



Clinical trial results:

A Randomized, Blinded, Double-dummy, Parallel-group Study to Evaluate the Efficacy and Safety of Umeclidinium (UMEC) 62.5 mcg compared with Tiotropium 18 mcg in Subjects with Chronic Obstructive Pulmonary Disease (COPD)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-000884-42 |
| Trial protocol | DE IT DK |
| Global end of trial date | 15 June 2015 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 27 May 2016 |
| First version publication date | 27 May 2016 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 201316 |
|-----------------------|--------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | GlaxoSmithKline |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |
| Scientific contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 31 August 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 June 2015 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the efficacy and safety of umeclidinium (UMEC) 62.5 microgram (mcg) with tiotropium 18 mcg in subjects with chronic obstructive pulmonary disease (COPD) over 12 weeks of treatment.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 30 September 2014 |
| 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 | Argentina: 11 |
| Country: Number of subjects enrolled | Canada: 171 |
| Country: Number of subjects enrolled | Chile: 65 |
| Country: Number of subjects enrolled | Denmark: 80 |
| Country: Number of subjects enrolled | France: 48 |
| Country: Number of subjects enrolled | Germany: 123 |
| Country: Number of subjects enrolled | Italy: 50 |
| Country: Number of subjects enrolled | Korea, Republic of: 79 |
| Country: Number of subjects enrolled | Romania: 130 |
| Country: Number of subjects enrolled | Russian Federation: 261 |
| Country: Number of subjects enrolled | South Africa: 79 |
| Country: Number of subjects enrolled | Ukraine: 119 |
| Country: Number of subjects enrolled | United States: 43 |
| Worldwide total number of subjects | 1259 |
| EEA total number of subjects | 431 |

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) | 640 |
| From 65 to 84 years | 612 |
| 85 years and over | 7 |

Subject disposition

Recruitment

Recruitment details:

A complete double-blind was not possible since tiotropium inhalation capsules had trade markings that were not present on placebo capsules, although capsules were closely matched in color. Study staff involved with safety and efficacy assessments were not present during dosing in the clinic to limit the possibility of capsule identification.

Pre-assignment

Screening details:

Participants (Par.), with clinical history of chronic obstructive pulmonary disease, who met eligibility criteria at screening were enrolled in a 7 to 14 days run-in period. Eligible par. were randomized (1:1) to receive umeclidinium or tiotropium. A total of 1214 par. were screened; 1017 par. were randomized and entered into the study.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|----------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Umeclidinium 62.5 mcg+Placebo QD |

Arm description:

Participants received umeclidinium (UMEC) inhalation powder 62.5 microgram (mcg) once-daily (QD) in morning via a novel dry powder inhaler (nDPI) and placebo QD via alternative dry powder inhaler (DPI) for 12 weeks (For participants enrolled in Germany, the duration of treatment was 24 weeks). Participants also received albuterol/salbutamol via metered-dose-inhaler (MDI) or nebulas as rescue medication throughout the study for use as needed.

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Umeclidinium |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Single dose of umeclidinium (UMEC) 62.5 microgram (mcg) in morning once daily (QD) via novel Dry Powder Inhaler (nDPI) for 12 weeks. For participants enrolled in Germany, the duration of treatment was 24 weeks.

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

Dosage and administration details:

Single dose of matching placebo in morning QD via Handihaler inhaler for 12 weeks. For participants enrolled in Germany, the duration of treatment was 24 weeks.

| | |
|------------------|------------------------------|
| Arm title | Tiotropium 18 mcg+Placebo QD |
|------------------|------------------------------|

Arm description:

Participants received tiotropium (TIO) 18 mcg QD in morning via DPI and placebo QD via nDPI for 12 weeks (For participants enrolled in Germany, the duration of treatment was 24 weeks). Participants also received albuterol/salbutamol via MDI or nebulas as rescue medication throughout the study for use as

needed.

| | |
|--|---------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Tiotropium |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Single dose of Tiotropium 18 mcg in morning QD via Handihaler inhaler for 12 weeks. For participants enrolled in Germany, the duration of treatment was 24 weeks.

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

Dosage and administration details:

Single dose of matching placebo in morning QD via nDPI for 12 weeks. For participants enrolled in Germany, the duration of treatment was 24 weeks.

| Number of subjects in period 1^[1] | Umeclidinium 62.5 mcg+Placebo QD | Tiotropium 18 mcg+Placebo QD |
|---|----------------------------------|------------------------------|
| Started | 509 | 508 |
| Completed | 467 | 474 |
| Not completed | 42 | 34 |
| Adverse event, serious fatal | - | 2 |
| Adverse event, non-fatal | 10 | 7 |
| Protocol deviation | 5 | 4 |
| Lost to follow-up | 2 | 2 |
| Withdrew consent | 18 | 14 |
| Lack of efficacy | 7 | 5 |

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: Participants (Par.), with clinical history of chronic obstructive pulmonary disease, who met eligibility criteria at screening were enrolled in a 7 to 14 days run-in period. Eligible par. were randomized (1:1) to receive umeclidinium and tiotropium. A total of 1214 par. were screened; 1017 par. were randomized and entered into the study.

Baseline characteristics

Reporting groups

| | |
|---|----------------------------------|
| Reporting group title | Umeclidinium 62.5 mcg+Placebo QD |
| Reporting group description: Participants received umeclidinium (UMEC) inhalation powder 62.5 microgram (mcg) once-daily (QD) in morning via a novel dry powder inhaler (nDPI) and placebo QD via alternative dry powder inhaler (DPI) for 12 weeks (For participants enrolled in Germany, the duration of treatment was 24 weeks). Participants also received albuterol/salbutamol via metered-dose-inhaler (MDI) or nebulas as rescue medication throughout the study for use as needed. | |
| Reporting group title | Tiotropium 18 mcg+Placebo QD |
| Reporting group description: Participants received tiotropium (TIO) 18 mcg QD in morning via DPI and placebo QD via nDPI for 12 weeks (For participants enrolled in Germany, the duration of treatment was 24 weeks). Participants also received albuterol/salbutamol via MDI or nebulas as rescue medication throughout the study for use as needed. | |

| Reporting group values | Umeclidinium 62.5 mcg+Placebo QD | Tiotropium 18 mcg+Placebo QD | Total |
|---|----------------------------------|------------------------------|-------|
| Number of subjects | 509 | 508 | 1017 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: | 64.4 ± 8.12 | 64.1 ± 8.28 | - |
| Gender categorical Units: Subjects | | | |
| Female | 145 | 137 | 282 |
| Male | 364 | 371 | 735 |
| Race, Customized Units: Subjects | | | |
| African American/African Heritage | 9 | 9 | 18 |
| American Indian or Alaska Native | 1 | 0 | 1 |
| Central/South Asian Heritage | 0 | 1 | 1 |
| Japanese/East Asian/South East Asian Heritage | 38 | 37 | 75 |
| White | 458 | 457 | 915 |
| African American/African Heritage & White | 3 | 4 | 7 |

End points

End points reporting groups

| | |
|---|----------------------------------|
| Reporting group title | Umeclidinium 62.5 mcg+Placebo QD |
| Reporting group description: Participants received umeclidinium (UMEC) inhalation powder 62.5 microgram (mcg) once-daily (QD) in morning via a novel dry powder inhaler (nDPI) and placebo QD via alternative dry powder inhaler (DPI) for 12 weeks (For participants enrolled in Germany, the duration of treatment was 24 weeks). Participants also received albuterol/salbutamol via metered-dose-inhaler (MDI) or nebulas as rescue medication throughout the study for use as needed. | |
| Reporting group title | Tiotropium 18 mcg+Placebo QD |
| Reporting group description: Participants received tiotropium (TIO) 18 mcg QD in morning via DPI and placebo QD via nDPI for 12 weeks (For participants enrolled in Germany, the duration of treatment was 24 weeks). Participants also received albuterol/salbutamol via MDI or nebulas as rescue medication throughout the study for use as needed. | |

Primary: Change from Baseline in trough forced expiratory volume in one second (FEV1) on Day 85

| | |
|---|--|
| End point title | Change from Baseline in trough forced expiratory volume in one second (FEV1) on Day 85 |
| End point description: FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. Trough FEV1 on Day 85 is defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Day 84 (Week 12). Trough FEV1 was measured using spirometry. Baseline trough FEV1 is the mean of the two assessments made -30 and -5 minutes (min) pre-dose on Day 1. Change from baseline was calculated as the trough FEV1 value on Day 85 minus the BL value. Analysis performed using a repeated measures model with covariates of treatment, baseline FEV1, centre group, 24 hour subset flag, Day, Day by baseline and Day by treatment interactions. Per Protocol (PP) Population: Comprised of all participants in the Intent-To-Treat (ITT) population who did not have a full protocol deviation considered to impact efficacy. Only participants with data available at specific time point were analyzed. | |
| End point type | Primary |
| End point timeframe: Baseline (BL) and Day 85 | |

| End point values | Umeclidinium 62.5 mcg+Placebo QD | Tiotropium 18 mcg+Placebo QD | | |
|-------------------------------------|----------------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 392 ^[1] | 416 ^[2] | | |
| Units: Liter | | | | |
| least squares mean (standard error) | 0.154 (± 0.0107) | 0.095 (± 0.0106) | | |

Notes:

[1] - PP population

[2] - PP population

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| Participants represent those with data available at time point presented; however, all participants in the PP population without missing covariate information and ≥ 1 post Baseline measurement are included in analysis. | |
| Comparison groups | Umeclidinium 62.5 mcg+Placebo QD v Tiotropium 18 mcg+Placebo QD |
| Number of subjects included in analysis | 808 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.059 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.029 |
| upper limit | 0.088 |

Notes:

[3] - Alternate hypothesis: the difference between the trt means (umeclidinium minus tiotropium) would be > -50 milliliters (mL). If the lower CI (2.5% 1-sided significance level) of the statistical test should fall above -50 mL, then umeclidinium may be deemed statistically non-inferior to tiotropium. If the lower CI (2.5% 1-sided significance) of the statistical testing exceeded 0 then, umeclidinium may be deemed statistically superior to tiotropium.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment(trt) non-serious adverse events(AEs) and serious AEs are events occurring while par were on trt or events with an onset during follow-up period(up to 13 weeks). AE data for German subjects are only included for the first 12 weeks of trt.

Adverse event reporting additional description:

On-treatment SAEs and non-serious AEs were reported for the ITT Population comprised all participants randomized to treatment who received at least one dose of randomized study medication in the treatment period.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------------|
| Reporting group title | Tiotropium 18 mcg+Placebo QD |
|-----------------------|------------------------------|

Reporting group description:

Participants received tiotropium (TIO) 18 mcg QD in morning via DPI and placebo QD via nDPI for 12 weeks (For participants enrolled in Germany, the duration of treatment was 24 weeks). Participants also received albuterol/salbutamol via MDI or nebulas as rescue medication throughout the study for use as needed.

| | |
|-----------------------|----------------------------------|
| Reporting group title | Umeclidinium 62.5 mcg+Placebo QD |
|-----------------------|----------------------------------|

Reporting group description:

Participants received umeclidinium (UMEC) inhalation powder 62.5 microgram (mcg) once-daily (QD) in morning via a novel dry powder inhaler (nDPI) and placebo QD via alternative dry powder inhaler (DPI) for 12 weeks (For participants enrolled in Germany, the duration of treatment was 24 weeks). Participants also received albuterol/salbutamol via metered-dose-inhaler (MDI) or nebulas as rescue medication throughout the study for use as needed.

| Serious adverse events | Tiotropium 18 mcg+Placebo QD | Umeclidinium 62.5 mcg+Placebo QD | |
|---|------------------------------|----------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 508 (3.15%) | 17 / 509 (3.34%) | |
| number of deaths (all causes) | 2 | 0 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 508 (0.00%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-Hodgkin's lymphoma | | | |
| subjects affected / exposed | 1 / 508 (0.20%) | 0 / 509 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Lung adenocarcinoma metastatic subjects affected / exposed | 0 / 508 (0.00%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial carcinoma subjects affected / exposed | 0 / 508 (0.00%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Tibia fracture subjects affected / exposed | 0 / 508 (0.00%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture subjects affected / exposed | 1 / 508 (0.20%) | 0 / 509 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture subjects affected / exposed | 0 / 508 (0.00%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alcohol poisoning subjects affected / exposed | 1 / 508 (0.20%) | 0 / 509 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertension subjects affected / exposed | 1 / 508 (0.20%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis subjects affected / exposed | 0 / 508 (0.00%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Cardiac disorders | | | |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 0 / 508 (0.00%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 508 (0.00%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 508 (0.00%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 508 (0.20%) | 0 / 509 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 508 (0.20%) | 0 / 509 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 508 (0.20%) | 0 / 509 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 508 (0.00%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 6 / 508 (1.18%) | 2 / 509 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 6 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 508 (0.00%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 508 (0.00%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 508 (0.20%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 1 / 508 (0.20%) | 0 / 509 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lobar pneumonia | | | |
| subjects affected / exposed | 0 / 508 (0.00%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective exacerbation of chronic obstructive airway disease | | | |
| subjects affected / exposed | 1 / 508 (0.20%) | 0 / 509 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 0 / 508 (0.00%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Metabolism and nutrition disorders | | | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 508 (0.00%) | 1 / 509 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Tiotropium 18 mcg+Placebo QD | Umeclidinium 62.5 mcg+Placebo QD | |
|---|------------------------------|----------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 52 / 508 (10.24%) | 50 / 509 (9.82%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 32 / 508 (6.30%) | 30 / 509 (5.89%) | |
| occurrences (all) | 44 | 49 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 23 / 508 (4.53%) | 27 / 509 (5.30%) | |
| occurrences (all) | 26 | 28 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 22 May 2014 | <p>This protocol amendment has been created predominantly to extend the duration of the study from 12 weeks to 24 weeks for subjects enrolled across all study sites in Germany. For these subjects, blinded treatment will continue for a further 12 weeks from the end of the initial 12 week treatment period.</p> <p>The data analysis and statistical considerations section of the protocol (Section 8) has been amended to include a new Intent-To-Treat (ITT) population for Germany and also to revise statistical considerations with regards to the analysis of additional data (St. George's Respiratory Questionnaire [SGRQ], Chronic Obstructive Pulmonary Disease Assessment Test [CAT], rescue medication use and safety) for those subjects enrolled in Germany.</p> <p>Exclusion criterion number 6 has been revised to exclude subjects with both moderate and severe renal impairment (as opposed to severe renal impairment only) unless in the opinion of the investigator, the benefit is likely to outweigh the risk in accordance with the tiotropium label (SmPC; Summary of Product Characteristics).</p> <p>The medical monitor contact information has been revised to include two new medical monitors responsible for specific regions. New text has been included with regards to recent approvals of the UMEC monotherapy 62.5 mcg dose in Canada, USA and in Europe (European Economic Area).</p> <p>Other minor corrections and edits have been made.</p> |
| 26 September 2014 | <p>The amendment has been created to clarify that a single dose from the nDPI will consist of 1 inhalation from the nDPI and that a single dose of tiotropium or matching placebo will consist of 2 inhalations of the powder contents of a single capsule with the Handihaler. • Thus the sections, 5.1 (paragraph 7), 5.1.2 (paragraph 1), 5.2 (paragraph 5) have been revised in alignment with the above mentioned text to clarify that a single dose from the nDPI will consist of 1 inhalation from the nDPI and that a single dose of tiotropium or matching placebo will consist of 2 inhalations of the powder contents of a single capsule with the Handihaler. Also, Section 5.2 (paragraph 8) has been revised to clarify that an albuterol/salbutamol new container will be dispensed "as needed after Visit 1". Also, the following revisions are included to revise the medical monitor information, to clarify the calculation of compliance and to include the collection of pneumonia event specific information for pneumonia AEs in a specific Electronic Case Report Form (eCRF). The Disease Related Event (DRE) reporting in section 6.3.14 table was deleted as this is captured separately per explanation in Section 6.3.9: • The Medical Monitor information has been revised to update the global and add the new back-up Medical Monitors. • Section Protocol Summary has been revised for the primary endpoint to include formatting changes, second bullet formatting removed to reflect a single primary endpoint • Section 5.5 has been revised to clarify compliance with the Handihaler is to be determined by counting the number of "unused" capsules remaining • Section 6.3.7 has been added to include collection of pneumonia events specific information occurring after subject randomization in an eCRF. Section 6.3.14 has been revised to include pneumonia events for Prompt Reporting of Serious Adverse Events and Others Events to GlaxoSmithKline.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported