



Clinical trial results:

A randomised, double-blind, placebo- and active-controlled parallel group study to assess the efficacy of 12 weeks of once daily treatment of two doses of orally inhaled tiotropium + olodaterol fixed dose combination (delivered by the Respimat® inhaler) in patients with moderate to severe Chronic Obstructive Pulmonary Disease (COPD)

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2013-002264-24 |
| Trial protocol | SE AT SK GR |
| Global end of trial date | 24 November 2014 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 06 April 2016 |
| First version publication date | 06 April 2016 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | 1237.26 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02006732 |
| 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 | Boehringer Ingelheim Pharma GmbH & Co. KG, QRPE Processes and Systems Coordination, Clinical Trial, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | Boehringer Ingelheim Pharma GmbH & Co. KG, QRPE Processes and Systems Coordination, Clinical Trial, +1 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 | 13 January 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 October 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 November 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This trial was 1 of 2 randomised, double-blind, placebo- and active-controlled parallel group Phase IIIb trials with identical protocols (replicate trials with BI trial numbers 1237.25 and 1237.26) The objective of this trial was to evaluate maximal treatment effect in forced expiratory volume in one second (FEV1) response and St. George's Respiratory Questionnaire (SGRQ) total score and safety after 12 weeks of treatment with 2 different doses of tiotropium + olodaterol fixed dose combination solution (2.5/5µg and 5/5µg) delivered by the RESPIMAT® inhaler by comparison with placebo in patients with moderate to severe COPD.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be 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.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 20 November 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 | Australia: 65 |
| Country: Number of subjects enrolled | Austria: 58 |
| Country: Number of subjects enrolled | Canada: 65 |
| Country: Number of subjects enrolled | Germany: 213 |
| Country: Number of subjects enrolled | Greece: 39 |
| Country: Number of subjects enrolled | New Zealand: 16 |
| Country: Number of subjects enrolled | Norway: 49 |
| Country: Number of subjects enrolled | Slovakia: 39 |
| Country: Number of subjects enrolled | South Africa: 27 |
| Country: Number of subjects enrolled | Sweden: 48 |
| Country: Number of subjects enrolled | United States: 488 |
| Worldwide total number of subjects | 1107 |
| EEA total number of subjects | 446 |

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) | 541 |
| From 65 to 84 years | 557 |
| 85 years and over | 9 |

Subject disposition

Recruitment

Recruitment details:

809 patients were randomised and treated.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all strictly implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Treatment period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Once daily 2 puffs solution of placebo for inhalation with Respimat

| | |
|--|---------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

2 actuations once daily in the morning. Dose not applicable.

| | |
|------------------|-----------------|
| Arm title | Tiotropium 5 µg |
|------------------|-----------------|

Arm description:

Once daily 2 puffs solution of 2.5 µg tiotropium for inhalation with Respimat

| | |
|--|---------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Tiotropium Bromide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

2 actuations once daily in the morning, for a total dose of 5 µg.

| | |
|------------------|------------------------------------|
| Arm title | Tiotropium 2.5 µg+ Olodaterol 5 µg |
|------------------|------------------------------------|

Arm description:

Once daily 2 puffs solution of 1.25 µg tiotropium / 2.5 µg olodaterol for inhalation with Respimat as a fixed combination with a single inhaler.

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

| | |
|---|-----------------------------------|
| Investigational medicinal product name | Olodaterol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| 2 actuations once daily in the morning for a total dose of 5 µg | |
| Investigational medicinal product name | Tiotropium Bromide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| 2 actuations once daily in the morning for a total dose of 2.5 µg | |
| Arm title | Tiotropium 5 µg + Olodaterol 5 µg |

Arm description:

Once daily 2 puffs solution of 2.5 µg tiotropium / 2.5 µg olodaterol for inhalation with Respimat as a fixed combination with a single inhaler.

| | |
|--|---------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tiotropium Bromide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

2 actuations once daily in the morning, for a total dose of 5 µg.

| | |
|--|---------------------|
| Investigational medicinal product name | Olodaterol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

2 actuations once daily in the morning, for a total dose of 5 µg.

| Number of subjects in period 1^[1] | Placebo | Tiotropium 5 µg | Tiotropium 2.5 µg+ Olodaterol 5 µg |
|---|---------|-----------------|---------------------------------------|
| Started | 202 | 203 | 202 |
| Completed | 182 | 191 | 193 |
| Not completed | 20 | 12 | 9 |
| Consent withdrawn by subject | 3 | - | 4 |
| Adverse event, non-fatal | 10 | 7 | 4 |
| Lost to follow-up | - | 1 | - |
| Lack of efficacy | 6 | 3 | 1 |
| Protocol deviation | 1 | 1 | - |

| | |
|---------------------------------------|--------------------------------------|
| Number of subjects in period 1 | Tiotropium 5 µg + Olodaterol 5 µg |
|---------------------------------------|--------------------------------------|

| | |
|------------------------------|-----|
| [1] | |
| Started | 202 |
| Completed | 198 |
| Not completed | 4 |
| Consent withdrawn by subject | 1 |
| Adverse event, non-fatal | 2 |
| Lost to follow-up | - |
| Lack of efficacy | 1 |
| Protocol deviation | - |

Notes:

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

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

Baseline characteristics

Reporting groups

| | |
|--|------------------------------------|
| Reporting group title | Placebo |
| Reporting group description: Once daily 2 puffs solution of placebo for inhalation with Respimat | |
| Reporting group title | Tiotropium 5 µg |
| Reporting group description: Once daily 2 puffs solution of 2.5 µg tiotropium for inhalation with Respimat | |
| Reporting group title | Tiotropium 2.5 µg+ Olodaterol 5 µg |
| Reporting group description: Once daily 2 puffs solution of 1.25 µg tiotropium / 2.5 µg olodaterol for inhalation with Respimat as a fixed combination with a single inhaler. | |
| Reporting group title | Tiotropium 5 µg + Olodaterol 5 µg |
| Reporting group description: Once daily 2 puffs solution of 2.5 µg tiotropium / 2.5 µg olodaterol for inhalation with Respimat as a fixed combination with a single inhaler. | |

| Reporting group values | Placebo | Tiotropium 5 µg | Tiotropium 2.5 µg+ Olodaterol 5 µg |
|------------------------------------|---------|-----------------|---------------------------------------|
| Number of subjects | 202 | 203 | 202 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-------|-------|-------|
| Age Continuous | | | |
| Treated set (TS) which included all randomised patients who received at least one dose of trial medication represents the baseline analysis population. | | | |
| Units: years | | | |
| arithmetic mean | 64 | 64.7 | 64.4 |
| standard deviation | ± 8.3 | ± 8.4 | ± 8.6 |
| Gender, Male/Female | | | |
| Treated set (TS) which included all randomised patients who received at least one dose of trial medication represents the baseline analysis population. | | | |
| Units: participants | | | |
| Female | 85 | 73 | 76 |
| Male | 117 | 130 | 126 |

| Reporting group values | Tiotropium 5 µg + Olodaterol 5 µg | Total | |
|------------------------------------|--------------------------------------|-------|--|
| Number of subjects | 202 | 809 | |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-------|---|--|
| Age Continuous | | | |
| Treated set (TS) which included all randomised patients who received at least one dose of trial medication represents the baseline analysis population. | | | |
| Units: years | | | |
| arithmetic mean | 65.2 | | |
| standard deviation | ± 8.5 | - | |

| | | | |
|---|-----|-----|--|
| Gender, Male/Female | | | |
| Treated set (TS) which included all randomised patients who received at least one dose of trial medication represents the baseline analysis population. | | | |
| Units: participants | | | |
| Female | 69 | 303 | |
| Male | 133 | 506 | |

End points

End points reporting groups

| | |
|--|------------------------------------|
| Reporting group title | Placebo |
| Reporting group description: Once daily 2 puffs solution of placebo for inhalation with Respimat | |
| Reporting group title | Tiotropium 5 µg |
| Reporting group description: Once daily 2 puffs solution of 2.5 µg tiotropium for inhalation with Respimat | |
| Reporting group title | Tiotropium 2.5 µg+ Olodaterol 5 µg |
| Reporting group description: Once daily 2 puffs solution of 1.25 µg tiotropium / 2.5 µg olodaterol for inhalation with Respimat as a fixed combination with a single inhaler. | |
| Reporting group title | Tiotropium 5 µg + Olodaterol 5 µg |
| Reporting group description: Once daily 2 puffs solution of 2.5 µg tiotropium / 2.5 µg olodaterol for inhalation with Respimat as a fixed combination with a single inhaler. | |

Primary: FEV1 AUC0-3h response (change from baseline)

| | |
|---|--|
| End point title | FEV1 AUC0-3h response (change from baseline) |
| End point description: Forced expiratory volume in one second (FEV1) Area under the curve (AUC) 0-3h was calculated as the area under the FEV1-time curve from 0 to 3h post-dose using the trapezoidal rule, divided by the duration (3h) to report in litres. FEV1 AUC0-3h response was defined as FEV1 AUC0-3h minus baseline FEV1. The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom. The Full Analysis set (FAS) included all patients in the TS who had a baseline and at least one postbaseline measurement for any of the primary efficacy endpoints. | |
| End point type | Primary |
| End point timeframe: baseline and 12 weeks | |

| End point values | Placebo | Tiotropium 5 µg | Tiotropium 2.5 µg+ Olodaterol 5 µg | Tiotropium 5 µg + Olodaterol 5 µg |
|----------------------------------|--------------------|--------------------|------------------------------------|-----------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 199 ^[1] | 201 ^[2] | 200 ^[3] | 200 ^[4] |
| Units: Liter | | | | |
| arithmetic mean (standard error) | -0.006 (± 0.014) | 0.188 (± 0.013) | 0.279 (± 0.014) | 0.293 (± 0.013) |

Notes:

[1] - FAS including patients with available endpoint data at week 12

[2] - FAS including patients with available endpoint data at week 12

[3] - FAS including patients with available endpoint data at week 12

[4] - FAS including patients with available endpoint data at week 12

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| Placebo vs. Tiotropium 5 µg + Olodaterol 5 µg. FEV1 AUC0-3h response was defined as FEV1 AUC0-3h minus baseline FEV1. The adjusted mean and standard error (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom. | |
| Comparison groups | Placebo v Tiotropium 5 µg + Olodaterol 5 µg |
| Number of subjects included in analysis | 399 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.299 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.261 |
| upper limit | 0.336 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.019 |

| | |
|---|---|
| Statistical analysis title | Statistical analysis 2 |
| Statistical analysis description: | |
| Tiotropium 5 µg vs. Tiotropium 5 µg + 5 µg Olodaterol. FEV1 AUC0-3h response was defined as FEV1 AUC0-3h minus baseline FEV1. The adjusted mean and SE are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom. | |
| Comparison groups | Tiotropium 5 µg v Tiotropium 5 µg + Olodaterol 5 µg |
| Number of subjects included in analysis | 401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.105 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.069 |
| upper limit | 0.141 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.019 |

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

Statistical analysis description:

Placebo vs. Tiotropium 2.5 µg + Olodaterol 5 µg. FEV1 AUC0-3h response was defined as FEV1 AUC0-3h minus baseline FEV1. The adjusted mean and SE are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Placebo v Tiotropium 2.5 µg+ Olodaterol 5 µg |
| Number of subjects included in analysis | 399 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.284 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.246 |
| upper limit | 0.323 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.02 |

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

Statistical analysis description:

Tiotropium 5 µg vs. Tiotropium 2.5 µg + Olodaterol 5 µg. FEV1 AUC0-3h response was defined as FEV1 AUC0-3h minus baseline FEV1. The adjusted mean and SE are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Tiotropium 5 µg v Tiotropium 2.5 µg+ Olodaterol 5 µg |
| Number of subjects included in analysis | 401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.091 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.053 |
| upper limit | 0.128 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.019 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Placebo vs. Tiotropium 5 µg. FEV1 AUC0-3h response was defined as FEV1 AUC0-3h minus baseline FEV1. The adjusted mean and SE are obtained from fitting an MMRM including fixed effects of treatment,

planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Placebo v Tiotropium 5 µg |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.194 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.156 |
| upper limit | 0.232 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.019 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

Tiotropium 2.5 µg + Olodaterol 5 µg vs. Tiotropium 5 µg + Olodaterol 5 µg. FEV1 AUC0-3h response was defined as FEV1 AUC0-3h minus baseline FEV1. The adjusted mean and SE are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Tiotropium 2.5 µg+ Olodaterol 5 µg v Tiotropium 5 µg + Olodaterol 5 µg |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4499 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.014 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.023 |
| upper limit | 0.051 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.019 |

Primary: Trough FEV1 response (change from baseline)

| | |
|-----------------|---|
| End point title | Trough FEV1 response (change from baseline) |
|-----------------|---|

End point description:

Trough FEV1 was defined as the FEV1 value at the end of the dosing interval (24 hours). It was calculated as the mean of the 2 FEV1 measurements performed 23 h and at 23 h 50 min after inhalation

of study medication at day 85. Trough FEV1 response was defined as trough FEV1 minus baseline FEV1. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom. The Full Analysis set (FAS) included all patients in the TS who had a baseline and at least one postbaseline measurement for any of the primary efficacy endpoints.

| | |
|-----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| baseline and 12 weeks | |

| End point values | Placebo | Tiotropium 5 µg | Tiotropium 2.5 µg+ Olodaterol 5 µg | Tiotropium 5 µg + Olodaterol 5 µg |
|----------------------------------|--------------------|--------------------|------------------------------------|-----------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 193 ^[5] | 197 ^[6] | 200 ^[7] | 199 ^[8] |
| Units: Liter | | | | |
| arithmetic mean (standard error) | -0.003 (± 0.014) | 0.124 (± 0.013) | 0.166 (± 0.013) | 0.163 (± 0.013) |

Notes:

[5] - FAS including patients with available endpoint data at week 12

[6] - FAS including patients with available endpoint data at week 12

[7] - FAS including patients with available endpoint data at week 12

[8] - FAS including patients with available endpoint data at week 12

Statistical analyses

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

Statistical analysis description:

Placebo vs. Tiotropium 5 µg + Olodaterol 5 µg. Trough FEV1 response was defined as trough FEV1 minus baseline FEV1. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|---|
| Comparison groups | Placebo v Tiotropium 5 µg + Olodaterol 5 µg |
| Number of subjects included in analysis | 392 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.166 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.129 |
| upper limit | 0.203 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.019 |

| | |
|---|---|
| Statistical analysis title | Statistical analysis 2 |
| Statistical analysis description: | |
| Tiotropium 5 µg vs. Tiotropium 5 µg + Olodaterol 5 µg. Trough FEV1 response was defines as trough FEV1 minus baseline FEV1. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within–patient errors and Kenward–Roger approximation of denominator degrees of freedom. | |
| Comparison groups | Tiotropium 5 µg v Tiotropium 5 µg + Olodaterol 5 µg |
| Number of subjects included in analysis | 396 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0395 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.039 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.002 |
| upper limit | 0.076 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.019 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 3 |
| Statistical analysis description: | |
| Placebo vs. Tiotropium 2.5 µg + Olodaterol 5 µg. Trough FEV1 response was defines as trough FEV1 minus baseline FEV1. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within–patient errors and Kenward–Roger approximation of denominator degrees of freedom. | |
| Comparison groups | Placebo v Tiotropium 2.5 µg+ Olodaterol 5 µg |
| Number of subjects included in analysis | 393 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.169 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.132 |
| upper limit | 0.207 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.019 |

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

Statistical analysis description:

Tiotropium 5 µg vs. Tiotropium 2.5 µg + Olodaterol 5 µg. Trough FEV1 response was defines as trough FEV1 minus baseline FEV1. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Tiotropium 5 µg v Tiotropium 2.5 µg+ Olodaterol 5 µg |
| Number of subjects included in analysis | 397 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0269 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.042 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.005 |
| upper limit | 0.079 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.019 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Placebo vs. Tiotropium 5 µg. Trough FEV1 response was defines as trough FEV1 minus baseline FEV1. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Placebo v Tiotropium 5 µg |
| Number of subjects included in analysis | 390 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.127 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.09 |
| upper limit | 0.165 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.019 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

Tiotropium 2.5 µg + Olodaterol 5 µg vs. Tiotropium 5 µg + Olodaterol 5 µg. Trough FEV1 response was defines as trough FEV1 minus baseline FEV1. The adjusted mean (SE) are obtained from fitting an

MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Tiotropium 2.5 µg+ Olodaterol 5 µg v Tiotropium 5 µg + Olodaterol 5 µg |
| Number of subjects included in analysis | 399 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8669 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.003 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.04 |
| upper limit | 0.034 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.019 |

Primary: St. George's Respiratory Questionnaire (SGRQ) total score based on data from this individual study

| | |
|---|--|
| End point title | St. George's Respiratory Questionnaire (SGRQ) total score based on data from this individual study |
| End point description: | |
| The SGRQ ranges from 0 (no impairment of quality of life) to 100 (highest impairment of quality of life). The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom. An additional combined endpoint is defined and analysed for trial 1237.25 and 1237.26, however due to the platform limitations those could not be provided. Results can be found on CT.gov study number: NCT02006732. | |
| End point type | Primary |
| End point timeframe: | |
| 12 weeks treatment | |

| End point values | Placebo | Tiotropium 5 µg | Tiotropium 2.5 µg+ Olodaterol 5 µg | Tiotropium 5 µg + Olodaterol 5 µg |
|----------------------------------|--------------------|---------------------|------------------------------------|-----------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 184 ^[9] | 192 ^[10] | 195 ^[11] | 197 ^[12] |
| Units: units on a scale | | | | |
| arithmetic mean (standard error) | 42.575 (± 0.711) | 39.729 (± 0.694) | 38.909 (± 0.691) | 38.011 (± 0.683) |

Notes:

[9] - FAS including patients with available endpoint data at week 12

[10] - FAS including patients with available endpoint data at week 12

[11] - FAS including patients with available endpoint data at week 12

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|
| Statistical analysis description: | |
| Placebo vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom. | |
| Comparison groups | Placebo v Tiotropium 5 µg + Olodaterol 5 µg |
| Number of subjects included in analysis | 381 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -4.564 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.499 |
| upper limit | -2.629 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.986 |

| Statistical analysis title | Statistical analysis 2 |
|---|---|
| Statistical analysis description: | |
| Tiotropium 5 µg vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom. | |
| Comparison groups | Tiotropium 5 µg v Tiotropium 5 µg + Olodaterol 5 µg |
| Number of subjects included in analysis | 389 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.078 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.717 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.628 |
| upper limit | 0.193 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.974 |

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

Statistical analysis description:

Placebo vs. Tiotropium 2.5 µg + Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Placebo v Tiotropium 2.5 µg+ Olodaterol 5 µg |
| Number of subjects included in analysis | 379 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0002 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -3.666 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.611 |
| upper limit | -1.721 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.991 |

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

Statistical analysis description:

Tiotropium 5 µg vs. Tiotropium 2.5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Tiotropium 5 µg v Tiotropium 2.5 µg+ Olodaterol 5 µg |
| Number of subjects included in analysis | 387 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4028 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.741 |
| upper limit | 1.102 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.974 |

| | |
|--|--|
| Statistical analysis title | Statistical analysis 5 |
| Statistical analysis description: | |
| Placebo vs. Tiotropium 5 µg. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom. | |
| Comparison groups | Placebo v Tiotropium 5 µg |
| Number of subjects included in analysis | 376 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0042 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.846 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.796 |
| upper limit | -0.897 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.993 |

| | |
|--|--|
| Statistical analysis title | Statistical analysis 6 |
| Statistical analysis description: | |
| Tiotropium 2.5 µg+ Olodaterol 5 µg vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom. | |
| Comparison groups | Tiotropium 2.5 µg+ Olodaterol 5 µg v Tiotropium 5 µg + Olodaterol 5 µg |
| Number of subjects included in analysis | 392 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3555 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.898 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.804 |
| upper limit | 1.008 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.971 |

Secondary: Trough forced vital capacity (FVC) response (change from baseline)

| | |
|-----------------|--|
| End point title | Trough forced vital capacity (FVC) response (change from baseline) |
|-----------------|--|

End point description:

Trough FVC was defined as the FVC value at the end of the dosing interval (24 hours). It was calculated as the mean of the 2 FVC measurements performed 23 h and at 23 h 50 min after inhalation of study medication at day 85. Trough FVC response was defined as trough FVC minus baseline FVC. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

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

End point timeframe:

baseline and 12 weeks

| End point values | Placebo | Tiotropium 5 µg | Tiotropium 2.5 µg+ Olodaterol 5 µg | Tiotropium 5 µg + Olodaterol 5 µg |
|----------------------------------|---------------------|---------------------|------------------------------------|-----------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 193 ^[13] | 197 ^[14] | 200 ^[15] | 199 ^[16] |
| Units: Liter | | | | |
| arithmetic mean (standard error) | -0.021 (± 0.024) | 0.17 (± 0.023) | 0.284 (± 0.023) | 0.231 (± 0.023) |

Notes:

[13] - FAS including patients with available endpoint data at week 12

[14] - FAS including patients with available endpoint data at week 12

[15] - FAS including patients with available endpoint data at week 12

[16] - FAS including patients with available endpoint data at week 12

Statistical analyses

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

Statistical analysis description:

Placebo vs. Tiotropium 5 µg+ Olodaterol 5 µg. Trough FVC response was defined as trough FVC minus baseline FVC. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|---|
| Comparison groups | Placebo v Tiotropium 5 µg + Olodaterol 5 µg |
| Number of subjects included in analysis | 392 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.252 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.187 |
| upper limit | 0.317 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.033 |

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

Statistical analysis description:

Tiotropium 5 µg vs. Tiotropium 5 µg+ Olodaterol 5 µg. Trough FVC response was defined as trough FVC minus baseline FVC. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|---|
| Comparison groups | Tiotropium 5 µg v Tiotropium 5 µg + Olodaterol 5 µg |
| Number of subjects included in analysis | 396 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0614 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.061 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.003 |
| upper limit | 0.125 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.061 |

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

Statistical analysis description:

Placebo vs. Tiotropium 2.5 µg+ Olodaterol 5 µg. Trough FVC response was defined as trough FVC minus baseline FVC. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Placebo v Tiotropium 2.5 µg+ Olodaterol 5 µg |
| Number of subjects included in analysis | 393 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.305 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.24 |
| upper limit | 0.37 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.033 |

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

Statistical analysis description:

Tiotropium 5 µg vs. Tiotropium 2.5 µg+ Olodaterol 5 µg. Trough FVC response was defined as trough FVC minus baseline FVC. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Tiotropium 5 µg v Tiotropium 2.5 µg+ Olodaterol 5 µg |
| Number of subjects included in analysis | 397 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0005 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.114 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.049 |
| upper limit | 0.178 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.033 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Placebo vs. Tiotropium 5 µg. Trough FVC response was defined as trough FVC minus baseline FVC. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Placebo v Tiotropium 5 µg |
| Number of subjects included in analysis | 390 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.191 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.126 |
| upper limit | 0.256 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.033 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

Tiotropium 2.5 µg+ Olodaterol 5 µg vs. Tiotropium 5 µg+ Olodaterol 5 µg. Trough FVC response was defined as trough FVC minus baseline FVC. The adjusted mean (SE) are obtained from fitting an MMRM including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Tiotropium 2.5 µg+ Olodaterol 5 µg v Tiotropium 5 µg + Olodaterol 5 µg |
| Number of subjects included in analysis | 399 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1089 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.053 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.117 |
| upper limit | 0.012 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.033 |

Secondary: TDI focal score based on data from this individual study

| | |
|-----------------|--|
| End point title | TDI focal score based on data from this individual study |
|-----------------|--|

End point description:

Mahler Transitional Dyspnoea Index (TDI) focal score was performed to measure the effect of the treatment on patients' dyspnoea. (Rating scale of 3 components - change in functional impairment, change in magnitude of tasks, change in magnitude of efforts. Worst score = -9, best score = +9). The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom. An additional combined endpoint is defined and analysed for trial 1237.25 and 1237.26, however due to the platform limitations those could not be provided. Results can be found on CT.gov study number: NCT02006732.

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

End point timeframe:

12 weeks

| End point values | Placebo | Tiotropium 5 µg | Tiotropium 2.5 µg+ Olodaterol 5 µg | Tiotropium 5 µg + Olodaterol 5 µg |
|----------------------------------|---------------------|---------------------|------------------------------------|-----------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 183 ^[17] | 192 ^[18] | 195 ^[19] | 197 ^[20] |
| Units: Units on a scale | | | | |
| arithmetic mean (standard error) | 0.337 (± 0.195) | 0.95 (± 0.191) | 1.599 (± 0.189) | 1.531 (± 0.187) |

Notes:

[17] - FAS including patients with available endpoint data at week 12

[18] - FAS including patients with available endpoint data at week 12

[19] - FAS including patients with available endpoint data at week 12

[20] - FAS including patients with available endpoint data at week 12

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|
| Statistical analysis description: | |
| Placebo vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom. | |
| Comparison groups | Placebo v Tiotropium 5 µg + Olodaterol 5 µg |
| Number of subjects included in analysis | 380 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.195 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.665 |
| upper limit | 1.725 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.27 |

| Statistical analysis title | Statistical analysis 2 |
|---|---|
| Statistical analysis description: | |
| Tiotropium 5 µg vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom. | |
| Comparison groups | Tiotropium 5 µg v Tiotropium 5 µg + Olodaterol 5 µg |

| | |
|---|--|
| Number of subjects included in analysis | 389 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0296 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.582 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.058 |
| upper limit | 1.106 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.267 |

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

Statistical analysis description:

Placebo vs. Tiotropium 2.5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Placebo v Tiotropium 2.5 µg+ Olodaterol 5 µg |
| Number of subjects included in analysis | 378 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.263 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 1.796 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.272 |

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

Statistical analysis description:

Tiotropium 5 µg vs. Tiotropium 2.5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|-------------------|--|
| Comparison groups | Tiotropium 5 µg v Tiotropium 2.5 µg+ Olodaterol 5 µg |
|-------------------|--|

| | |
|---|--|
| Number of subjects included in analysis | 387 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0159 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.122 |
| upper limit | 1.178 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.269 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Placebo vs. Tiotropium 5 µg. The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Placebo v Tiotropium 5 µg |
| Number of subjects included in analysis | 375 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0248 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.613 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.078 |
| upper limit | 1.148 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.273 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

Tiotropium 2.5 µg+ Olodaterol 5 µg vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|-------------------|--|
| Comparison groups | Tiotropium 2.5 µg+ Olodaterol 5 µg v Tiotropium 5 µg + Olodaterol 5 µg |
|-------------------|--|

| | |
|---|--|
| Number of subjects included in analysis | 392 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7984 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.068 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.59 |
| upper limit | 0.454 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.266 |

Secondary: FVC AUC0-3h response (change from baseline)

| | |
|---|---|
| End point title | FVC AUC0-3h response (change from baseline) |
| End point description: | |
| The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom. | |
| End point type | Secondary |
| End point timeframe: | |
| baseline and 12 weeks | |

| End point values | Placebo | Tiotropium 5 µg | Tiotropium 2.5 µg+ Olodaterol 5 µg | Tiotropium 5 µg + Olodaterol 5 µg |
|----------------------------------|---------------------|---------------------|------------------------------------|-----------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 199 ^[21] | 201 ^[22] | 200 ^[23] | 200 ^[24] |
| Units: Liter | | | | |
| arithmetic mean (standard error) | -0.018 (± 0.025) | 0.266 (± 0.023) | 0.436 (± 0.024) | 0.414 (± 0.023) |

Notes:

[21] - FAS including patients with available endpoint data at week 12

[22] - FAS including patients with available endpoint data at week 12

[23] - FAS including patients with available endpoint data at week 12

[24] - FAS including patients with available endpoint data at week 12

Statistical analyses

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

Statistical analysis description:

Placebo vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|---|
| Comparison groups | Placebo v Tiotropium 5 µg + Olodaterol 5 µg |
| Number of subjects included in analysis | 399 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.432 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.366 |
| upper limit | 0.498 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.033 |

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

Statistical analysis description:

Tiotropium 5 µg vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|---|
| Comparison groups | Tiotropium 5 µg v Tiotropium 5 µg + Olodaterol 5 µg |
| Number of subjects included in analysis | 401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.148 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.084 |
| upper limit | 0.212 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.033 |

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

Statistical analysis description:

Placebo vs. Tiotropium 2.5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|-------------------|--|
| Comparison groups | Placebo v Tiotropium 2.5 µg+ Olodaterol 5 µg |
|-------------------|--|

| | |
|---|--|
| Number of subjects included in analysis | 399 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.455 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.387 |
| upper limit | 0.522 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.034 |

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

Statistical analysis description:

Tiotropium 5 µg vs. Tiotropium 2.5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Tiotropium 5 µg v Tiotropium 2.5 µg+ Olodaterol 5 µg |
| Number of subjects included in analysis | 401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.171 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.105 |
| upper limit | 0.236 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.034 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Placebo vs. Tiotropium 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|-------------------|---------------------------|
| Comparison groups | Placebo v Tiotropium 5 µg |
|-------------------|---------------------------|

| | |
|---|--|
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.284 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.217 |
| upper limit | 0.35 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.034 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

Tiotropium 2.5 µg+ Olodaterol 5 µg vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

| | |
|---|--|
| Comparison groups | Tiotropium 2.5 µg+ Olodaterol 5 µg v Tiotropium 5 µg + Olodaterol 5 µg |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4974 |
| Method | Mixed Effects Model for Repeated Measure |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.022 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.087 |
| upper limit | 0.042 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.033 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first drug administration to the last drug administration plus 21 days up to 112 days.

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | Treatment period Placebo |
|-----------------------|--------------------------|

Reporting group description:

Once daily 2 puffs solution of placebo for inhalation with Respimat

| | |
|-----------------------|----------------------------------|
| Reporting group title | Treatment period Tiotropium 5 µg |
|-----------------------|----------------------------------|

Reporting group description:

Once daily 2 puffs solution of 2.5 µg tiotropium for inhalation with Respimat

| | |
|-----------------------|---|
| Reporting group title | Treatment period Tiotropium 2.5 µg+ Olodaterol 5 µg |
|-----------------------|---|

Reporting group description:

Once daily 2 puffs solution of 1.25 µg tiotropium / 2.5 µg olodaterol for inhalation with Respimat.

| | |
|-----------------------|---|
| Reporting group title | Treatment period Tiotropium 5 µg+ Olodaterol 5 µg |
|-----------------------|---|

Reporting group description:

Once daily 2 puffs solution of 2.5 µg tiotropium / 2.5 µg olodaterol for inhalation with Respimat.

| Serious adverse events | Treatment period Placebo | Treatment period Tiotropium 5 µg | Treatment period Tiotropium 2.5 µg+ Olodaterol 5 µg |
|---|-----------------------------|-------------------------------------|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 202 (1.98%) | 12 / 203 (5.91%) | 4 / 202 (1.98%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 0 / 203 (0.00%) | 0 / 202 (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 |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | 0 / 202 (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 |
| Squamous cell carcinoma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | 0 / 202 (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 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 0 / 203 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | 0 / 202 (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 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | 0 / 202 (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 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 0 / 203 (0.00%) | 0 / 202 (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 |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | 0 / 202 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 0 / 203 (0.00%) | 0 / 202 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 2 / 203 (0.99%) | 0 / 202 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Supraventricular tachycardia subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | 0 / 202 (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 |
| Nervous system disorders | | | |
| Carotid artery stenosis subjects affected / exposed | 0 / 202 (0.00%) | 0 / 203 (0.00%) | 0 / 202 (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 |
| Eye disorders | | | |
| Blindness subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | 0 / 202 (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 |
| Gastrointestinal disorders | | | |
| Large intestine polyp subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | 0 / 202 (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 |
| Nausea subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | 0 / 202 (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 |
| Umbilical hernia subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | 0 / 202 (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 | | | |
| Acute respiratory failure subjects affected / exposed | 0 / 202 (0.00%) | 0 / 203 (0.00%) | 0 / 202 (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 |
| Chronic obstructive pulmonary disease | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 202 (0.50%) | 1 / 203 (0.49%) | 0 / 202 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 0 / 203 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 0 / 203 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Alcoholism | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | 0 / 202 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 2 / 203 (0.99%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 0 / 203 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | 0 / 202 (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 |

| | | | |
|------------------------------------|---|--|--|
| Serious adverse events | Treatment period Tiotropium 5 µg+ Olodaterol 5 µg | | |
| Total subjects affected by serious | | | |

| | | | |
|---|-----------------|--|--|
| adverse events | | | |
| subjects affected / exposed | 6 / 202 (2.97%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute myocardial infarction | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 202 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Blindness | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Nausea | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Alcoholism | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal chest pain | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Treatment period Placebo | Treatment period Tiotropium 5 µg | Treatment period Tiotropium 2.5 µg+ Olodaterol 5 µg |
|--|-----------------------------|-------------------------------------|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 34 / 202 (16.83%) | 15 / 203 (7.39%) | 25 / 202 (12.38%) |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 14 / 202 (6.93%) | 7 / 203 (3.45%) | 17 / 202 (8.42%) |
| occurrences (all) | 14 | 7 | 17 |
| Dyspnoea | | | |
| subjects affected / exposed | 14 / 202 (6.93%) | 4 / 203 (1.97%) | 4 / 202 (1.98%) |
| occurrences (all) | 14 | 4 | 4 |
| Cough | | | |
| subjects affected / exposed | 12 / 202 (5.94%) | 5 / 203 (2.46%) | 5 / 202 (2.48%) |
| occurrences (all) | 12 | 5 | 5 |

| Non-serious adverse events | Treatment period Tiotropium 5 µg+ Olodaterol 5 µg | | |
|--|---|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 14 / 202 (6.93%) | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---------------------------------------|-----------------|--|--|
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 9 / 202 (4.46%) | | |
| occurrences (all) | 9 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 202 (0.99%) | | |
| occurrences (all) | 2 | | |
| Cough | | | |
| subjects affected / exposed | 3 / 202 (1.49%) | | |
| occurrences (all) | 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 12 May 2014 | In this administrative revision of the trial protocol, medication restrictions and washout periods for bronchodilator medications were updated to define washout periods for bronchodilator medications marketed after finalisation of original protocol. Web cast training was added for sites that did not participate in hands-on training of MasterScope equipment during the investigator meeting to ensure that at least one staff member at each site was fully trained in the use of the ERT equipment. |
| 28 August 2014 | In this administrative revision of the trial protocol, the hypothesis testing strategy, text describing the hypothesis testing strategy and corresponding figure were updated to maintain consistency within the project. It was made explicit that safety laboratory tests and ECGs were to be performed locally and not collected in the database, and hence would not be analysed. Further details were added to provide clear guidance on visit rescheduling for patients recovering from acute exacerbations of COPD. |

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.

Additional combined primary and secondary endpoints are defined and analysed for trial 1237.25 and 1237.26, however due to the platform limitations those could not be provided. Results can be found on CT.gov study number: NCT02006732.

Notes: