| Tiotropium+Olodaterol (T+O) FDC (5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching Fluticasone propionate+Salmeterol (F+S) FDC inhalation powder via Accuhaler® twice daily in period 1, followed with F+S FDC (500 µg/50 µg) inhalation powder via Accuhaler® twice daily followed and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 2, followed with T+O FDC (2.5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 3, then followed with F+S FDC (250 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 4. Each treatment period was 6 wks and washing-out period 3 wks. Treatment sequence was 33 wks including 4 treatment periods and 3 washing-out periods. | |
| Arm type | Treatment sequence |
| Investigational medicinal product name | Tiotropium 2.5 µg / Olodaterol 5 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Tiotropium+Olodaterol (2.5/5 µg) FDC inhalation solution was administered via the Respimat® inhaler once daily. | |
| Investigational medicinal product name | Tiotropium 5 µg / Olodaterol 5 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:
Tiotropium+Olodaterol (2.5/5 µg) FDC inhalation solution was administered via the Respimat® inhaler once daily.

| | |
|--|--|
| Investigational medicinal product name | Fluticasone propionate 250 µg / Salmeterol 50 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:
Fluticasone propionate+Salmeterol (250/50 µg) FDC inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

| | |
|--|--|
| Investigational medicinal product name | Fluticasone propionate 500 µg / Salmeterol 50 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:
Fluticasone propionate+Salmeterol (500/50 µg) FDC inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

| | |
|--|--|
| Investigational medicinal product name | Placebo matching Tiotropium / Oladaterol_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:
Tiotropium+Olodaterol placebo inhalation solution was administered via the Respimat® inhaler once daily.

| | |
|--|--|
| Investigational medicinal product name | Placebo matching Fluticasone propionate / Salmeterol_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:
Fluticasone propionate+Salmeterol placebo inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

| | |
|------------------|---|
| Arm title | F+S 250/50 / T+O 2.5/5 / F+S 500/50 / T+O 5/5 |
|------------------|---|

Arm description:

Fluticasone propionate+Salmeterol (F+S) FDC (250 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching Tiotropium+Olodaterol (T+O) FDC inhalation solution via Respimat® inhaler once daily in the morning in period 1, followed with T+O FDC (2.5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 2, followed with F+S FDC (500 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 3, then followed T+O FDC (5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning with placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 4. Each treatment period was 6 wks and washing-out period 3 wks. Treatment sequence was 33 wks including 4 treatment periods and 3 washing-out periods.

| | |
|--|---------------------------------------|
| Arm type | Treatment sequence |
| Investigational medicinal product name | Tiotropium 5 µg / Olodaterol 5 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:
Tiotropium+Olodaterol (5/5 µg) FDC inhalation solution was administered via the Respimat® inhaler once daily.

| | |
|---|--|
| Investigational medicinal product name | Tiotropium 2.5 µg / Olodaterol 5 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Tiotropium+Olodaterol (2.5/5 µg) FDC inhalation solution was administered via the Respimat® inhaler once daily. | |
| Investigational medicinal product name | Fluticasone propionate 250 µg / Salmeterol 50 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Fluticasone propionate+Salmeterol (250/50 µg) FDC inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. | |
| Investigational medicinal product name | Fluticasone propionate 500 µg / Salmeterol 50 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Fluticasone propionate+Salmeterol (500/50 µg) FDC inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. | |
| Investigational medicinal product name | Placebo matching Tiotropium / Oladaterol_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Tiotropium+Olodaterol placebo inhalation solution was administered via the Respimat® inhaler once daily. | |
| Investigational medicinal product name | Placebo matching Fluticasone propionate / Salmeterol_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Fluticasone propionate+Salmeterol placebo inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. | |
| Arm title | F+S 500/50 / F+S 250/50 / T+O 5/5 / T+O 2.5/5 |
| Arm description: | |
| Fluticasone propionate+Salmeterol (F+S) FDC (500 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching Tiotropium+Olodaterol (T+O) FDC inhalation solution via Respimat® inhaler once daily in the morning in period 1, followed with F+S FDC (250 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 2, followed with T+O FDC (5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 3, then followed with T+O FDC (2.5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 4. Each treatment period was 6 wks and washing-out period 3 wks. Treatment sequence was 33 wks including 4 treatment periods and 3 washing-out periods. | |
| Arm type | Treatment sequence |

| | |
|--|---|
| Investigational medicinal product name | Tiotropium 2.5 µg / Olodaterol 5 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Tiotropium+Olodaterol (2.5/5 µg) FDC inhalation solution was administered via the Respimat® inhaler once daily.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Tiotropium 5 µg / Olodaterol 5 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Tiotropium+Olodaterol (5/5 µg) FDC inhalation solution was administered via the Respimat® inhaler once daily.

| | |
|--|--|
| Investigational medicinal product name | Fluticasone propionate 250 µg / Salmeterol 50 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Fluticasone propionate+Salmeterol (250/50 µg) FDC inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

| | |
|--|--|
| Investigational medicinal product name | Fluticasone propionate 500 µg / Salmeterol 50 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Fluticasone propionate+Salmeterol (500/50 µg) FDC inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

| | |
|--|--|
| Investigational medicinal product name | Placebo matching Tiotropium / Oladaterol_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Tiotropium+Olodaterol placebo inhalation solution was administered via the Respimat® inhaler once daily.

| | |
|--|--|
| Investigational medicinal product name | Placebo matching Fluticasone propionate / Salmeterol_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Fluticasone propionate+Salmeterol placebo inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

| Number of subjects in period 1 | T+O 2.5/5 / T+O 5/5 / F+S 250/50 / F+S 500/50 | T+O 5/5 / F+S 500/50 / T+O 2.5/5 / F+S 250/50 | F+S 250/50 / T+O 2.5/5 / F+S 500/50 / T+O 5/5 |
|--------------------------------------|---|---|---|
| Started | 58 | 69 | 50 |
| Completed | 54 | 57 | 45 |
| Not completed | 4 | 12 | 5 |
| Adverse event, serious fatal | - | - | 1 |
| Non compliant with protocol | 1 | 1 | - |
| Adverse event, non-fatal | 3 | 8 | 2 |
| Other not defined | - | 2 | - |
| Discontinued during washout periods. | - | 1 | 1 |
| Lack of efficacy | - | - | 1 |

| Number of subjects in period 1 | F+S 500/50 / F+S 250/50 / T+O 5/5 / T+O 2.5/5 |
|--------------------------------------|---|
| Started | 52 |
| Completed | 46 |
| Not completed | 6 |
| Adverse event, serious fatal | - |
| Non compliant with protocol | 2 |
| Adverse event, non-fatal | 2 |
| Other not defined | - |
| Discontinued during washout periods. | 2 |
| Lack of efficacy | - |

Period 2

| | |
|------------------------------|-------------------------------------|
| Period 2 title | Overall trial (treatment period) |
| Is this the baseline period? | Yes ^[1] |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Data analyst |

Arms

| | |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | No |
| Arm title | T+O 2.5/5 / F+S placebo |

Arm description:

Subjects were administered with Fixed Dose Combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg. Tiotropium+Olodaterol FDC inhalation solutions were administered via the Respimat® inhaler once daily. Fluticasone propionate+Salmeterol placebo inhalation powders were inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|---|
| Investigational medicinal product name | Tiotropium 2.5 µg / Olodaterol 5 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Tiotropium+Olodaterol (2.5/5 µg) FDC inhalation solutions were administered via the Respimat® inhaler once daily.

| | |
|--|--|
| Investigational medicinal product name | Placebo matching Fluticasone propionate / Salmeterol_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Fluticasone propionate+Salmeterol placebo inhalation powders were inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

| | |
|------------------|-----------------------|
| Arm title | T+O 5/5 / F+S placebo |
|------------------|-----------------------|

Arm description:

Subjects were administered with Fixed dose combination (FDC) of Tiotropium 5 µg and Olodaterol 5 µg. Tiotropium+Olodaterol FDC inhalation solutions were administered via the Respimat® inhaler once daily. Fluticasone propionate+Salmeterol placebo inhalation powders were inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Tiotropium 5 µg / Olodaterol 5 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Tiotropium+Olodaterol (5 µg/5 µg) FDC inhalation solutions were administered via the Respimat® inhaler once daily.

| | |
|--|--|
| Investigational medicinal product name | Placebo matching Fluticasone propionate / Salmeterol_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Fluticasone propionate+Salmeterol placebo inhalation powders were inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

| | |
|------------------|--------------------------|
| Arm title | F+S 250/50 / T+O placebo |
|------------------|--------------------------|

Arm description:

Subjects were administered with Fixed dose combination (FDC) of Fluticasone propionate 250 µg and Salmeterol 50 µg. Fluticasone propionate+Salmeterol FDC inhalation powders were inhaled orally twice daily via Accuhaler®. Tiotropium+Olodaterol placebo inhalation solutions were administered via the Respimat® inhaler once daily. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Fluticasone propionate 250 µg / Salmeterol 50 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Fluticasone propionate+Salmeterol (250/50 µg) FDC inhalation powders were inhaled orally twice daily via Accuhaler®.

| | |
|--|--|
| Investigational medicinal product name | Placebo matching Tiotropium / Olodaterol_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Tiotropium+Olodaterol placebo inhalation solutions were administered via the Respimat® inhaler once daily.

| | |
|------------------|--------------------------|
| Arm title | F+S 500/50 / T+O placebo |
|------------------|--------------------------|

Arm description:

Subjects were administered with Fixed dose combination (FDC) of Fluticasone propionate 500 µg and Salmeterol 50 µg. Fluticasone propionate+Salmeterol FDC inhalation powders were inhaled orally twice daily via Accuhaler®. Tiotropium+Olodaterol placebo inhalation solutions were administered via the Respimat® inhaler once daily. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Fluticasone propionate 500 µg / Salmeterol 50 µg_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Fluticasone propionate+Salmeterol (500/50 µg) FDC inhalation powders were inhaled orally twice daily via Accuhaler®.

| | |
|--|--|
| Investigational medicinal product name | Placebo matching Tiotropium / Olodaterol_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Tiotropium+Olodaterol placebo inhalation solutions were administered via the Respimat® inhaler once daily.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: In this study, Period 1 evaluates by sequence and baseline characteristics is defined based on overall trial by treatment period, thus period 2 was selected as a baseline period to define the baseline characteristics of this trial.

| Number of subjects in period 2 | T+O 2.5/5 / F+S placebo | T+O 5/5 / F+S placebo | F+S 250/50 / T+O placebo |
|---------------------------------------|-------------------------|-----------------------|--------------------------|
| Started | 215 | 221 | 212 |
| Completed | 210 | 213 | 209 |
| Not completed | 5 | 8 | 3 |
| Adverse event, serious fatal | - | 1 | - |
| Non compliant with protocol | 1 | 1 | - |
| Adverse event, non-fatal | 3 | 5 | 2 |
| Other not defined | 1 | 1 | - |
| Lack of efficacy | - | - | 1 |

| Number of subjects in period 2 | F+S 500/50 / T+O placebo |
|---------------------------------------|-------------------------------------|
| Started | 219 |
| Completed | 212 |
| Not completed | 7 |
| Adverse event, serious fatal | - |
| Non compliant with protocol | 2 |
| Adverse event, non-fatal | 5 |
| Other not defined | - |
| Lack of efficacy | - |

Baseline characteristics

Reporting groups^[1]

| | |
|-----------------------|----------------------------------|
| Reporting group title | Overall trial (treatment period) |
|-----------------------|----------------------------------|

Reporting group description: -

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

| Reporting group values | Overall trial (treatment period) | Total | |
|------------------------|-------------------------------------|-------|--|
| Number of subjects | 229 | 229 | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|-------|-----|--|
| Age Continuous | | | |
| Treated Set: All randomised patients who received any dose of the trial medication. | | | |
| Units: years | | | |
| arithmetic mean | 63.6 | | |
| standard deviation | ± 7.6 | - | |
| Gender, Male/Female | | | |
| Units: Participants | | | |
| Female | 81 | 81 | |
| Male | 148 | 148 | |

End points

End points reporting groups

| | |
|-----------------------|---|
| Reporting group title | T+O 2.5/5 / T+O 5/5 / F+S 250/50 / F+S 500/50 |
|-----------------------|---|

Reporting group description:

Tiotropium+Olodaterol (T+O) FDC (2.5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching Fluticasone propionate+Salmeterol (F+S) FDC inhalation powder via Accuhaler® twice daily in period 1, followed with T+O FDC (5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 2, followed with F+S FDC (250 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 3, then followed with F+S FDC (500 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 4. Each treatment period was 6 weeks (wks) and washing-out period 3 wks. Treatment sequence was 33 wks including 4 treatment periods and 3 washing-out periods.

| | |
|-----------------------|---|
| Reporting group title | T+O 5/5 / F+S 500/50 / T+O 2.5/5 / F+S 250/50 |
|-----------------------|---|

Reporting group description:

Tiotropium+Olodaterol (T+O) FDC (5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching Fluticasone propionate+Salmeterol (F+S) FDC inhalation powder via Accuhaler® twice daily in period 1, followed with F+S FDC (500 µg/50 µg) inhalation powder via Accuhaler® twice daily followed and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 2, followed with T+O FDC (2.5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 3, then followed with F+S FDC (250 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 4. Each treatment period was 6 wks and washing-out period 3 wks. Treatment sequence was 33 wks including 4 treatment periods and 3 washing-out periods.

| | |
|-----------------------|---|
| Reporting group title | F+S 250/50 / T+O 2.5/5 / F+S 500/50 / T+O 5/5 |
|-----------------------|---|

Reporting group description:

Fluticasone propionate+Salmeterol (F+S) FDC (250 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching Tiotropium+Olodaterol (T+O) FDC inhalation solution via Respimat® inhaler once daily in the morning in period 1, followed with T+O FDC (2.5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 2, followed with F+S FDC (500 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 3, then followed T+O FDC (5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning with placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 4. Each treatment period was 6 wks and washing-out period 3 wks. Treatment sequence was 33 wks including 4 treatment periods and 3 washing-out periods.

| | |
|-----------------------|---|
| Reporting group title | F+S 500/50 / F+S 250/50 / T+O 5/5 / T+O 2.5/5 |
|-----------------------|---|

Reporting group description:

Fluticasone propionate+Salmeterol (F+S) FDC (500 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching Tiotropium+Olodaterol (T+O) FDC inhalation solution via Respimat® inhaler once daily in the morning in period 1, followed with F+S FDC (250 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 2, followed with T+O FDC (5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 3, then followed with T+O FDC (2.5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 4. Each treatment period was 6 wks and washing-out period 3 wks. Treatment sequence was 33 wks including 4 treatment periods and 3 washing-out periods.

| | |
|-----------------------|-------------------------|
| Reporting group title | T+O 2.5/5 / F+S placebo |
|-----------------------|-------------------------|

Reporting group description:

Subjects were administered with Fixed Dose Combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg. Tiotropium+Olodaterol FDC inhalation solutions were administered via the Respimat® inhaler once daily. Fluticasone propionate+Salmeterol placebo inhalation powders were inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

| | |
|-----------------------|-----------------------|
| Reporting group title | T+O 5/5 / F+S placebo |
|-----------------------|-----------------------|

Reporting group description:

Subjects were administered with Fixed dose combination (FDC) of Tiotropium 5 µg and Olodaterol 5 µg. Tiotropium+Olodaterol FDC inhalation solutions were administered via the Respimat® inhaler once daily.

Fluticasone propionate+Salmeterol placebo inhalation powders were inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

| | |
|-----------------------|--------------------------|
| Reporting group title | F+S 250/50 / T+O placebo |
|-----------------------|--------------------------|

Reporting group description:

Subjects were administered with Fixed dose combination (FDC) of Fluticasone propionate 250 µg and Salmeterol 50 µg. Fluticasone propionate+Salmeterol FDC inhalation powders were inhaled orally twice daily via Accuhaler®. Tiotropium+Olodaterol placebo inhalation solutions were administered via the Respimat® inhaler once daily. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

| | |
|-----------------------|--------------------------|
| Reporting group title | F+S 500/50 / T+O placebo |
|-----------------------|--------------------------|

Reporting group description:

Subjects were administered with Fixed dose combination (FDC) of Fluticasone propionate 500 µg and Salmeterol 50 µg. Fluticasone propionate+Salmeterol FDC inhalation powders were inhaled orally twice daily via Accuhaler®. Tiotropium+Olodaterol placebo inhalation solutions were administered via the Respimat® inhaler once daily. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

Primary: FEV1 AUC (0–12h) Change from Patient Baseline after 6 Weeks of Treatment

| | |
|-----------------|--|
| End point title | FEV1 AUC (0–12h) Change from Patient Baseline after 6 Weeks of Treatment |
|-----------------|--|

End point description:

Change from patient baseline in Forced Expiratory Volume in one second (FEV1) Area Under the FEV1-time Curve from 0 to 12hours post-dose (AUC 0-12h) [L] after 6 weeks of treatment. Measured values presented are actually adjusted means. The period baseline is defined as the pre-dose measurement taken at on the day 1 of each period. The patient baseline is defined as the mean of non-missing period baselines for each patient.

Full Analysis Set (FAS): Included all randomised patients who were documented to have had received any dose of trial medication and who had both period baseline and any evaluable post-baseline measurement for the primary efficacy endpoint.

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

End point timeframe:

Baseline and 6 weeks.

| End point values | T+O 2.5/5 / F+S placebo | T+O 5/5 / F+S placebo | F+S 250/50 / T+O placebo | F+S 500/50 / T+O placebo |
|----------------------------------|-------------------------|-----------------------|--------------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 214 ^[1] | 216 ^[2] | 211 ^[3] | 217 ^[4] |
| Units: Litres | | | | |
| arithmetic mean (standard error) | 0.295 (± 0.014) | 0.317 (± 0.014) | 0.192 (± 0.015) | 0.188 (± 0.014) |

Notes:

[1] - Full Analysis Set (FAS)

[2] - Full Analysis Set (FAS)

[3] - Full Analysis Set (FAS)

[4] - Full Analysis Set (FAS)

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. | |
| Comparison groups | T+O 5/5 / F+S placebo v F+S 250/50 / T+O placebo |
| Number of subjects included in analysis | 427 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | < 0.0001 ^[6] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.125 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.103 |
| upper limit | 0.147 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.011 |

Notes:

[5] - The actual number of subjects analyzed is 221. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis below (427) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S placebo - F+S 250/50 / T+O placebo adjusted mean FEV1 AUC 0-12h change from patient baseline (L).

[6] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

| | |
|--|--|
| Statistical analysis title | Statistical analysis 2 |
| Statistical analysis description: | |
| The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. | |
| Comparison groups | T+O 5/5 / F+S placebo v F+S 500/50 / T+O placebo |
| Number of subjects included in analysis | 433 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[7] |
| P-value | < 0.0001 ^[8] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.129 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.107 |
| upper limit | 0.15 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.011 |

Notes:

[7] - The actual number of subjects analyzed is 221. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (433) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S placebo - F+S

500/50 / T+O placebo adjusted mean FEV1 AUC 0-12h change from patient baseline (L).

[8] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | T+O 2.5/5 / F+S placebo v F+S 250/50 / T+O placebo |
| Number of subjects included in analysis | 425 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[9] |
| P-value | < 0.0001 ^[10] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.103 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.081 |
| upper limit | 0.124 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.011 |

Notes:

[9] - The actual number of subjects analyzed is 221. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (425) does not reflect the actual number. Difference calculated as T+O 2.5/5 / F+S placebo - F+S 250/50 / T+O placebo adjusted mean FEV1 AUC 0-12h change from patient baseline (L).

[10] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | T+O 2.5/5 / F+S placebo v F+S 500/50 / T+O placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[11] |
| P-value | < 0.0001 ^[12] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.106 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.085 |
| upper limit | 0.128 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.011 |

Notes:

[11] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (431) does not reflect the actual number. Difference calculated as T+O 2.5/5 / F+S placebo - F+S 500/50 / T+O placebo adjusted mean FEV1 AUC 0-12h change from patient baseline (L).

[12] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Secondary: FEV1 AUC (0–24h) Change from Patient Baseline after 6 Weeks of Treatment

| | |
|-----------------|--|
| End point title | FEV1 AUC (0–24h) Change from Patient Baseline after 6 Weeks of Treatment |
|-----------------|--|

End point description:

Change from patient baseline in Forced Expiratory Volume in one second (FEV1) Area Under the FEV1-time Curve from 0 to 24 hours post-dose (AUC 0-24h) [L] after 6 weeks of treatment. Measured values presented are actually adjusted means. The period baseline is defined as the pre-dose measurement taken at on the day 1 of each period. The patient baseline is defined as the mean of non-missing period baselines for each patient.

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

End point timeframe:

Baseline and 6 weeks.

| End point values | T+O 2.5/5 / F+S placebo | T+O 5/5 / F+S placebo | F+S 250/50 / T+O placebo | F+S 500/50 / T+O placebo |
|----------------------------------|-------------------------|-----------------------|--------------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 214 ^[13] | 216 ^[14] | 211 ^[15] | 217 ^[16] |
| Units: Litres | | | | |
| arithmetic mean (standard error) | 0.228 (± 0.014) | 0.244 (± 0.014) | 0.162 (± 0.014) | 0.159 (± 0.014) |

Notes:

[13] - Full Analysis Set (FAS)

[14] - Full Analysis Set (FAS)

[15] - Full Analysis Set (FAS)

[16] - Full Analysis Set (FAS)

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | T+O 5/5 / F+S placebo v F+S 250/50 / T+O placebo |
| Number of subjects included in analysis | 427 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[17] |
| P-value | < 0.0001 ^[18] |
| Method | Mixed models analysis |
| Parameter estimate | Median difference (net) |
| Point estimate | 0.082 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.061 |
| upper limit | 0.103 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.011 |

Notes:

[17] - The actual number of subjects analyzed is 221. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (427) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S Placebo - F+S 250/50 / T+O Placebo adjusted mean FEV1 AUC 0-24h change from patient baseline (L).

[18] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | T+O 5/5 / F+S placebo v F+S 500/50 / T+O placebo |
| Number of subjects included in analysis | 433 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[19] |
| P-value | < 0.0001 ^[20] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.086 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.065 |
| upper limit | 0.107 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.011 |

Notes:

[19] - The actual number of subjects analyzed is 221. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (433) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S Placebo - F+S 500/50 / T+O Placebo adjusted mean FEV1 AUC 0-24h change from patient baseline (L).

[20] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|-------------------|--|
| Comparison groups | T+O 2.5/5 / F+S placebo v F+S 250/50 / T+O placebo |
|-------------------|--|

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 425 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[21] |
| P-value | < 0.0001 ^[22] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.065 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.045 |
| upper limit | 0.086 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.011 |

Notes:

[21] - The actual number of subjects analyzed is 215. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (425) does not reflect the actual number. Difference calculated as T+O 2.5/5 / F+S Placebo - F+S 250/50 / T+O Placebo adjusted mean FEV1 AUC 0-24h change from patient baseline (L).

[22] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | T+O 2.5/5 / F+S placebo v F+S 500/50 / T+O placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[23] |
| P-value | < 0.0001 ^[24] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.069 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.048 |
| upper limit | 0.09 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.011 |

Notes:

[23] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (431) does not reflect the actual number. Difference calculated as T+O 2.5/5 / F+S Placebo - F+S 500/50 / T+O Placebo adjusted mean FEV1 AUC 0-24h change from patient baseline (L).

[24] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Secondary: Trough FEV1 Change from Patient Baseline after 6 Weeks of Treatment

| | |
|-----------------|---|
| End point title | Trough FEV1 Change from Patient Baseline after 6 Weeks of Treatment |
|-----------------|---|

End point description:

Change from patient baseline in trough Forced Expiratory Volume in one second (FEV1) after 6 weeks of treatment. Trough FEV1 was defined as the mean of the 23h and 23h 50min (minutes) post-dose FEV1 measurements. Measured values presented are actually adjusted means. The period baseline is defined as the pre-dose measurement taken at on the day 1 of each period. The patient baseline is defined as the mean of non-missing period baselines for each patient.

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

End point timeframe:

Baseline and 6 weeks.

| End point values | T+O 2.5/5 / F+S placebo | T+O 5/5 / F+S placebo | F+S 250/50 / T+O placebo | F+S 500/50 / T+O placebo |
|----------------------------------|-------------------------|-----------------------|--------------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 214 ^[25] | 216 ^[26] | 211 ^[27] | 217 ^[28] |
| Units: Litres | | | | |
| arithmetic mean (standard error) | 0.192 (± 0.014) | 0.197 (± 0.014) | 0.15 (± 0.014) | 0.139 (± 0.014) |

Notes:

[25] - Full Analysis Set (FAS)

[26] - Full Analysis Set (FAS)

[27] - Full Analysis Set (FAS)

[28] - Full Analysis Set (FAS)

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | T+O 5/5 / F+S placebo v F+S 250/50 / T+O placebo |
| Number of subjects included in analysis | 427 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[29] |
| P-value | = 0.0002 ^[30] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.047 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.022 |
| upper limit | 0.071 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.012 |

Notes:

[29] - The actual number of subjects analyzed is 221. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (427) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S Placebo - F+S 250/50 / T+O Placebo adjusted mean trough FEV1 change from patient baseline (L).

[30] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | T+O 5/5 / F+S placebo v F+S 500/50 / T+O placebo |
| Number of subjects included in analysis | 433 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[31] |
| P-value | < 0.0001 ^[32] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.058 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.034 |
| upper limit | 0.082 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.012 |

Notes:

[31] - The actual number of subjects analyzed is 221. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (433) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S Placebo - F+S 500/50 / T+O Placebo adjusted mean trough FEV1 change from patient baseline (L).

[32] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | T+O 2.5/5 / F+S placebo v F+S 250/50 / T+O placebo |
| Number of subjects included in analysis | 425 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[33] |
| P-value | = 0.0007 ^[34] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.042 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.018 |
| upper limit | 0.067 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.012 |

Notes:

[33] - The actual number of subjects analyzed is 215. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (425) does not reflect the actual number. Difference calculated as T+O 2.5/5 / F+S Placebo - F+S 250/50 / T+O Placebo adjusted mean trough FEV1 change from patient baseline (L).

[34] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | T+O 2.5/5 / F+S placebo v F+S 500/50 / T+O placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[35] |
| P-value | < 0.0001 ^[36] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.054 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.029 |
| upper limit | 0.078 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.012 |

Notes:

[35] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (431) does not reflect the actual number. Difference calculated as T+O 2.5/5 / F+S Placebo - F+S 500/50 / T+O Placebo adjusted mean trough FEV1 change from patient baseline (L).

[36] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Secondary: FEV1 AUC (12–24h) Change from Patient Baseline after 6 Weeks of Treatment

| | |
|-----------------|---|
| End point title | FEV1 AUC (12–24h) Change from Patient Baseline after 6 Weeks of Treatment |
|-----------------|---|

End point description:

Change from patient baseline in Forced Expiratory Volume in one second (FEV1) Area Under the FEV1-time Curve from 12 to 24 hours post-dose (AUC 12-24h) [L] after 6 weeks of treatment. Measured values presented are actually adjusted means. The period baseline is defined as the pre-dose measurement taken at on the day 1 of each period. The patient baseline is defined as the mean of non-missing period baselines for each patient.

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

End point timeframe:

Baseline and 6 weeks.

| End point values | T+O 2.5/5 / F+S placebo | T+O 5/5 / F+S placebo | F+S 250/50 / T+O placebo | F+S 500/50 / T+O placebo |
|----------------------------------|-------------------------|-----------------------|--------------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 214 ^[37] | 216 ^[38] | 211 ^[39] | 217 ^[40] |
| Units: Litres | | | | |
| arithmetic mean (standard error) | 0.164 (± 0.014) | 0.172 (± 0.014) | 0.132 (± 0.014) | 0.129 (± 0.014) |

Notes:

[37] - Full Analysis Set (FAS)

[38] - Full Analysis Set (FAS)

[39] - Full Analysis Set (FAS)

[40] - Full Analysis Set (FAS)

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | T+O 5/5 / F+S placebo v F+S 250/50 / T+O placebo |
| Number of subjects included in analysis | 427 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[41] |
| P-value | = 0.0007 ^[42] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.039 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.017 |
| upper limit | 0.062 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.012 |

Notes:

[41] - The actual number of subjects analyzed is 221. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (427) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S Placebo - F+S 250/50 / T+O Placebo adjusted mean FEV1 AUC (12-24h) change from patient baseline (L).

[42] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

| Statistical analysis title | Statistical analysis 2 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|-------------------|--|
| Comparison groups | T+O 5/5 / F+S placebo v F+S 500/50 / T+O placebo |
|-------------------|--|

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 433 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[43] |
| P-value | = 0.0002 ^[44] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.043 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.021 |
| upper limit | 0.065 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.011 |

Notes:

[43] - The actual number of subjects analyzed is 221. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (433) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S Placebo - F+S 500/50 / T+O Placebo adjusted mean FEV1 AUC (12–24h) change from patient baseline (L).

[44] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within–patient variation and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | T+O 2.5/5 / F+S placebo v F+S 250/50 / T+O placebo |
| Number of subjects included in analysis | 425 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[45] |
| P-value | = 0.0146 ^[46] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.028 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.006 |
| upper limit | 0.051 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.011 |

Notes:

[45] - The actual number of subjects analyzed is 215. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (425) does not reflect the actual number. Difference calculated as T+O 2.5/5 / F+S Placebo - F+S 250/50 / T+O Placebo adjusted mean FEV1 AUC (12–24h) change from patient baseline (L).

[46] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound

symmetry covariance structure for within-patient variation and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | T+O 2.5/5 / F+S placebo v F+S 500/50 / T+O placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[47] |
| P-value | = 0.0055 ^[48] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.032 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.009 |
| upper limit | 0.054 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.011 |

Notes:

[47] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (431) does not reflect the actual number. Difference calculated as T+O 2.5/5 / F+S Placebo - F+S 500/50 / T+O Placebo adjusted mean FEV1 AUC (12–24h) change from patient baseline (L).

[48] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Secondary: FEV1 Peak (0–3h) Change from Patient Baseline after 6 Weeks of Treatment

| | |
|-----------------|--|
| End point title | FEV1 Peak (0–3h) Change from Patient Baseline after 6 Weeks of Treatment |
|-----------------|--|

End point description:

Change from patient baseline in Forced Expiratory Volume in one second (FEV1) peak (0-3 hours) after 6 weeks of treatment. FEV1 peak (0-3 hours) was defined as the maximum FEV1 value measured within the first three hours post dosing. Measured values presented are actually adjusted means.

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

End point timeframe:

Baseline and 6 weeks.

| End point values | T+O 2.5/5 / F+S placebo | T+O 5/5 / F+S placebo | F+S 250/50 / T+O placebo | F+S 500/50 / T+O placebo |
|----------------------------------|-------------------------|-----------------------|--------------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 214 ^[49] | 216 ^[50] | 211 ^[51] | 217 ^[52] |
| Units: Litres | | | | |
| arithmetic mean (standard error) | 0.401 (± 0.016) | 0.432 (± 0.016) | 0.291 (± 0.016) | 0.285 (± 0.015) |

Notes:

[49] - Full Analysis Set (FAS)

[50] - Full Analysis Set (FAS)

[51] - Full Analysis Set (FAS)

[52] - Full Analysis Set (FAS)

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. | |
| Comparison groups | T+O 5/5 / F+S placebo v F+S 250/50 / T+O placebo |
| Number of subjects included in analysis | 427 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[53] |
| P-value | < 0.0001 ^[54] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.142 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.118 |
| upper limit | 0.166 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.012 |

Notes:

[53] - The actual number of subjects analyzed is 221. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (427) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S Placebo - F+S 250/50 / T+O placebo adjusted mean FEV1 peak (0-3h) change from patient baseline (L).

[54] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

| | |
|--|--|
| Statistical analysis title | Statistical analysis 2 |
| Statistical analysis description: | |
| The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. | |
| Comparison groups | T+O 5/5 / F+S placebo v F+S 500/50 / T+O placebo |
| Number of subjects included in analysis | 433 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[55] |
| P-value | < 0.0001 ^[56] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.147 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.123 |
| upper limit | 0.171 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.012 |

Notes:

[55] - The actual number of subjects analyzed is 221. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (433) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S placebo - F+S

500/50 / T+O placebo adjusted mean FEV1 peak (0–3h) change from patient baseline (L).

[56] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within–patient variation and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | T+O 2.5/5 / F+S placebo v F+S 250/50 / T+O placebo |
| Number of subjects included in analysis | 425 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[57] |
| P-value | < 0.0001 ^[58] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.111 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.087 |
| upper limit | 0.135 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.012 |

Notes:

[57] - The actual number of subjects analyzed is 215. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (425) does not reflect the actual number. Difference calculated as T+O 2.5/5 / F+S placebo - F+S 250/50 / T+O placebo adjusted mean FEV1 peak (0–3h) change from patient baseline (L).

[58] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within–patient variation and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | T+O 2.5/5 / F+S placebo v F+S 500/50 / T+O placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[59] |
| P-value | < 0.0001 ^[60] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.116 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.092 |
| upper limit | 0.14 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.012 |

Notes:

[59] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (431) does not reflect the actual number. Difference calculated as T+O 2.5/5 / F+S placebo - F+S 500/50 / T+O placebo adjusted mean FEV1 peak (0–3h) change from patient baseline (L).

[60] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided $\alpha=0.05$.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug intake until 21 days after last drug intake, up to 88 days.

Adverse event reporting additional description:

AEs are displayed by treatment, however in total patients were in the study for up to 223 days.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | T+O 2.5/5 / F+S placebo |
|-----------------------|-------------------------|

Reporting group description:

Subjects were administered with Fixed Dose Combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg. Tiotropium+Olodaterol FDC inhalation solutions were administered via the Respimat® inhaler once daily. Fluticasone propionate+Salmeterol placebo inhalation powders were inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

| | |
|-----------------------|--------------------------|
| Reporting group title | F+S 250/50 / T+O placebo |
|-----------------------|--------------------------|

Reporting group description:

Subjects were administered with Fixed dose combination (FDC) of Fluticasone propionate 250 µg and Salmeterol 50 µg. Fluticasone propionate+Salmeterol FDC inhalation powders were inhaled orally twice daily via Accuhaler®. Tiotropium+Olodaterol placebo inhalation solutions were administered via the Respimat® inhaler once daily. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

| | |
|-----------------------|--------------------------|
| Reporting group title | F+S 500/50 / T+O placebo |
|-----------------------|--------------------------|

Reporting group description:

Subjects were administered with Fixed dose combination (FDC) of Fluticasone propionate 500 µg and Salmeterol 50 µg. Fluticasone propionate+Salmeterol FDC inhalation powders were inhaled orally twice daily via Accuhaler®. Tiotropium+Olodaterol placebo inhalation solutions were administered via the Respimat® inhaler once daily. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

| | |
|-----------------------|-----------------------|
| Reporting group title | T+O 5/5 / F+S placebo |
|-----------------------|-----------------------|

Reporting group description:

Subjects were administered with Fixed dose combination (FDC) of Tiotropium 5 µg and Olodaterol 5 µg. Tiotropium+Olodaterol FDC inhalation solutions were administered via the Respimat® inhaler once daily. Fluticasone propionate+Salmeterol placebo inhalation powders were inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

| Serious adverse events | T+O 2.5/5 / F+S placebo | F+S 250/50 / T+O placebo | F+S 500/50 / T+O placebo |
|---|-------------------------|--------------------------|--------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 215 (2.79%) | 4 / 212 (1.89%) | 9 / 219 (4.11%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Fibula fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 215 (0.47%) | 0 / 212 (0.00%) | 0 / 219 (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 |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 215 (0.47%) | 0 / 212 (0.00%) | 0 / 219 (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 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 215 (0.00%) | 1 / 212 (0.47%) | 0 / 219 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular graft occlusion | | | |
| subjects affected / exposed | 1 / 215 (0.47%) | 0 / 212 (0.00%) | 1 / 219 (0.46%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 215 (0.00%) | 0 / 212 (0.00%) | 1 / 219 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 215 (0.47%) | 0 / 212 (0.00%) | 0 / 219 (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 |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 215 (0.47%) | 0 / 212 (0.00%) | 0 / 219 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 215 (0.00%) | 0 / 212 (0.00%) | 1 / 219 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 215 (0.00%) | 0 / 212 (0.00%) | 0 / 219 (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 |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 215 (0.00%) | 0 / 212 (0.00%) | 0 / 219 (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 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 215 (0.00%) | 1 / 212 (0.47%) | 0 / 219 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 0 / 215 (0.00%) | 0 / 212 (0.00%) | 0 / 219 (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 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 215 (0.00%) | 0 / 212 (0.00%) | 1 / 219 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 215 (0.00%) | 0 / 212 (0.00%) | 0 / 219 (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 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 215 (0.00%) | 1 / 212 (0.47%) | 0 / 219 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 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 | 2 / 215 (0.93%) | 2 / 212 (0.94%) | 4 / 219 (1.83%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 215 (0.00%) | 0 / 212 (0.00%) | 0 / 219 (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 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 215 (0.00%) | 0 / 212 (0.00%) | 0 / 219 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 215 (0.00%) | 0 / 212 (0.00%) | 1 / 219 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 215 (0.00%) | 0 / 212 (0.00%) | 0 / 219 (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 |
| Lobar pneumonia | | | |
| subjects affected / exposed | 0 / 215 (0.00%) | 1 / 212 (0.47%) | 0 / 219 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 215 (0.47%) | 0 / 212 (0.00%) | 0 / 219 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 215 (0.00%) | 1 / 212 (0.47%) | 1 / 219 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Sialoadenitis | | | |
| subjects affected / exposed | 1 / 215 (0.47%) | 0 / 212 (0.00%) | 0 / 219 (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 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 215 (0.00%) | 0 / 212 (0.00%) | 0 / 219 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------------|--|--|
| Serious adverse events | T+O 5/5 / F+S placebo | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 221 (3.17%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 221 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 221 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 221 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular graft occlusion | | | |
| subjects affected / exposed | 0 / 221 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Angina pectoris | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 0 / 221 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 221 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 221 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 221 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 221 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 221 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 221 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 1 / 221 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

| | | | |
|---|-----------------|--|--|
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 221 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 221 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 221 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 221 (0.90%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 221 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 221 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 221 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------------------------|--|--|
| Infections and infestations Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 221 (0.45%) 0 / 1 0 / 0 | | |
| Lobar pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 221 (0.00%) 0 / 0 0 / 0 | | |
| Osteomyelitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 221 (0.00%) 0 / 0 0 / 0 | | |
| Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 221 (0.00%) 0 / 0 0 / 0 | | |
| Sialoadenitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 221 (0.00%) 0 / 0 0 / 0 | | |
| Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 221 (0.45%) 0 / 1 0 / 0 | | |

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

| Non-serious adverse events | T+O 2.5/5 / F+S placebo | F+S 250/50 / T+O placebo | F+S 500/50 / T+O placebo |
|---|-------------------------|--------------------------|--------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 21 / 215 (9.77%) | 19 / 212 (8.96%) | 24 / 219 (10.96%) |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|------------------------|------------------------|------------------------|
| Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) | 10 / 215 (4.65%) 10 | 7 / 212 (3.30%) 8 | 15 / 219 (6.85%) 15 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 12 / 215 (5.58%) 12 | 13 / 212 (6.13%) 13 | 11 / 219 (5.02%) 11 |

| | | | |
|--|------------------------|--|--|
| Non-serious adverse events | T+O 5/5 / F+S placebo | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 28 / 221 (12.67%) | | |
| Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) | 18 / 221 (8.14%) 20 | | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 12 / 221 (5.43%) 12 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 25 April 2014 | Global Amendment 1 included clarifications and administrative changes that did not require IRB/IEC/CA approval prior to implementation. Weather station, Accuhaler training and visit 10 for pregnancy testing was added. "patients taking Tiotropium prior to study entry" was changed to "patients taking a LAMA prior to study entry". Update with data from Phase III studies and Tiospir results. Further clarification of medication restrictions, dosing times and "rescheduling prior to randomisation" was provided. All hypotheses were changed to two-sided hypotheses with $\alpha=0.05$. Handling of missing data and provided more details in the TSAP. Definition of period baseline was updated, correction to listedness section and comparator SPC was added. |
| 04 February 2015 | Amendment 2 was a change in the hierarchical testing strategy. The testing hierarchy was modified such that the primary and key secondary endpoints were first tested on the Tio+Olo 5/5 µg dose followed by the Tio+Olo 2.5/5 µg dose because Tio+Olo 5/5 µg was the dose planned for marketing. Global Amendment 2 did not require IRB/IEC/CA approval prior to implementation. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

1 subject with missing information for number of enrolled subjects has been included in age range Elderly (From 65-84 years) as the missing category is not available.
Update initiated unnecessarily; Results in version 1 and version 2 are same.

Notes: