ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: January 18, 2018

ClinicalTrials.gov ID: NCT02014480

## Study Identification

| | |
|---|---|
| Unique Protocol ID: | 116132 |
| Brief Title: | A Cross-Over Study to Evaluate Lung Function Response After Treatment With Umeclidinium (UMEC) 62.5 Micrograms (mcg), Vilanterol (VI) 25 mcg, and Umeclidinium/Vilanterol (UMEC/VI) 62.5/25 mcg Once-Daily in Subjects With Chronic Obstructive Pulmonary Disease (COPD) |
| Official Title: | A Randomized, Double-Blind, 3-Way, Cross-Over Study to Evaluate Lung Function Response After Treatment With Umeclidinium 62.5 mcg, Vilanterol 25 mcg, and Umeclidinium/Vilanterol 62.5/25 mcg Once-Daily in Subjects With Chronic Obstructive Pulmonary Disease (COPD) |
| Secondary IDs: | |

## Study Status

| | |
|---|---|
| Record Verification: | January 2018 |
| Overall Status: | Completed |
| Study Start: | February 1, 2013 [] |
| Primary Completion: | June 1, 2013 [Actual] |
| Study Completion: | June 11, 2013 [Actual] |

## Sponsor/Collaborators

| | |
|---|---|
| Sponsor: | GlaxoSmithKline |
| Responsible Party: | Sponsor |
| Collaborators: | |

## Oversight

| | |
|---|---|
| U.S. FDA-regulated Drug: | |
| U.S. FDA-regulated Device: | |
| Unapproved/Uncleared Device: | No |
| U.S. FDA IND/IDE: | No |
| Human Subjects Review: | Board Status: Approved<br>Approval Number: 2921/2012-RU20/17006<br>Board Name: Etická komisia košického samosprávneho kraja<br>Board Affiliation: Etická komisia košického samosprávneho kraja<br>Phone: +421 55 72681 41<br>Email:<br>Address: |
| Data Monitoring: | No |
| FDA Regulated Intervention: | Yes |
| Section 801 Clinical Trial: | Yes |

## Study Description

| | |
|---|---|
| Brief Summary: | This is a multicenter, randomized, double-blind, 3-way crossover study to evaluate the lung function response to UMEC 62.5 mcg, VI 25 mcg, and UMEC/VI 62.525 mcg, administered once-daily via a novel dry powder inhaler (NDPI) over 14 days in subjects with COPD.<br><br>The study consisted of Run in Phase (5 to 7 days), Treatment Phase (made up of 3 treatment periods of 14 days each separated by 10 to 14 days Washout Period) and Follow-up Phase (7 to 9 days after completion of final visit or premature discontinuation). Eligible subjects will be randomized to a sequence of UMEC 62.5 mcg, VI 25 mcg, and UMEC/VI 62.5/25 mcg such that all subjects will receive each treatment.<br><br>Serial spirometry assessments will be conducted on Day 1 and Day 14 and trough spirometry will be conducted on Day 2 and Day 15 of each treatment period. On Day 1 and 14 of each treatment period vital signs will be assessed and adverse event (AE)s will be recorded throughout the total duration of the study (approximately 12 weeks). |
| Detailed Description: | |

## Conditions

| | |
|---|---|
| Conditions: | Pulmonary Disease, Chronic Obstructive |

Keywords: Long-acting beta-agonist
Chronic Obstructive Pulmonary Disease
Umeclidinium
Long-acting muscarinic antagonist
Vilanterol

## Study Design

Study Type: Interventional
Primary Purpose: Treatment
Study Phase: Phase 3
Interventional Study Model: Crossover Assignment
Number of Arms: 3
Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Allocation: Randomized
Enrollment: 207 [Actual]

## Arms and Interventions

| Arms | Assigned Interventions |
|---|---|
| Experimental: Umeclidinium<br>All subjects will receive UMEC in the dose of 62.5 mcg as inhalation powder in the NDPI once daily in the morning over 14 days in a cross over design. | Device: Umeclidinium 62.5 mcg<br>Umeclidinium 62.5 mcg once daily in the morning via NDPI. |
| Experimental: Vilanterol<br>All subjects will receive VI in the dose of 25 mcg as inhalation powder in the NDPI once daily in the morning over 14 days in a cross over design. | Device: Vilanterol 25 mcg<br>Vilanterol 25 mcg once daily in the morning via NDPI. |
| Experimental: Umeclidinium/Vilanterol<br>All subjects will receive UMEC/VI in the dose of 62.5/25 mcg as inhalation powder in the NDPI once daily in the morning over 14 days in a cross over design. | Device: Umeclidinium/Vilanterol 62.5/25 mcg<br>Umeclidinium/Vilanterol 62.5/25 mcg once daily in the morning via NDPI. |

## Outcome Measures

[See Results Section.]

## Eligibility

| | |
|---|---|
| Minimum Age: | 40 Years |
| Maximum Age: | |
| Sex: | All |
| Gender Based: | |
| Accepts Healthy Volunteers: | No |

Criteria: Inclusion Criteria:

- Type of Patient: Outpatient.
- Informed Consent: A signed and dated written informed consent prior to study participation.
- Age: Subjects 40 years of age or older at Visit 1.
- Gender: Male or female subjects.
- A female is eligible to enter and participate in the study if she is of: Non-child bearing potential. Surgically sterile females are defined as those with a documented hysterectomy and/or bilateral oophorectomy or tubal ligation. Post-menopausal females are defined as being amenorrhoeic for greater than 1 year with an appropriate clinical profile, e.g. age appropriate, >45 years, in the absence of hormone replacement therapy. OR Child bearing potential, has a negative pregnancy test at screening, and agrees to one of the acceptable contraceptive methods used consistently and correctly.
- Diagnosis: An established clinical history of COPD in accordance with the definition by the American Thoracic Society/ European Respiratory Society.
- Smoking History: Current or former cigarette smokers with a history of cigarette smoking of >= 10 pack-years at Visit 1.
- Severity of Disease: A pre- and post-salbutamol FEV1/forced vital capacity (FVC) ratio of <0.70 and a pre- and post-salbutamol FEV1 of <=70% of predicted normal values at Visit 1 calculated using Nutrition Health and Examination Survey (NHANES) III reference Equations.

Exclusion Criteria:

- Pregnancy: Women who are pregnant or lactating or are planning on becoming pregnant during the study.
- Asthma: A current diagnosis of asthma.
- Other Respiratory Disorders: Known alpha-1 antitrypsin deficiency, active lung infections (such as tuberculosis), and lung cancer are absolute exclusionary conditions. A subject, who, in the opinion of the investigator, has any other significant respiratory condition in addition to COPD, should be excluded. Examples may include clinically significant bronchiectasis, pulmonary hypertension, sarcoidosis, or interstitial lung disease. Allergic rhinitis is not exclusionary. Other Diseases/ Abnormalities: Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled and/or a previous history of cancer in remission for <5 years prior to Visit 1 (localized carcinoma of the skin that has been resected for cure is not exclusionary).
- Contraindications: A history of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate or a medical condition such as of narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the study physician contraindicates study participation or use of an inhaled anticholinergic.
- Hospitalization: Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1.
- Lung Resection: Subjects with lung volume reduction surgery within the 12 months prior to Visit 1.

- 12-Lead ECG: An abnormal and significant electrocardiogram (ECG) finding from the 12-lead ECG conducted at Visit 1, Investigators will be provided with ECG reviews conducted by a centralized independent cardiologist to assist in evaluation of subject eligibility. The study investigator will determine the medical significance of any ECG abnormalities.
- Medication Prior to Spirometry: Unable to withhold salbutamol for the 4 hour period required prior to spirometry testing at each study visit and at each spirometry test performed at home.
- Medications Prior to Screening: Use of the following medications according to the following defined time intervals prior to Visit 1: Depot corticosteroids (12 weeks), oral or parenteral corticosteroids (6 weeks), antibiotics (for lower respiratory tract infection) (6 weeks), cytochrome P450 3A4 strong inhibitors2 (6 weeks), long-acting beta agonist (LABA)/ inhaled corticosteroid (ICS) combination products if LABA/ICS therapy is discontinued completely (30 days), use of ICS at a dose >1000 mcg/day of fluticasone propionate or equivalent (30 days), initiation or discontinuation of ICS use (30 days), tiotropium (7 days), roflumilast (14 days), theophyllines (48 hours), oral leukotriene inhibitors (zafirlukast, montelukast, zileuton) (48 hours), oral beta-agonists long-acting (48 hours), short-acting (12 hours), inhaled long acting beta2-agonists (LABA, e.g., salmeterol, formoterol, indacaterol) (48 hours), LABA/ICS combination products only if discontinuing LABA therapy and switching to ICS monotherapy (48 hours for the LABA component), inhaled sodium cromoglycate or nedocromil sodium (24 hours), inhaled short acting beta2-agonists (4 hours), inhaled short-acting anticholinergic/short-acting beta2-agonist combination products (4 hours) and any other investigational medication 30 days or within 5 drug half-lives (whichever is longer).
- Oxygen: Use of long-term oxygen therapy (LTOT) described as oxygen therapy prescribed for greater than 12 hours a day. As-needed oxygen use (i.e., <=12 hours per day) is not exclusionary.
- Nebulized Therapy: Regular use (prescribed for use every day, not for as-needed use) of short-acting bronchodilators (e.g., salbutamol, ipratropium bromide) via nebulized therapy.
- Pulmonary Rehabilitation Program: Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1. Subjects who are in the maintenance phase of a pulmonary rehabilitation program are not excluded.
- Drug or Alcohol Abuse: A known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1.
- Affiliation with Investigator Site: Is an investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member of the aforementioned that is involved in this study.
- Inability to read: In the opinion of the Investigator, any subject who is unable to read and/or would not be able to complete a questionnaire.

## Contacts/Locations

Central Contact Person: US GSK Clinical Trials Call Center
Telephone: 877-379-3718
Email: GSKClinicalSupportHD@gsk.com

Central Contact Backup:

Study Officials: GSK Clinical Trials
Study Director
GlaxoSmithKline

Locations: Ukraine
GSK Investigational Site
Kyiv, Ukraine, 02232

Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

GSK Investigational Site
Kyiv, Ukraine, 03049
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

Slovakia
GSK Investigational Site
Sala, Slovakia, 927 01
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

Ukraine
GSK Investigational Site
Kyiv, Ukraine, 03038
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

GSK Investigational Site
Kyiv, Ukraine, 03680
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

GSK Investigational Site
Poltava, Ukraine, 36024
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

GSK Investigational Site
Kiev, Ukraine, 03680
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

GSK Investigational Site
Donetsk, Ukraine, 83003
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

Slovakia
GSK Investigational Site
Poprad, Slovakia, 058 01
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

Ukraine
GSK Investigational Site
Mykolayiv, Ukraine, 54003
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

GSK Investigational Site
Kharkiv, Ukraine, 61035
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

GSK Investigational Site
Donetsk, Ukraine, 83099
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

Slovakia
GSK Investigational Site
Humenne, Slovakia, 066 01
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

Ukraine
GSK Investigational Site
Ivano-Frankivsk, Ukraine, 76018
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

GSK Investigational Site
Vinnytsia, Ukraine, 21018
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

GSK Investigational Site
Sympheropol, Ukraine, 95017
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

GSK Investigational Site
Kyiv, Ukraine, 01114
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

GSK Investigational Site
Kyiv, Ukraine, 03680
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com

Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

GSK Investigational Site
Vinnytsia, Ukraine, 21029
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

Slovakia
GSK Investigational Site
Vrable, Slovakia, 952 01
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

Ukraine
GSK Investigational Site
Simferopol, Ukraine, 95043
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

Slovakia
GSK Investigational Site
Poprad, Slovakia, 058 01
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

GSK Investigational Site
Humenne, Slovakia, 066 01
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

GSK Investigational Site
Kralovsky Chlmec, Slovakia, 077 01
Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com
Contact: EU GSK Clinical Trials Call Center +44 (0) 20 8990 4466 GSKClinicalSupportHD@gsk.com

## IPDSharing

Plan to Share IPD: Yes
Patient-level data for this study will be made available through www.clinicalstudydatarequest.com following the timelines and process described on this site.

Supporting Information:

Time Frame:
Access Criteria:

URL: http://

## References

Citations:

Links: URL: https://www.clinicalstudydatarequest.com
Description Researchers can use this site to request access to anonymised patient level data and/or supporting documents from clinical studies to conduct further research.

Available IPD/Information: Type: Individual Participant Data Set
URL: https://www.clinicalstudydatarequest.com
Identifier: 116132
For additional information about this study please refer to the GSK Clinical Study Register

Type: Clinical Study Report
URL: https://www.clinicalstudydatarequest.com
Identifier: 116132
For additional information about this study please refer to the GSK Clinical Study Register

Type: Informed Consent Form
URL: https://www.clinicalstudydatarequest.com
Identifier: 116132
For additional information about this study please refer to the GSK Clinical Study Register

Type: Study Protocol
URL: https://www.clinicalstudydatarequest.com
Identifier: 116132
For additional information about this study please refer to the GSK Clinical Study Register

Type: Other [Dataset Specification]
URL: https://www.clinicalstudydatarequest.com
Identifier: 116132
For additional information about this study please refer to the GSK Clinical Study Register

Type: Statistical Analysis Plan
URL: https://www.clinicalstudydatarequest.com
Identifier: 116132
For additional information about this study please refer to the GSK Clinical Study Register

Type: Other [Annotated Case Report Form]
URL: https://www.clinicalstudydatarequest.com
Identifier: 116132
For additional information about this study please refer to the GSK Clinical Study Register

# Study Results

## Participant Flow

| | |
|---|---|
| Pre-assignment Details | Participants who met the eligibility criteria at Screening (Visit 1) completed a 5- to 7-day Run-in Period prior to being randomized to 1 of 6 treatment sequences. The treatment phase was comprised of three 14-day treatment periods, each separated by a 10- to 14-day washout period. |

Reporting Groups

| | Description |
|---|---|
| Sequence 1: UMEC 62.5 µg, VI 25 µg, UMEC/VI 62.5/25 µg | Participants received umeclidinium (UMEC) 62.5 micrograms (µg), vilanterol trifenatate (VI) 25 µg, and UMEC/VI 62.5/25 µg in Treatment Periods 1, 2, and 3, respectively. Participants received all treatments once a day (QD) for 14 days from a Dry Powder Inhaler (DPI). The three treatment periods were separated by a washout period of 10 to 14 days. |
| Sequence 2: VI 25 µg, UMEC/VI 62.5/25 µg, UMEC 62.5 µg | Participants received VI 25 µg, UMEC/VI 62.5/25 µg, and UMEC 62.5 µg in Treatment Periods 1, 2, and 3, respectively. Participants received all treatments QD for 14 days from a DPI. The three treatment periods were separated by a washout period of 10 to 14 days. |
| Sequence 3: UMEC/VI 62.5/25 µg, UMEC 62.5 µg, VI 25 µg | Participants received UMEC/VI 62.5/25 µg, UMEC 62.5 µg, and VI 25 µg in Treatment Periods 1, 2, and 3, respectively. Participants received all treatments QD for 14 days from a DPI. The three treatment periods were separated by a washout period of 10 to 14 days. |
| Sequence 4: UMEC 62.5 µg, UMEC/VI 62.5/25 µg, VI 25 µg | Participants received UMEC 62.5 µg, UMEC/VI 62.5/25 µg, and VI 25 µg in Treatment Periods 1, 2, and 3, respectively. Participants received all treatments QD for 14 days from a DPI. The three treatment periods were separated by a washout period of 10 to 14 days. |
| Sequence 5: VI 25 µg, UMEC 62.5 µg, UMEC/VI 62.5/25 µg | Participants received VI 25 µg, UMEC 62.5 µg, and UMEC/VI 62.5/25 µg in Treatment Periods 1, 2, and 3, respectively. Participants received all treatments QD for 14 days from a DPI. The three treatment periods were separated by a washout period of 10 to 14 days. |
| Sequence 6: UMEC/VI 62.5/25 µg, VI 25 µg, UMEC 62.5 µg | Participants received UMEC/VI 62.5/25 µg, VI 25 µg, and UMEC 62.5 µg in Treatment Periods 1, 2, and 3, respectively. Participants received all treatments QD for 14 days from a DPI. The three treatment periods were separated by a washout period of 10 to 14 days. |

Treatment Period 1 (14 Days)

| | Sequence 1: UMEC 62.5 µg, VI 25 µg, UMEC/VI 62.5/25 µg | Sequence 2: VI 25 µg, UMEC/VI 62.5/25 µg, UMEC 62.5 µg | Sequence 3: UMEC/VI 62.5/25 µg, UMEC 62.5 µg, VI 25 µg | Sequence 4: UMEC 62.5 µg, UMEC/VI 62.5/25 µg, VI 25 µg | Sequence 5: VI 25 µg, UMEC 62.5 µg, UMEC/VI 62.5/25 µg | Sequence 6: UMEC/VI 62.5/25 µg, VI 25 µg, UMEC 62.5 µg |
|---|---|---|---|---|---|---|
| Started | 35 | 35 | 34 | 34 | 35 | 34 [1] |

| | Sequence 1: UMEC 62.5 µg, VI 25 µg, UMEC/ VI 62.5/25 µg | Sequence 2: VI 25 µg, UMEC/ VI 62.5/25 µg, UMEC 62.5 µg | Sequence 3: UMEC/VI 62.5/25 µg, UMEC 62.5 µg, VI 25 µg | Sequence 4: UMEC 62.5 µg, UMEC/VI 62.5/25 µg, VI 25 µg | Sequence 5: VI 25 µg, UMEC 62.5 µg, UMEC/ VI 62.5/25 µg | Sequence 6: UMEC/VI 62.5/25 µg, VI 25 µg, UMEC 62.5 µg |
|---|---|---|---|---|---|---|
| Completed | 35 | 34 | 33 | 32 | 34 | 34 |
| Not Completed | 0 | 1 | 1 | 2 | 1 | 0 |
| Lack of Efficacy | 0 | 0 | 1 | 0 | 0 | 0 |
| Withdrawal by Subject | 0 | 1 | 0 | 2 | 1 | 0 |

[1] One participant randomized to Sequence 6 actually received UMEC in Treatment Periods 2 and 3.

Washout Period 1 (10 to 14 Days)

| | Sequence 1: UMEC 62.5 µg, VI 25 µg, UMEC/ VI 62.5/25 µg | Sequence 2: VI 25 µg, UMEC/ VI 62.5/25 µg, UMEC 62.5 µg | Sequence 3: UMEC/VI 62.5/25 µg, UMEC 62.5 µg, VI 25 µg | Sequence 4: UMEC 62.5 µg, UMEC/VI 62.5/25 µg, VI 25 µg | Sequence 5: VI 25 µg, UMEC 62.5 µg, UMEC/ VI 62.5/25 µg | Sequence 6: UMEC/VI 62.5/25 µg, VI 25 µg, UMEC 62.5 µg |
|---|---|---|---|---|---|---|
| Started | 35 | 34 | 33 | 32 | 34 | 34 |
| Completed | 35 | 34 | 32 | 32 | 34 | 34 |
| Not Completed | 0 | 0 | 1 | 0 | 0 | 0 |
| Lack of Efficacy | 0 | 0 | 1 | 0 | 0 | 0 |

Treatment Period 2 (14 Days)

| | Sequence 1: UMEC 62.5 µg, VI 25 µg, UMEC/ VI 62.5/25 µg | Sequence 2: VI 25 µg, UMEC/ VI 62.5/25 µg, UMEC 62.5 µg | Sequence 3: UMEC/VI 62.5/25 µg, UMEC 62.5 µg, VI 25 µg | Sequence 4: UMEC 62.5 µg, UMEC/VI 62.5/25 µg, VI 25 µg | Sequence 5: VI 25 µg, UMEC 62.5 µg, UMEC/ VI 62.5/25 µg | Sequence 6: UMEC/VI 62.5/25 µg, VI 25 µg, UMEC 62.5 µg |
|---|---|---|---|---|---|---|
| Started | 35 | 34 | 32 | 32 | 34 | 34 |
| Completed | 34 | 33 | 30 | 31 | 34 | 34 |
| Not Completed | 1 | 1 | 2 | 1 | 0 | 0 |
| Protocol Violation | 1 | 1 | 2 | 1 | 0 | 0 |

Washout Period 2 (10 to 14 Days)

| | Sequence 1: UMEC 62.5 µg, VI 25 µg, UMEC/ VI 62.5/25 µg | Sequence 2: VI 25 µg, UMEC/ VI 62.5/25 µg, UMEC 62.5 µg | Sequence 3: UMEC/VI 62.5/25 µg, UMEC 62.5 µg, VI 25 µg | Sequence 4: UMEC 62.5 µg, UMEC/VI 62.5/25 µg, VI 25 µg | Sequence 5: VI 25 µg, UMEC 62.5 µg, UMEC/ VI 62.5/25 µg | Sequence 6: UMEC/VI 62.5/25 µg, VI 25 µg, UMEC 62.5 µg |
|---|---|---|---|---|---|---|
| Started | 34 | 33 | 30 | 31 | 34 | 34 |
| Completed | 34 | 33 | 30 | 31 | 34 | 34 |
| Not Completed | 0 | 0 | 0 | 0 | 0 | 0 |

