



Clinical trial results:

A randomized, multi-center, double-blind, doubledummy, parallel group study to evaluate the efficacy and safety of umeclidinium/vilanterol compared with fluticasone propionate/salmeterol over 12 weeks in subjects with COPD.

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2012-002156-16 |
| Trial protocol | RO |
| Global end of trial date | 09 January 2014 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 27 April 2016 |
| First version publication date | 01 May 2015 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | DB2114951 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01879410 |
| 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 | 13 March 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 January 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Compare the efficacy and safety of UMEC/VI Inhalation Powder (62.5/25 µg oncedaily) with fluticasone propionate/salmeterol (250/50 µg twice-daily) over 12 weeks in subjects with COPD who have a history of infrequent COPD exacerbations

Protection of trial subjects:

Several measures were taken to protect trials participants: these included adverse event monitoring throughout the study, frequent clinic visits (approximately every 4 weeks) to monitor participant status, exclusion of participants with clinically significant and uncontrolled medical conditions and/or ECG findings, and use of treatment arms where all participants received pharmacologic treatment that was appropriate for the disease and disease severity under study.

Fluticasone propionate/salmeterol combination inhalation powder is a marketed product and was administered according to the local label. Fluticasone propionate/salmeterol has an acceptable safety profile for use. This conclusion is supported by the results of previously performed clinical studies and post-marketing experience (see local label).

All participants were on active treatment.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 13 June 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 | Chile: 100 |
| Country: Number of subjects enrolled | Mexico: 50 |
| Country: Number of subjects enrolled | Russian Federation: 269 |
| Country: Number of subjects enrolled | South Africa: 110 |
| Country: Number of subjects enrolled | United States: 232 |
| Country: Number of subjects enrolled | Norway: 70 |
| Country: Number of subjects enrolled | Romania: 135 |
| Worldwide total number of subjects | 966 |
| EEA total number of subjects | 205 |

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) | 518 |
| From 65 to 84 years | 438 |
| 85 years and over | 10 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 700 participants (par.) representing the enrolled participants, were randomized to study treatment. Of these, 697 comprised the Intent-to-Treat Population (participants randomized to treatment who received ≥ 1 dose of randomized study medication in the treatment period).

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, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | UMEC/VI 62.5/25 µg |

Arm description:

Participants received umeclidinium bromide/vilanterol (UMEC/VI) 62.5/25 micrograms (µg) once daily (QD) in the morning via a dry powder inhaler (DPI) and placebo in the morning and evening via a separate DPI for 12 weeks.

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

Dosage and administration details:

62.5/25 µg once-daily via dry powder inhaler

| | |
|------------------|---------------|
| Arm title | FSC 250/50 µg |
|------------------|---------------|

Arm description:

Participants received fluticasone propionate/salmeterol (FSC) 250/50 µg twice daily (BID) in the morning and evening via a DPI and placebo in the morning via a separate DPI for 12 weeks.

| | |
|--|---|
| Arm type | Active comparator |
| Investigational medicinal product name | fluticasone propionate/salmeterol Inhalation Powder |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Respiratory use |

Dosage and administration details:

250/50 µg twice-daily via dry powder inhaler

| Number of subjects in period 1^[1] | UMEC/VI 62.5/25 µg | FSC 250/50 µg |
|---|--------------------|---------------|
| Started | 349 | 348 |
| Completed | 326 | 312 |
| Not completed | 23 | 36 |
| Adverse event, serious fatal | 2 | 3 |
| Consent withdrawn by subject | 7 | 8 |
| Adverse event, non-fatal | 7 | 11 |
| Lost to follow-up | 2 | 1 |
| Lack of efficacy | 4 | 6 |
| Protocol deviation | 1 | 7 |

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: Although 966 participants were enrolled in the trial worldwide, only 700 were randomized to treatment. Of these, 697 participants comprised the Intent-to-Treat Population (participants randomized to treatment who received ≥ 1 dose of randomized study medication in the treatment period).

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | UMEC/VI 62.5/25 µg |
|-----------------------|--------------------|

Reporting group description:

Participants received umeclidinium bromide/vilanterol (UMEC/VI) 62.5/25 micrograms (µg) once daily (QD) in the morning via a dry powder inhaler (DPI) and placebo in the morning and evening via a separate DPI for 12 weeks.

| | |
|-----------------------|---------------|
| Reporting group title | FSC 250/50 µg |
|-----------------------|---------------|

Reporting group description:

Participants received fluticasone propionate/salmeterol (FSC) 250/50 µg twice daily (BID) in the morning and evening via a DPI and placebo in the morning via a separate DPI for 12 weeks.

| Reporting group values | UMEC/VI 62.5/25 µg | FSC 250/50 µg | Total |
|------------------------|--------------------|---------------|-------|
| Number of subjects | 349 | 348 | 697 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|--------|--------|-----|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 63.2 | 64 | |
| standard deviation | ± 8.57 | ± 8.53 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 85 | 84 | 169 |
| Male | 264 | 264 | 528 |
| Race | | | |
| Units: Subjects | | | |
| African American/African Heritage | 18 | 13 | 31 |
| American Indian or Alaska Native | 7 | 2 | 9 |
| Asian | 4 | 2 | 6 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| White | 317 | 326 | 643 |
| American Indian or Alaska Native & White | 3 | 5 | 8 |

End points

End points reporting groups

| | |
|---|--------------------|
| Reporting group title | UMEC/VI 62.5/25 µg |
| Reporting group description: Participants received umeclidinium bromide/vilanterol (UMEC/VI) 62.5/25 micrograms (µg) once daily (QD) in the morning via a dry powder inhaler (DPI) and placebo in the morning and evening via a separate DPI for 12 weeks. | |
| Reporting group title | FSC 250/50 µg |
| Reporting group description: Participants received fluticasone propionate/salmeterol (FSC) 250/50 µg twice daily (BID) in the morning and evening via a DPI and placebo in the morning via a separate DPI for 12 weeks. | |

Primary: Change from Baseline (BL) in 0 to 24 hour weighted mean forced expiratory volume over 1 second (FEV1) at Day 84

| | |
|---|---|
| End point title | Change from Baseline (BL) in 0 to 24 hour weighted mean forced expiratory volume over 1 second (FEV1) at Day 84 |
| 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. The weighted mean was calculated from the pre-dose FEV1 and post-dose FEV1 measurements at 5 and 15 minutes and 1, 3, 6, 9, 12 hours (pre-evening dose), 13, 15, 18, 23, and 24 hours after the morning dose. Baseline is defined as the mean of the assessments made 30 and 5 minutes (min) pre-dose on treatment Day 1. Analysis was performed using an analysis of covariance model with covariates of baseline FEV1 (mean of the two assessments made 30 mins and 5 mins pre-dose on Day 1), smoking status, and treatment. Change from baseline was calculated as the value at Day 84 minus the value at Baseline. Participants analyzed were those with data available at the presented time point; but, all participants without missing covariate information and with \geq post BL measurement were included in the analysis. | |
| End point type | Primary |
| End point timeframe: Baseline and Day 84 | |

| End point values | UMEC/VI 62.5/25 µg | FSC 250/50 µg | | |
|-------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 322 ^[1] | 311 ^[2] | | |
| Units: Liters | | | | |
| least squares mean (standard error) | 0.213 (± 0.0137) | 0.112 (± 0.0139) | | |

Notes:

[1] - Intent-to-Treat (ITT) Population

[2] - ITT Population

Statistical analyses

| | |
|----------------------------|------------------------------------|
| Statistical analysis title | Analysis 1 |
| Comparison groups | UMEC/VI 62.5/25 µg v FSC 250/50 µg |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 633 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.101 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.063 |
| upper limit | 0.139 |

Notes:

[3] - Least squares mean difference=UMEC/VI 62.5/25 µg minus FSC 250/50 µg.

Secondary: Change from Baseline(BL) in trough forced expiratory volume in one second (FEV1) at Day 85

| | |
|-----------------|--|
| End point title | Change from Baseline(BL) in trough forced expiratory volume in one second (FEV1) at 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. BL is defined as the mean of the assessments made 30 and 5 min pre-dose on treatment (trt) Day 1. Trough FEV1 on Day 85 is defined as the mean of the FEV1 values obtained 23 and 24 hours after morning dosing on Day 84. Analysis was performed using a repeated measures model with covariates of trt, BL (mean of the 2 assessments made 30 and 5 min pre-dose on Day 1), smoking status, day, day by BL and day by trt interactions. The model used all available trough FEV1 values recorded on Days 28, 56, 84, and 85. Missing data were not directly imputed in this analysis; however, all non-missing data for a par. were used to estimate the trt effect for trough FEV1 at Day 85. Change from BL=value at Day 84 minus value at BL. Par. analyzed were those with data available at the time point; but, all par. without missing covariate information were included in the analysis.

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

End point timeframe:

Baseline and Day 85

| End point values | UMEC/VI 62.5/25 µg | FSC 250/50 µg | | |
|-------------------------------------|-----------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 323 ^[4] | 311 ^[5] | | |
| Units: Liters | | | | |
| least squares mean (standard error) | 0.185 (± 0.0138) | 0.087 (± 0.014) | | |

Notes:

[4] - ITT Population

[5] - ITT Population

Statistical analyses

| | |
|----------------------------|------------------------------------|
| Statistical analysis title | Analysis 2 |
| Comparison groups | UMEC/VI 62.5/25 µg v FSC 250/50 µg |

| | |
|---|-------------------|
| Number of subjects included in analysis | 634 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | Repeated measures |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.059 |
| upper limit | 0.137 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious adverse events (AEs) collected from the start of study treatment up to the Follow-up Visit or premature withdrawal (up to Day 94)

Adverse event reporting additional description:

SAEs and non-serious AEs are reported for members of the ITT Population, comprised of all randomized participants who received at least 1 dose of randomized study drug in the treatment period.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | UMEC/VI 62.5/25 µg |
|-----------------------|--------------------|

Reporting group description:

Participants received UMEC/VI 62.5/25 µg QD in the morning via a DPI and placebo in the morning and evening via a separate DPI for 12 weeks

| | |
|-----------------------|---------------|
| Reporting group title | FSC 250/50 µg |
|-----------------------|---------------|

Reporting group description:

Participants received FSC 250/50 µg BID in the morning and evening via a DPI and placebo in the morning via a separate DPI for 12 weeks.

| Serious adverse events | UMEC/VI 62.5/25 µg | FSC 250/50 µg | |
|---|--------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 11 / 349 (3.15%) | 13 / 348 (3.74%) | |
| number of deaths (all causes) | 2 | 3 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 348 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 348 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small cell lung cancer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 348 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vascular disorders | | | |
| Peripheral artery thrombosis | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 348 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 348 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 348 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 1 / 348 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleurisy | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 348 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax spontaneous | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 348 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 348 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 4 / 349 (1.15%) | 4 / 348 (1.15%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Alcohol abuse | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 348 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 348 (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 | 1 / 349 (0.29%) | 0 / 348 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Perirectal abscess | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 348 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 348 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 4 / 348 (1.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |

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

| Non-serious adverse events | UMEC/VI 62.5/25 µg | FSC 250/50 µg | |
|---|--------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 36 / 349 (10.32%) | 28 / 348 (8.05%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 24 / 349 (6.88%) | 23 / 348 (6.61%) | |
| occurrences (all) | 52 | 41 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 14 / 349 (4.01%) | 6 / 348 (1.72%) | |
| occurrences (all) | 17 | 7 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported