Protocol Registration Receipt
02/13/2014

Cross-Over Study in Subjects With COPD, Evaluating Lung Function Response After Treatment With Once Daily Umeclidinium 62.5mcg, Vilanterol 25mcg, and Umeclidinium/Vilanterol 62.5/25mcg

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT01716520

Purpose

The purpose of this study is to evaluate the lung function response to UMEC/VI, UMEC, and VI in individual patients using a cross-over design. This is a multicenter, randomized, double-blind, 3-way crossover study. Eligible subjects will be randomized to a sequence of UMEC 62.5mcg, VI 25mcg, and UMEC/VI 62.5/25mcg. All subjects will receive each treatment once-daily for 14 days, and each treatment will be separated by a 10-14 day washout period. There will be a 5-7 day run-in period prior to randomization.

Condition	Intervention	Phase
Pulmonary Disease, Chronic Obstructive	Device: Umeclidinium/Vilanterol 62.5/25 mcg Device: Umeclidinium 62.5 mcg Device: Vilanterol 25 mcg	Phase 3

Study Type: Interventional
Study Design: Treatment, Crossover Assignment, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Randomized, Safety/Efficacy Study
Official Title: A Randomized, Double-Blind, 3-Way, Cross-Over Study to Evaluate Lung Function Response After Treatment With Umeclidinium 62.5mcg, Vilanterol 25mcg, and Umeclidinium/Vilanterol 62.5/25mcg Once-Daily in Subjects With Chronic Obstructive Pulmonary Disease (COPD)

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- 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 [Time Frame: Baseline and Day 14 of each treatment period (up to study day 83)] [Designated as safety issue: No]

  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. Participants could have been classified as responders to both UMEC and VI.

Secondary Outcome Measures:

- Number of Participants (Par.) Who Were Responsive to UMEC/VI, UMEC, or VI According to FEV1 at Day 1 of Each Treatment Period (TP) [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 71)] [Designated as safety issue: No]

  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.

- 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 [Time Frame: Baseline and Day 14 of each treatment period (up to study day 83)] [Designated as safety issue: No]

  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.

- Change From Baseline in Trough FEV1 on Day 15 of Each Treatment Period [Time Frame: Baseline and Day 15 of each treatment period (up to study day 84)] [Designated as safety issue: No]

  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.

Enrollment: 182
Study Start Date: October 2012
Study Completion Date: May 2013
Primary Completion Date: May 2013

Arms	Assigned Interventions
Experimental: Umeclidinium/Vilanterol 62.5/25 mcg Umeclidinium/Vilanterol 62.5/25 mcg once daily in the morning via novel dry powder inhaler (NDPI)	Device: Umeclidinium/Vilanterol 62.5/25 mcg Umeclidinium/Vilanterol 62.5/25 mcg once daily in the morning via novel dry powder inhaler (NDPI)
Experimental: Umeclidinium 62.5 mcg Umeclidinium 62.5 mcg once daily in the morning via novel dry powder inhaler	Device: Umeclidinium 62.5 mcg Umeclidinium 62.5 mcg once daily in the morning via novel dry powder inhaler (NDPI)

Arms	Assigned Interventions
(NDPI)	
Experimental: Vilanterol 25 mcg Vilanterol 25 mcg once daily in the morning via novel dry powder inhaler (NDPI)	Device: Vilanterol 25 mcg Vilanterol 25 mcg once daily in the morning via novel dry powder inhaler (NDPI)

Eligibility

Ages Eligible for Study: 40 Years and older
Genders Eligible for Study: Both

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.
- COPD diagnosis: As defined by the American Thoracic Society/European Respiratory Society (ATS/ERS)
- Severity of disease: A pre- and post-salbutamol FEV1/FVC ratio of <0.70 and a pre- and post-salbutamol FEV1 of ≤ 70% of predicted normal values at Visit 1
- Smoking History: Current or former cigarette smokers with a history of cigarette smoking of ≥ 10 pack-years at Visit 1
- Female subject of non child-bearing potential OR a female subject of child bearing potential, with a negative pregnancy test at screening, and agreeing to consistently and correctly use one of the acceptable contraceptive methods

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.
- 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

- 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 ECG finding from the 12-lead ECG conducted at Visit 1
- Screening Labs: Significantly abnormal finding from clinical chemistry or hematology tests at Visit 1 as determined by the study investigator.
- 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 prohibited medications according to defined time intervals prior to Visit 1
- 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 and Locations

Locations

Estonia

GSK Investigational Site
Haapsalu, Estonia, 90502

GSK Investigational Site
Tallinn, Estonia, 13619

GSK Investigational Site
Tallinn, Estonia, 10138

GSK Investigational Site
Tallinn, Estonia, 10117

GSK Investigational Site

Tartu, Estonia, 51014

Germany

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Muenchen, Bayern, Germany, 80339

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Nuernberg, Bayern, Germany, 90402

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Berlin, Berlin, Germany, 13086

GSK Investigational Site

Berlin, Berlin, Germany, 13581

GSK Investigational Site

Berlin, Berlin, Germany, 10367

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Potsdam, Brandenburg, Germany, 14467

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Potsdam, Brandenburg, Germany, 14469

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Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Responsible Party:	GlaxoSmithKline
Study ID Numbers:	116133
Health Authority:	Estonia: State Agency of Medicines
	Germany: Bundesinstitut für Arzneimittel und Medizinprodukte

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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, starting on Day 15.

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 (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.

	Description
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	31	30	30	30	31	30
Completed	29	29	28	29	31	29
Not Completed	2	1	2	1	0	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
Adverse Event	1	0	0	0	0	0
Protocol-defined Stopping Criteria	1	0	2	1	0	1
Withdrawal by Subject	0	1	0	0	0	0

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	29	29	28	29	31	29
Completed	29	28	27	29	31	27
Not Completed	0	1	1	0	0	2
Adverse Event	0	1	0	0	0	0
Lack of Efficacy	0	0	0	0	0	1
Withdrawal by Subject	0	0	1	0	0	1

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	29	28	27	29	31	27
Completed	29	28	27	28	29	27
Not Completed	0	0	0	1	2	0
Adverse Event	0	0	0	0	1	0
Protocol Violation	0	0	0	0	1	0
Protocol-defined Stopping Criteria	0	0	0	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	29	28	27	28	29	27
Completed	27	27	26	28	29	25
Not Completed	2	1	1	0	0	2
Adverse Event	1	0	1	0	0	1
Lack of Efficacy	1	0	0	0	0	0
Protocol-defined Stopping Criteria	0	0	0	0	0	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
Withdrawal by Subject	0	1	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	27	27	26	28	29	25
Completed	27	27	25	28	29	23
Not Completed	0	0	1	0	0	2
Lack of Efficacy	0	0	0	0	0	2
Withdrawal by Subject	0	0	1	0	0	0

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

	Description
	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
Number of Participants	182
Age, Continuous [units: Years] Mean (Standard Deviation)	63.2 (8.19)
Gender, Male/Female [units: Participants]	
Female	55
Male	127
Race/Ethnicity, Customized White - White/Caucasian/European Heritage [units: participants]	182

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. Participants could have been classified as responders to both UMEC and VI.
Time Frame	Baseline and Day 14 of each treatment period (up to study day 83)
Safety Issue?	No

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

	Description
	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
Number of Participants Analyzed	171	171	173
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 [units: Liters] Least Squares Mean (Standard Error)			
Responder to UMEC, n=90, 90, 88	0.216 (0.0166)	0.201 (0.0167)	0.337 (0.0166)
Responder to VI, n=99, 102, 100	0.189 (0.0150)	0.233 (0.0147)	0.331 (0.0148)
Responder to Neither, n=36, 37, 36	0.077 (0.0243)	0.057 (0.0240)	0.130 (0.0243)

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

Groups	UMEC 62.5 µg, UMEC/VI 62.5/25 µg
Method	ANCOVA
P-Value	<0.001
Mean Difference (Final Values)	0.121
95% Confidence Interval	0.085 to 0.157

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

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.

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

Other relevant estimation information:

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

Groups	VI 25 µg, UMEC/VI 62.5/25 µg
Method	ANCOVA
P-Value	<0.001
Mean Difference (Final Values)	0.135
95% Confidence Interval	0.100 to 0.171

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

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.

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

Other relevant estimation information:

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

Groups	UMEC 62.5 µg, UMEC/VI 62.5/25 µg
Method	ANCOVA
P-Value	<0.001
Mean Difference (Final Values)	0.142
95% Confidence Interval	0.110 to 0.174

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

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.

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

Other relevant estimation information:

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

Groups	VI 25 µg, UMEC/VI 62.5/25 µg
Method	ANCOVA
P-Value	<0.001
Mean Difference (Final Values)	0.098
95% Confidence Interval	0.067 to 0.130

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

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.

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

Other relevant estimation information:

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

Groups	UMEC 62.5 µg, UMEC/VI 62.5/25 µg
Method	ANCOVA

P-Value	0.047
Mean Difference (Final Values)	0.052
95% Confidence Interval	0.001 to 0.104

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

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.

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

Other relevant estimation information:

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

Groups	VI 25 µg, UMEC/VI 62.5/25 µg
Method	ANCOVA
P-Value	0.006
Mean Difference (Final Values)	0.073
95% Confidence Interval	0.021 to 0.124

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

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.

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

Other relevant estimation information:

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 71)

Safety Issue?	No

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
Number of Participants Analyzed	171	171	173
Number of Participants (Par.) Who Were Responsive to UMEC/VI, UMEC, or VI According to FEV1 at Day 1 of Each Treatment Period (TP) [units: participants]			
Responders	92	104	124
Non-responders	79	67	49

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 83)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants available at the specified time point were analyzed.

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.

	Description
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.

Measured Values

	UMEC 62.5 µg	VI 25 µg
Number of Participants Analyzed	162	163
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 [units: participants]		
Improved on UMEC/VI	113	121
Not Improved on UMEC/VI	49	42

4. Secondary Outcome Measure:

Measure Title	Change From Baseline in Trough FEV1 on 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 84)
Safety Issue?	No

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
Number of Participants Analyzed	171	171	173
Change From Baseline in Trough FEV1 on Day 15 of Each Treatment Period [units: Liters] Least Squares Mean (Standard Error)			
Responder to UMEC, n=90, 89, 87	0.159 (0.0178)	0.134 (0.0180)	0.242 (0.0179)
Responder to VI, n=99, 101, 99	0.135 (0.0160)	0.161 (0.0158)	0.268 (0.0159)
Responder to Neither, n=35, 37, 36	0.060 (0.0263)	0.035 (0.0257)	0.092 (0.0260)

Reported Adverse Events

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.

Time Frame

Serious adverse events (SAEs) and non-serious AEs were collected from the start of study medication to the end of the treatment period (up to Study Week 12).

Additional 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.

Serious Adverse Events

	UMEC 62.5 µg	VI 25 µg	UMEC/VI 62.5/25 µg
Total # participants affected/at risk	3/171 (1.75%)	1/171 (0.58%)	3/173 (1.73%)
Cardiac disorders			
Angina pectoris † [A]			
# participants affected/at risk	0/171 (0%)	0/171 (0%)	1/173 (0.58%)
# events			
Infections and infestations			
Abscess limb † [A]			
# participants affected/at risk	0/171 (0%)	0/171 (0%)	1/173 (0.58%)
# events			
Injury, poisoning and procedural complications			
Spinal fracture † [A]			

	UMEC 62.5 µg	VI 25 µg	UMEC/VI 62.5/25 µg
# participants affected/at risk	0/171 (0%)	1/171 (0.58%)	0/173 (0%)
# events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer † [A]			
# participants affected/at risk	0/171 (0%)	0/171 (0%)	1/173 (0.58%)
# events			
Oesophageal carcinoma † [A]			
# participants affected/at risk	1/171 (0.58%)	0/171 (0%)	0/173 (0%)
# events			
Pancreatic carcinoma † [A]			
# participants affected/at risk	1/171 (0.58%)	0/171 (0%)	0/173 (0%)
# events			
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease † [A]			

	UMEC 62.5 µg	VI 25 µg	UMEC/VI 62.5/25 µg
# participants affected/at risk	2/171 (1.17%)	0/171 (0%)	0/173 (0%)
# events			

† 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
Total # participants affected/at risk	8/171 (4.68%)	13/171 (7.6%)	13/173 (7.51%)
Infections and infestations			
Nasopharyngitis † [A]			
# participants affected/at risk	5/171 (2.92%)	11/171 (6.43%)	7/173 (4.05%)
# events			
Nervous system disorders			
Headache † [A]			
# participants affected/at risk	3/171 (1.75%)	2/171 (1.17%)	6/173 (3.47%)
# events			

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

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.

Limitations and Caveats:

Results Point of Contact:

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