Treatment Period 3 (14 Days)

| | Sequence 1: UMEC 62.5 µg, VI 25 µg, UMEC/ VI 62.5/25 µg | Sequence 2: VI 25 µg, UMEC/ VI 62.5/25 µg, UMEC 62.5 µg | Sequence 3: UMEC/VI 62.5/25 µg, UMEC 62.5 µg, VI 25 µg | Sequence 4: UMEC 62.5 µg, UMEC/VI 62.5/25 µg, VI 25 µg | Sequence 5: VI 25 µg, UMEC 62.5 µg, UMEC/ VI 62.5/25 µg | Sequence 6: UMEC/VI 62.5/25 µg, VI 25 µg, UMEC 62.5 µg |
|---|---|---|---|---|---|---|
| Started | 34 | 33 | 30 | 31 | 34 | 34 |
| Completed | 34 | 32 | 29 | 31 | 34 | 32 |
| Not Completed | 0 | 1 | 1 | 0 | 0 | 2 |
| Withdrawal by Subject | 0 | 1 | 0 | 0 | 0 | 0 |
| Adverse Event | 0 | 0 | 1 | 0 | 0 | 1 |
| Lack of Efficacy | 0 | 0 | 0 | 0 | 0 | 1 |

## Baseline Characteristics

Reporting Groups

| | Description |
|---|---|
| UMEC 62.5 µg, VI 25 µg, UMEC/VI 62.5/25 µg | All participants received one of the following three treatments in one of three treatment periods QD from the DPI for 14 days: UMEC 62.5 µg inhalation powder; VI 25 µg inhalation powder; and UMEC/VI 62.5/25 µg inhalation powder. Participants were randomized to receive treatment in one of the six following sequences: (1) UMEC 62.5 µg, VI 25 µg, UMEC/VI 62.5/25 µg; (2) VI 25 µg, UMEC/VI 62.5/25 µg, UMEC 62.5 µg; (3) UMEC/ VI 62.5/25 µg, UMEC 62.5 µg, VI 25 µg; (4) UMEC 62.5 µg, UMEC/VI 62.5/25 µg, VI 25 µg; (5) VI 25 µg, UMEC 62.5 µg, UMEC/VI 62.5/25 µg; (6) UMEC/VI 62.5/25 µg, VI 25 µg, UMEC 62.5 µg. The three treatment periods were separated by a washout period of 10 to 14 days. |

Baseline Measures

| | | UMEC 62.5 µg, VI 25 µg, UMEC/VI 62.5/25 µg |
|---|---|---|
| Overall Number of Participants | | 207 |
| Age, Continuous<br>Mean (Standard Deviation)<br>Unit of measure: Years | Number Analyzed | 207 participants |
| | | 60.5 (7.99) |
| Sex: Female, Male<br>Measure Type: Count of Participants<br>Unit of measure: participants | Number Analyzed | 207 participants |
| | Female | 38 18.36% |
| | Male | 169 81.64% |
| Race/Ethnicity, Customized<br>Measure Type: Number<br>Unit of measure: participants | Number Analyzed | 207 participants |
| White - White/ Caucasian/ European Heritage | | 207 |

## Outcome Measures

1. Primary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline (BL) in Weighted Mean (WM) 0-6 Hour Forced Expiratory Volume in One Second (FEV1) Obtained Post-dose at Day 14 of Each Treatment Period (TP) by Response Type |
| Measure Description | FEV1 is a measure of lung function and the maximal amount of air that can be forcefully exhaled in one second. The WM FEV1 was derived by calculating the area under the FEV1/time curve (AUC) using the trapezoidal rule, and then dividing the value by the time interval over which the AUC was calculated. The WM FEV1 was calculated using 0-6 hour post-dose measurements at Day 14 of each TP, which included pre-dose (trough value for Day 14 [mean of the 23 and 24 hour assessments post Day 13 dosing]) and post-dose 15 minutes (min), 30 min, and 1, 3, and 6 hours. BL is the mean FEV1 values recorded 30 min and 5 min pre-dose on Day 1 of each TP, mean BL is the mean of the BLs for each participant, and period BL is the difference between the BL and the mean BL in each TP for each participant. Change from BL for each TP is the Day 14 value minus the BL value for that TP. |
| Time Frame | Baseline and Day 14 of each treatment period (up to study day 85) |

Analysis Population Description

Intent-to-Treat (ITT) Population: all participants (par.) randomized to treatment who received >=1 dose of randomized study medication in a TP. Only par. available at the specified time points were analyzed. Different par. may have been analyzed for different parameters; the overall number of par, analyzed reflects everyone in the ITT Population.

Reporting Groups

| | Description |
|---|---|
| UMEC 62.5 µg | Participants received UMEC 62.5 µg inhalation powder QD from the DPI for 14 days during one of the three treatment periods. Each treatment period was followed by a washout period of 10-14 days. |
| VI 25 µg | Participants received VI 25 µg inhalation powder QD from the DPI for 14 days during one of the three treatment periods. Each treatment period was followed by a washout period of 10-14 days. |
| UMEC/VI 62.5/25 µg | Participants received UMEC/VI 62.5/25 µg inhalation powder QD from the DPI for 14 days during one of the three treatment periods. Each treatment period was followed by a washout period of 10-14 days. |

Measured Values

| | UMEC 62.5 µg | VI 25 µg | UMEC/VI 62.5/25 µg |
|---|---|---|---|
| Overall Number of Participants Analyzed | 202 | 200 | 202 |
| Change From Baseline (BL) in Weighted Mean (WM) 0-6 Hour Forced Expiratory Volume in One Second (FEV1) Obtained Post-dose at Day 14 of Each Treatment Period (TP) by Response Type<br>Least Squares Mean (Standard Error)<br>Unit of measure: Liters | | | |
| Responder to UMEC, n=79, 78, 81 | 0.155 (0.0184) | 0.156 (0.0185) | 0.263 (0.0179) |
| Responder to VI, n=78, 77, 80 | 0.135 (0.0182) | 0.182 (0.0183) | 0.264 (0.0180) |
| Responder to Neither, n=80, 79, 80 | 0.014 (0.0179) | 0.035 (0.0180) | 0.092 (0.0179) |

Statistical Analysis 1 for Change From Baseline (BL) in Weighted Mean (WM) 0-6 Hour Forced Expiratory Volume in One Second (FEV1) Obtained Post-dose at Day 14 of Each Treatment Period (TP) by Response Type

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Group Selection | UMEC 62.5 µg, UMEC/VI 62.5/25 µg |
| | Comments | [Not specified] |
| | Type of Statistical Test | Superiority or Other (legacy) |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | <0.001 |
| | Comments | Analysis was performed using an Analysis of Covariance (ANCOVA) model with covariates of treatment, period, mean Baseline, period Baseline, response type and treatment by response type interaction. |
| | Method | ANCOVA |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | 0.108 |
| | Confidence Interval | (2-Sided) 95%<br>0.065 to 0.151 |
| | Estimation Comments | Responders to UMEC=responders to UMEC or to both monotherapies, as defined by a participant with an increase from Baseline of >=12% and 200 milliliters (mL) at >=1 time point over 0-6 hours post-dose in FEV1 on Day 1. |

Statistical Analysis 2 for Change From Baseline (BL) in Weighted Mean (WM) 0-6 Hour Forced Expiratory Volume in One Second (FEV1) Obtained Post-dose at Day 14 of Each Treatment Period (TP) by Response Type

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Group Selection | VI 25 µg, UMEC/VI 62.5/25 µg |
| | Comments | [Not specified] |
| | Type of Statistical Test | Superiority or Other (legacy) |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | <0.001 |
| | Comments | Analysis was performed using an Analysis of Covariance (ANCOVA) model with covariates of treatment, period, mean Baseline, period Baseline, response type and treatment by response type interaction. |
| | Method | ANCOVA |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | 0.107 |
| | Confidence Interval | (2-Sided) 95%<br>0.064 to 0.149 |
| | Estimation Comments | Responders to UMEC=responders to UMEC or to both monotherapies, as defined by a participant with an increase from Baseline of >=12% and 200 mL at >=1 time point over 0-6 hours post-dose in FEV1 on Day 1. |

Statistical Analysis 3 for Change From Baseline (BL) in Weighted Mean (WM) 0-6 Hour Forced Expiratory Volume in One Second (FEV1) Obtained Post-dose at Day 14 of Each Treatment Period (TP) by Response Type

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Group Selection | UMEC 62.5 µg, UMEC/VI 62.5/25 µg |
| | Comments | [Not specified] |
| | Type of Statistical Test | Superiority or Other (legacy) |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | <0.001 |
| | Comments | Analysis was performed using an Analysis of Covariance (ANCOVA) model with covariates of treatment, period, mean Baseline, period Baseline, response type and treatment by response type interaction. |
| | Method | ANCOVA |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | 0.129 |
| | Confidence Interval | (2-Sided) 95%<br>0.086 to 0.171 |
| | Estimation Comments | Responders to VI=responders to VI or to both monotherapies, as defined by a participant with an increase from Baseline of >=12% and 200 mL at >=1 time point over 0-6 hours post-dose in FEV1 on Day 1. |

Statistical Analysis 4 for Change From Baseline (BL) in Weighted Mean (WM) 0-6 Hour Forced Expiratory Volume in One Second (FEV1) Obtained Post-dose at Day 14 of Each Treatment Period (TP) by Response Type

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Group Selection | VI 25 µg, UMEC/VI 62.5/25 µg |
| | Comments | [Not specified] |
| | Type of Statistical Test | Superiority or Other (legacy) |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | <0.001 |
| | Comments | Analysis was performed using an Analysis of Covariance (ANCOVA) model with covariates of treatment, period, mean Baseline, period Baseline, response type and treatment by response type interaction. |
| | Method | ANCOVA |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | 0.082 |
| | Confidence Interval | (2-Sided) 95%<br>0.040 to 0.125 |
| | Estimation Comments | Responders to VI=responders to VI or to both monotherapies, as defined by a participant with an increase from Baseline of >=12% and 200 mL at >=1 time point over 0-6 hours post-dose in FEV1 on Day 1. |

Statistical Analysis 5 for Change From Baseline (BL) in Weighted Mean (WM) 0-6 Hour Forced Expiratory Volume in One Second (FEV1) Obtained Post-dose at Day 14 of Each Treatment Period (TP) by Response Type

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Group Selection | UMEC 62.5 µg, UMEC/VI 62.5/25 µg |
| | Comments | [Not specified] |
| | Type of Statistical Test | Superiority or Other (legacy) |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | <0.001 |
| | Comments | Analysis was performed using an Analysis of Covariance (ANCOVA) model with covariates of treatment, period, mean Baseline, period Baseline, response type and treatment by response type interaction. |
| | Method | ANCOVA |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | 0.078 |
| | Confidence Interval | (2-Sided) 95%<br>0.036 to 0.120 |
| | Estimation Comments | Responders to Neither=responders to neither UMEC nor VI, as defined by a participant with at least one FEV1 assessment over 0-6 hours post-dose on Day 1 but no increase from Baseline of >=12% and 200 mL at any assessment(s). |

Statistical Analysis 6 for Change From Baseline (BL) in Weighted Mean (WM) 0-6 Hour Forced Expiratory Volume in One Second (FEV1) Obtained Post-dose at Day 14 of Each Treatment Period (TP) by Response Type

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Group Selection | VI 25 µg, UMEC/VI 62.5/25 µg |
| | Comments | [Not specified] |
| | Type of Statistical Test | Superiority or Other (legacy) |

| | | |
|---|---|---|
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | 0.008 |
| | Comments | Analysis was performed using an Analysis of Covariance (ANCOVA) model with covariates of treatment, period, mean Baseline, period Baseline, response type and treatment by response type interaction. |
| | Method | ANCOVA |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | 0.057 |
| | Confidence Interval | (2-Sided) 95%<br>0.015 to 0.099 |
| | Estimation Comments | Responders to Neither=responders to neither UMEC nor VI, as defined by a participant with at least one FEV1 assessment over 0-6 hours post-dose on Day 1 but no increase from Baseline of >=12% and 200 mL at any assessment(s). |

2. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Number of Participants (Par.) Who Were Responsive to UMEC/VI, UMEC or, VI According to FEV1 at Day 1 of Each Treatment Period (TP) |
| Measure Description | A responder is a par. with an increase from BL of >=12% and 200 milliliters (mL) at >=1 time point over 0-6 hours post-dose (PD) in FEV1 on Day 1. A non-responder (NR) is a par. with >=1 FEV1 assessment over 0-6 hours PD on Day 1 but no increase from BL of >=12% and 200 mL at any assessment(s). Missing: no FEV1 data recorded over 0-6 hours PD on Day 1. Response type is defined based on a par.'s response to each individual monotherapy treatment. A responder to UMEC is a par. who is a responder in the UMEC treatment period (TP) and either a NR or has missing data in the VI TP. A responder to VI is a par. who is a responder in the VI TP and either a NR or has missing data in the UMEC TP. A responder to UMEC and VI is a par. who is a responder in both the UMEC and VI TPs. A responder to neither is a par. who is a NR in both the UMEC and VI TPs. Missing: a par. who has missing data in both the UMEC and VI TPs, or who has missing data in one monotherapy period and is a NR in the other. |
| Time Frame | Baseline (BL) and 0-6 hours post-dose (15 minutes, 30 minutes, and 1, 3, and 6 hours post-dose) on Day 1 of each treatment period (up to study day 66) |

Analysis Population Description

ITT Population

Reporting Groups

| | Description |
|---|---|
| UMEC 62.5 µg | Participants received UMEC 62.5 µg inhalation powder QD from the DPI for 14 days during one of the three treatment periods. Each treatment period was followed by a washout period of 10-14 days. |
| VI 25 µg | Participants received VI 25 µg inhalation powder QD from the DPI for 14 days during one of the three treatment periods. Each treatment period was followed by a washout period of 10-14 days. |
| UMEC/VI 62.5/25 µg | Participants received UMEC/VI 62.5/25 µg inhalation powder QD from the DPI for 14 days during one of the three treatment periods. Each treatment period was followed by a washout period of 10-14 days. |

Measured Values

| | UMEC 62.5 µg | VI 25 µg | UMEC/VI 62.5/25 µg |
|---|---|---|---|
| Overall Number of Participants Analyzed | 202 | 200 | 202 |
| Number of Participants (Par.) Who Were Responsive to UMEC/VI, UMEC or, VI According to FEV1 at Day 1 of Each Treatment Period (TP)<br>Measure Type: Number<br>Unit of measure: participants | | | |
| Responder | 81 | 81 | 103 |
| Non-responder | 121 | 119 | 99 |

3. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Number of Participants With a Larger Change From Baseline in 0-6 Hour Weighted Mean FEV1 at Day 14 of Each Treatment Period With UMEC/VI Compared With UMEC and VI Alone |
| Measure Description | The number of participants with a larger change from Baseline in weighted mean FEV1 with UMEC/VI compared with UMEC and VI alone was recorded. Participants who improved on UMEC/VI had a larger change from Baseline difference in 0-6 hour weighted mean FEV1 on Day 14 on UMEC/VI compared to UMEC or VI alone. Baseline is the mean FEV1 values recorded 30 min and 5 min pre-dose on Day 1 of each treatment period, mean Baseline is the mean of the Baselines for each participant, and period Baseline is the difference between the Baseline and the mean Baseline in each treatment period for each participant. Change from Baseline for each treatment period is the Day 14 value minus the Baseline value for that treatment period. |
| Time Frame | Baseline and Day 14 of each treatment period (up to study day 85) |

Analysis Population Description

ITT Population. Only those participants available at the indicated time point were assessed.

Reporting Groups

| | Description |
|---|---|
| UMEC 62.5 µg | Participants received UMEC 62.5 µg inhalation powder QD from the DPI for 14 days during one of the three treatment periods. Each treatment period was followed by a washout period of 10-14 days. |
| VI 25 µg | Participants received VI 25 µg inhalation powder QD from the DPI for 14 days during one of the three treatment periods. Each treatment period was followed by a washout period of 10-14 days. |
| UMEC/VI 62.5/25 µg | Participants received UMEC/VI 62.5/25 µg inhalation powder QD from the DPI for 14 days during one of the three treatment periods. Each treatment period was followed by a washout period of 10-14 days. |

Measured Values

| | UMEC 62.5 µg | VI 25 µg | UMEC/VI 62.5/25 µg |
|---|---|---|---|
| Overall Number of Participants Analyzed | 193 | 192 | 0 |
| Number of Participants With a Larger Change From Baseline in 0-6 Hour Weighted Mean FEV1 at Day 14 of Each Treatment Period With UMEC/VI Compared With UMEC and VI Alone<br>Measure Type: Number<br>Unit of measure: participants | | | |
| Improved on UMEC/VI | 124 | 130 | --- |
| Not improved on UMEC/VI | 69 | 62 | --- |

4. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Clinic Visit Pre-dose Trough FEV1 at Day 15 of Each Treatment Period |
| Measure Description | Trough FEV1 on Treatment Day 15 is defined as the mean of the FEV1 values obtained at 23 and 24 hours after dosing on Day 14. Analysis was performed using an ANCOVA model with covariates of treatment, period, mean Baseline (BL), period BL, response type, and treatment by response type interaction. A participant is a reponder to UMEC if they were a responder to UMEC monotherapy or a responder to both UMEC monotherapy and VI monotherapy. A participant is a responder to VI if they were a responder to VI monotherapy or a responder to both UMEC monotherapy or VI monotherapy. BL is the mean FEV1 recorded 30 min and 5 min pre-dose on Day 1 of each treatment period, mean BL is the mean of the BLs for each participant, and period BL is the difference between BL and the mean BL in each treatment period for each participant. Change from BL for each treatment period is the Day 15 value minus the BL value for that treatment period. |
| Time Frame | Baseline and Day 15 of each treatment period (up to study day 81) |

Analysis Population Description

ITT Population. Only those participants available at the specified time points were analyzed. Different participants may have been analyzed for different parameters; the overall number of participants analyzed reflects everyone in the ITT Population.

Reporting Groups

| | Description |
|---|---|
| UMEC 62.5 µg | Participants received UMEC 62.5 µg inhalation powder QD from the DPI for 14 days during one of the three treatment periods. Each treatment period was followed by a washout period of 10-14 days. |
| VI 25 µg | Participants received VI 25 µg inhalation powder QD from the DPI for 14 days during one of the three treatment periods. Each treatment period was followed by a washout period of 10-14 days. |
| UMEC/VI 62.5/25 µg | Participants received UMEC/VI 62.5/25 µg inhalation powder QD from the DPI for 14 days during one of the three treatment periods. Each treatment period was followed by a washout period of 10-14 days. |

Measured Values

| | UMEC 62.5 µg | VI 25 µg | UMEC/VI 62.5/25 µg |
|---|---|---|---|
| Overall Number of Participants Analyzed | 202 | 200 | 202 |
| Change From Baseline in Clinic Visit Pre-dose Trough FEV1 at Day 15 of Each Treatment Period<br>Least Squares Mean (Standard Error)<br>Unit of measure: Liters | | | |
| Responder to UMEC, n=79, 78, 80 | 0.105 (0.0196) | 0.086 (0.0197) | 0.170 (0.0191) |
| Responder to VI, n=78, 78, 80 | 0.088 (0.0194) | 0.106 (0.0193) | 0.166 (0.0191) |
| Responder to Neither, n=80, 79, 79 | 0.016 (0.0190) | 0.004 (0.0191) | 0.062 (0.0191) |

## Reported Adverse Events

| | |
|---|---|
| Time Frame | Serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of the study medication to the end of treatment (up to Week 24). |
| Adverse Event Reporting Description | SAEs and non-serious AEs were reported for members of the Intent-to-Treat (ITT) Population, comprised of all participants randomized to treatment who received at least one dose of trial medication during the treatment period. |

Reporting Groups

| | Description |
|---|---|
| UMEC 62.5 µg | Participants received UMEC 62.5 µg inhalation powder QD from the DPI for 14 days during one of the three treatment periods. Each treatment period was followed by a washout period of 10-14 days. |
| VI 25 µg | Participants received VI 25 µg inhalation powder QD from the DPI for 14 days during one of the three treatment periods. Each treatment period was followed by a washout period of 10-14 days. |
| UMEC/VI 62.5/25 µg | Participants received UMEC/VI 62.5/25 µg inhalation powder QD from the DPI for 14 days during one of the three treatment periods. Each treatment period was followed by a washout period of 10-14 days. |

All-Cause Mortality

| | UMEC 62.5 µg | VI 25 µg | UMEC/VI 62.5/25 µg |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Total All-Cause Mortality | / | / | / |

Serious Adverse Events

| | UMEC 62.5 µg | VI 25 µg | UMEC/VI 62.5/25 µg |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Total | 1/202 (0.5%) | 1/200 (0.5%) | 1/202 (0.5%) |
| Infections and infestations | | | |
| Gastroenteritis [A] † | 0/202 (0%) | 0/200 (0%) | 1/202 (0.5%) |
| Orchitis [A] † | 1/202 (0.5%) | 0/200 (0%) | 0/202 (0%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Squamous cell carcinoma [A] † | 0/202 (0%) | 1/200 (0.5%) | 0/202 (0%) |

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 3%

| | UMEC 62.5 µg | VI 25 µg | UMEC/VI 62.5/25 µg |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Total | 5/202 (2.48%) | 10/200 (5%) | 10/202 (4.95%) |
| Nervous system disorders | | | |

| | UMEC 62.5 µg | VI 25 µg | UMEC/VI 62.5/25 µg |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Headache [A] † | 5/202 (2.48%) | 10/200 (5%) | 10/202 (4.95%) |

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA

## Limitations and Caveats

[Not specified]

## More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

GSK agreements may vary with individual investigators, but will not prohibit any investigator from publishing. GSK supports the publication of results from all centers of a multi-center trial but requests that reports based on single-site data not precede the primary publication of the entire clinical trial.

Results Point of Contact:

Name/Official Title: GSK Response Center
Organization: GlaxoSmithKline
Phone: 866-435-7343
Email: