Protocol Registration Receipt
07/31/2014

Grantor: CDER IND/IDE Number: 106616 Serial Number:

An Exercise Endurance Study to Evaluate the Effects of Treatment of Chronic Obstructive Pulmonary Disease (COPD) Patients With a Dual Bronchodilator: GSK573719/GW642444. Study A

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT01328444

Purpose

This is a phase III multicenter, randomized, double-blind, placebo-controlled, combination and component, two-period, incomplete block design cross-over study using GSK573719/GW642444. The primary objective is to evaluate lung function and exercise endurance time after 12 weeks of once-daily administration of GSK573719/GW642444 Inhalation Powder (125/25mcg and 62.5/25mcg), GSK573719 Inhalation Powder (125mcg and 62.5mcg), GW642444 Inhalation Powder 25 mcg and placebo delivered by a Novel dry powder inhaler (Novel DPI)

Condition	Intervention	Phase
Pulmonary Disease, Chronic Obstructive	Drug: GSK 573719 +GW642444 125/25 Drug: GSK573719 + GW642444 62.5/25 Drug: GSK 573719 125 Drug: GSK 573719 62.5 Drug: GW642444 25 Drug: Plb	Phase 3

Study Type: Interventional
Study Design: Treatment, Crossover Assignment, Double Blind (Subject, Investigator), Randomized, Efficacy Study
Official Title: An Exercise Endurance Study to Evaluate the Effects of Treatment of Chronic Obstructive Pulmonary Disease (COPD) Patients With a Dual Bronchodilator: GSK573719/GW642444. Study A

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Change From Baseline in Exercise Endurance Time Post-dose at Week 12 of Each Treatment Period [Time Frame: Week 12 of each treatment period (up to Study Week 29)] [Designated as safety issue: No]

  Exercise endurance time (EET) post-dose at Week 12 is defined as the EET obtained 3 hours after dosing at Week 12. EET was measured using the externally paced field walking test called the endurance shuttle walk test (ESWT). Analysis performed using a repeated measures model with covariates of period walking speed, mean walking speed, period, treatment, visit, smoking status, center group, visit by period walking speed, visit by mean walking speed and visit by treatment interactions. The model used all available 3-hour post-dose change from baseline EET values recorded on Day 2, Week 6 and Week 12. Baseline was the EET assessment obtained prior to dosing on Day 1 of each period. The mean walking speed for each participant is the mean of the levels used for the ESWT in each of the two treatment periods. The period walking speed for each participant and treatment period is the difference between the level for that participant and period and the mean walking speed for that participant.
- Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Week 12 of Each Treatment Period [Time Frame: Week 12 of each treatment period (up to Study Week 29)] [Designated as safety issue: No]

  FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. Trough FEV1 measurements were taken electronically by spirometry on Day 2, Week 6 and Week 12. Baseline is the FEV1 value recorded 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. Clinic visit trough (pre-bronchodilator and pre-dose) FEV1 at Week 12 (Treatment Day 85) is defined as the FEV1 value obtained 24 hours after dosing on Treatment Day 84. Analysis performed using a repeated measures model with covariates of period Baseline, mean Baseline, period, treatment, visit, smoking status, center group, visit by period Baseline, visit by mean Baseline and visit by treatment interactions.

Secondary Outcome Measures:

- Change From Baseline in Inspiratory Capacity (Trough and 3-hours Post-dose) at Week 12 of Each Treatment Period [Time Frame: Week 12 of each treatment period (up to Study Week 29)] [Designated as safety issue: No]

  Inspiratory capacity (IC) is defined as the maximum amount of air that can be inhaled into the lungs from the normal resting position after breathing out normally. Baseline is the IC value recorded 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. Trough IC is measured pre-dose on Treatment Week 12 of each treatment period. IC 3-hours post-dose is measured from the value obtained 3 hours after dosing on Treatment Week 12 of each treatment period. Analysis performed using a repeated measures model with covariates of period Baseline, mean Baseline, period, treatment, visit, smoking status, center group, visit by period Baseline, visit by mean Baseline and visit by treatment interactions. IC measurements were taken electronically by plethysmography on Day 2, Week 6 and Week 12.

- Change From Baseline in Functional Residual Capacity (Trough and 3-hours Post-dose) at Week 12 of Each Treatment Period [Time Frame: Week 12 of each treatment period (up to Study Week 29)] [Designated as safety issue: No]

  Functional Residual Capacity (FRC) is defined as the amount of air still left in the lungs after breathing out normally. Baseline is the FRC value recorded 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. Trough FRC is measured pre-dose on Treatment Week 12. FRC 3-hours post-dose is measured from the value obtained 3 hours after dosing on Treatment Week 12. Analysis performed using a repeated measures model with covariates of period Baseline, mean Baseline, period, treatment, visit, smoking status, center group, visit by period Baseline, visit by mean Baseline and visit by treatment interactions. FRC measurements were taken electronically by plethysmography on Day 2, Week 6 and Week 12.

- Change From Baseline in Residual Volume (Trough and 3-hours Post-dose) at Week 12 of Each Treatment Period [Time Frame: Week 12 of each treatment period (up to Study Week 29)] [Designated as safety issue: No]

  Residual Volume (RV) is defined as the air that remains in the lungs after breathing out as fully as possible. Baseline is the RV value recorded 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. Trough RV is measured pre-dose on Treatment Week 12. RV 3-hours post-dose is measured from the value obtained 3 hours after dosing on Treatment Week 12. Analysis performed using a repeated measures model with covariates of period Baseline, mean Baseline, period, treatment, visit, smoking status, center group, visit by period Baseline, visit by mean Baseline and visit by treatment interactions. RV measurements were taken electronically by plethysmography on Day 2, Week 6 and Week 12.

- Change From Baseline in 3-hours Post-dose FEV1 at Week 12 of Each Treatment Period [Time Frame: Week 12 of each treatment period (up to Study Week 29)] [Designated as safety issue: No]

  FEVI is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. Baseline is the FEV1 value recorded 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. Clinic visit post-dose FEV1 at Week 12 (Treatment Day 85) is defined as the FEV1 value obtained 3 hours after dosing on Treatment Day 85. Analysis performed using a repeated measures model with covariates of period Baseline, mean Baseline, period, treatment, visit, smoking status, center group, visit by period Baseline, visit by mean Baseline and visit by treatment interactions 3 hour post-dose FEV1 measurements were taken electronically by spirometry on Day 2, Week 6 and Week 12.

Enrollment: 349
Study Start Date: March 2011
Study Completion Date: June 2012
Primary Completion Date: June 2012

Arms	Assigned Interventions
Experimental: GSK 573719 + GW642444 125/25 125mcg/25mcg nDPI	Drug: GSK573719 + GW642444 62.5/25 62.5mcg/25mcg Other Names: Low Dose Dual Drug: GSK 573719 125 125mcg Other Names: High Dose 719 Drug: GW642444 25 25mcg Other Names: LABA (444) Drug: Plb Comparator Other Names: Placebo
Experimental: GSK 573719 +GW642444 62.5/25 62.5mcg/25mcg nDPI	Drug: GSK 573719 +GW642444 125/25 125mcg/ 25mcg Other Names: High Dose Dual Drug: GSK 573719 62.5 62.5mcg Other Names: Low Dose 719

Arms	Assigned Interventions
	Drug: GW642444 25 25mcg Other Names: LABA (444) Drug: Plb Comparator Other Names: Placebo
Experimental: GSK 573719 125 125mcg nDPI	Drug: GSK 573719 +GW642444 125/25 125mcg/ 25mcg Other Names: High Dose Dual Drug: Plb Comparator Other Names: Placebo
Experimental: GSK 573719 62.5 62.5 mcg nDPI	Drug: GSK573719 + GW642444 62.5/25 62.5mcg/25mcg Other Names: Low Dose Dual Drug: GW642444 25 25mcg Other Names: LABA (444) Drug: Plb Comparator Other Names: Placebo

Arms	Assigned Interventions
Experimental: GW 642444 25 25mcg nDPI	Drug: GSK 573719 +GW642444 125/25 125mcg/ 25mcg Other Names: High Dose Dual Drug: GSK573719 + GW642444 62.5/25 62.5mcg/25mcg Other Names: Low Dose Dual Drug: Plb Comparator Other Names: Placebo
Placebo Comparator: Plb Plb nDPI	Drug: GSK 573719 +GW642444 125/25 125mcg/ 25mcg Other Names: High Dose Dual Drug: GSK573719 + GW642444 62.5/25 62.5mcg/25mcg Other Names: Low Dose Dual Drug: GSK 573719 125 125mcg Other Names: High Dose 719 Drug: GSK 573719 62.5 62.5mcg Other Names: Low Dose 719

Expiratory airflow limitation is the most obvious physiological change associated with chronic obstructive pulmonary disease (COPD). A consequence of airflow limitation is gas trapping as expiration becomes flow limited. This may occur at rest with more severe airway obstruction and is most evident during exercise as lung emptying is reduced and increased ventilation does not allow full expiration. This increased gas trapping or hyperinflation is the cause of much of the increased work of breathing, dyspnea, and exercise intolerance in subjects with COPD (O'Donnell 1997; O'Donnell, 1993). Spirometric measurement of airflow limitation, particularly as assessed by forced expiratory volume in one second (FEV1), is commonly used for the diagnosis of and assessment of response to pharmacotherapeutic intervention in COPD. However, changes in FEV1 may not fully predict symptomatic responses and alternative measures of lung hyperinflation such as exercise tolerance and exertional dyspnea may be more sensitive to therapeutic intervention and/or more clinically relevant than FEV1 [O'Donnell1999; Bauerle, 1998; O'Donnell, 1998; Officer, 1998]. GSK573719/GW642444 Inhalation Powder, a combination of the long-acting muscarinic antagonist (LAMA) bronchodilator GSK573719 and the long-acting beta2-agonist (LABA) bronchodilator GW642444, is in development for the maintenance treatment of airflow obstruction associated with COPD. Development of this product is supported by studies showing improvement in lung function with similar safety when use of combinations of long-acting bronchodilators with different mechanisms of action are compared with single bronchodilator therapy [van Noord 2005; van Noord van Noord 2006; Tashkin 2008]. Previous studies have demonstrated that treatment with short- and long-acting bronchodilators including ipratropium, tiotropium, and salmeterol reduces resting lung hyperinflation as measured by functional residual capacity (FRC), residual volume (RV), and inspiratory capacity (IC), with associated improvements in exercise endurance time and exertional dyspnoea in subjects with COPD [Ayers, 2001; O'Donnell 1998; O'Donnell 2004; Pepin 2005; Pepin 2007; Ramirez-Venegas 1997]. However, the effect of combined LAMA/LABA therapy on these measures is not well characterized.

This is a phase III multicenter, randomized, double-blind, placebo-controlled, combination and component, two-period, incomplete block design cross-over study using GSK573719/GW642444. The primary objective is to evaluate lung function and exercise endurance time after 12 weeks of once-daily administration of GSK573719/GW642444 Inhalation Powder (125/25mcg and 62.5/25mcg), GSK573719 Inhalation Powder (125mcg and 62.5mcg), GW642444 Inhalation Powder 25 mcg and placebo delivered by a Novel dry powder inhaler (Novel DPI) Approximately 312 subjects with moderate/severe chronic obstructive pulmonary disease (COPD) will be randomised in order to achieve 208 subjects completing both treatment periods of 3 months.. There will be a total of 12 study clinic visits conducted on an outpatient basis. Subjects who meet the eligibility criteria at Screening (Visit 1) will complete a 12 to 21 day run-in period followed by two 12-week treatment periods that are separated by a 14 day wash-out. Clinic visits will be conducted at Screening (Visit 1), twice during the run-in period (Visits 2 and 3), at randomization (Visit 4) and three times during the first treatment period, on Treatment Day 2 (Visit 5) and at 6 and 12 weeks (Visits 6 and 7 respectively). During the washout period of 14 days there will be 2 clinic visits (Visits 8 and 9). During the second treatment period there will be 3 clinic visits, on Treatment Day 2 (Visit 10) and at 6 and 12 weeks (Visits 11 and 12 respectively). A Safety Follow-Up assessment (Visit 13) to record adverse events will be conducted by telephone 7 days after the end of the second treatment period or early withdrawal. Efficacy measurements will include pre and post dose FEV1, lung volume measurements and exercise endurance time measured using the endurance shuttle walking test (ESWT). Oxycon mobile measurements will be conducted in a subgroup of approximately 104 patients to investigate cardio respiratory measures during exercise. Safety and tolerability will be assessed by collection of adverse events (AEs), vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory tests and incidence of COPD exacerbations. Dyspnea will be assessed using the Exercise Dyspnea Scale (EDS), a patient-reported outcome. Blood samples will also be collected for potential pharmacogenetics analysis

Eligibility

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

Inclusion Criteria:

- Type of subject: Outpatient.
- Informed Consent: A signed and dated written informed consent prior to study participation.
- Age: 40 years of age or older at Visit 1.
- Gender: Male or female subjects.
- Diagnosis: An established clinical history of COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society [Celli, 2004]
- Smoking History: Current or former cigarette smokers with a history of cigarette smoking of ≥ 10 pack-years
- Severity of Disease: A post-albuterol/salbutamol FEV1/FVC ratio of <0.70 and a post-albuterol/salbutamol FEV1 of >35% and <70% of predicted normal
- Dyspnea: A score of ≥2 on the Modified Medical Research Council Dyspnea Scale (mMRC) at Visit 1
- Resting Lung Volumes: A resting FRC of ≥120% of predicted normal FRC at Visit 1.

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 respiratory disorders other than COPD including but not limited to alpha-1 antitrypsin deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, and 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 haematological 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). Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study. Any physical or mental abnormality which would affect the patient carrying out exercise tests including peripheral vascular disease should be excluded at the investigators discretion.
- Chest X-Ray: A chest X-ray or computed tomography (CT) scan that reveals evidence of clinically significant abnormalities not believed to be due to the presence of COPD. A chest X-ray must be taken at Visit 1 if a chest X-ray or CT scan is not available within 6 months prior to Visit 1. For subjects in Germany, if a chest X-ray (or CT scan) is not available in the 6 months prior to Visit 1 the subject will not be eligible for the study.
- 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 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 Screening (Visit 1).
- 12-Lead ECG: An abnormal and significant ECG finding from the 12-lead ECG conducted at Visit 1, including the presence of a paced rhythm on a 12-lead

electrocardiogram (ECG) which causes the underlying rhythm and ECG to be obscured. Investigators will be provided with ECG reviews conducted by a centralized independent cardiologist to assist in evaluation of subject eligibility.

- Screening Labs: Significantly abnormal finding from clinical chemistry and hematology tests at Visit 1.
- Medication Prior to Spirometry: Unable to withhold albuterol/salbutamol for the 4 hour period required prior to spirometry testing at each study visit.
- Medications prior to Screening, including depot,oral corticosteroids, combinations of LABA/ICS, LABA, PDE4 inhibitors.
- 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., albuterol/salbutamol) 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

Contacts and Locations

Locations

United States, Arizona

GSK Investigational Site

Phoenix, Arizona, United States, 85006

United States, New Hampshire

GSK Investigational Site

Lebanon, New Hampshire, United States, 03756

United States, New York

GSK Investigational Site

Albany, New York, United States, 12205

United States, Ohio

GSK Investigational Site

Columbus, Ohio, United States, 43215

United States, Oregon

GSK Investigational Site

Medford, Oregon, United States, 97504

United States, South Carolina

GSK Investigational Site

Gaffney, South Carolina, United States, 29340

GSK Investigational Site

Greenville, South Carolina, United States, 29615

GSK Investigational Site

Greenville, South Carolina, United States, 29615

GSK Investigational Site

Spartanburg, South Carolina, United States, 29303

GSK Investigational Site

Spartanburg, South Carolina, United States, 29303

GSK Investigational Site

Union, South Carolina, United States, 29379

United States, Texas

GSK Investigational Site

Kingwood, Texas, United States, 77339

United States, Virginia

GSK Investigational Site

Richmond, Virginia, United States, 23229

Bulgaria

GSK Investigational Site

Plovdiv, Bulgaria, 4000

GSK Investigational Site

Sofia, Bulgaria, 1000

Estonia

GSK Investigational Site

Tallinn, Estonia, 13619

GSK Investigational Site

Tartu, Estonia, 51014

Germany

GSK Investigational Site

Berlin, Berlin, Germany, 10117

GSK Investigational Site

Berlin, Berlin, Germany, 10787

GSK Investigational Site

Hamburg, Hamburg, Germany, 20354

GSK Investigational Site

Hamburg, Hamburg, Germany, 20253

GSK Investigational Site

Gelnhausen, Hessen, Germany, 63571

GSK Investigational Site

Wiesbaden, Hessen, Germany, 65187

GSK Investigational Site

Bochum, Nordrhein-Westfalen, Germany, 44787

GSK Investigational Site

Solingen, Nordrhein-Westfalen, Germany, 42651

GSK Investigational Site

Witten, Nordrhein-Westfalen, Germany, 58452

GSK Investigational Site

Grosshansdorf, Schleswig-Holstein, Germany, 22927

Russian Federation

GSK Investigational Site

Barnaul, Russian Federation, 656 045

GSK Investigational Site

Chelyabinsk, Russian Federation, 454106

GSK Investigational Site

Moscow, Russian Federation, 105 077

GSK Investigational Site

Moscow, Russian Federation, 127018

GSK Investigational Site

St. Petersburg, Russian Federation, 197022

United Kingdom

GSK Investigational Site

Northwood, Middlesex, United Kingdom, HA6 2RN

Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Responsible Party: GlaxoSmithKline
Study ID Numbers: 114417
Health Authority: United States: Food and Drug Administration

---

Study Results

Participant Flow

Recruitment Details

Participants (par.) who were eligible completed a 12- to 21-day Run-in Period followed by two 12-week treatment periods.

Pre-Assignment Details

A total of 596 par. were enrolled and screened, 409 par. entered the Run-in Period, 349 par. were randomized and 348 par. received study treatment. Participant Flow data are presented by treatment rather than sequence. Par. received 2 out of the 6 interventions.

Reporting Groups

	Description
Placebo	Participants received matching placebo QD via a DPI in the morning for 12 weeks.
UMEC 62.5 µg QD	Participants received umeclidinium bromide (UMEC) 62.5 micrograms (µg) QD via a DPI in the morning for 12 weeks.
UMEC 125 µg QD	Participants received UMEC 125 µg QD via a DPI in the morning for 12 weeks.
VI 25 µg QD	Participants received vilanterol (VI) 25 µg QD via a DPI for 12 weeks.

	Description
UMEC/VI 62.5/25 µg QD	Participants received UMEC/VI 62.5/25 µg QD via a DPI in the morning for 12 weeks.
UMEC 125/25 µg QD	Participants received UMEC/VI 125/25 µg QD via a DPI in the morning for 12 weeks.

Treatment Period 1 (12 Weeks)

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC 125/25 µg QD
Started	94	26	28	41	81	78
Completed	83	21	25	33	67	72
Not Completed	11	5	3	8	14	6
Adverse Event	3	1	1	3	5	2
Lack of Efficacy	6	1	1	1	6	2
Protocol Violation	0	0	0	1	0	1
Met Protocol- Defined Stopping Criteria	0	1	0	0	2	0
Lost to Follow-up	2	0	0	1	0	1
Withdrawal by Subject	0	2	1	2	1	0

Washout Period (14 Days)

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC 125/25 µg QD
Started	83	21	25	33	67	72

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC 125/25 µg QD
Completed	82 [1]	20 [2]	25 [3]	32 [4]	66 [5]	68 [6]
Not Completed	1	1	0	1	1	4
Adverse Event	1	1	0	1	1	2
Lack of Efficacy	0	0	0	0	0	1
Withdrawal by Subject	0	0	0	0	0	1

[1] Participants withdrawing during washout are counted under the last treatment taken.

[2] Participants withdrawing during washout are counted under the last treatment taken.

[3] Participants withdrawing during washout are counted under the last treatment taken.

[4] Participants withdrawing during washout are counted under the last treatment taken.

[5] Participants withdrawing during washout are counted under the last treatment taken.

[6] Participants withdrawing during washout are counted under the last treatment taken.

Treatment Period 2 (12 Weeks)

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC 125/25 µg QD
Started	76 [1]	23 [2]	22 [3]	35 [4]	71 [5]	66 [6]
Completed	65	22	19	30	63	59
Not Completed	11	1	3	5	8	7
Adverse Event	5	0	1	1	1	0
Lack of Efficacy	5	1	1	2	3	4
Protocol Violation	1	0	0	0	1	0

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC 125/25 µg QD
Met Protocol Defined Stopping Criteria	0	0	0	1	1	0
Lost to Follow-up	0	0	1	1	1	2
Withdrawal by Subject	0	0	0	0	1	1

[1] By crossover design, participants were assigned to a different treatment arm in each period.

[2] By crossover design, participants were assigned to a different treatment arm in each period.

[3] By crossover design, participants were assigned to a different treatment arm in each period.

[4] By crossover design, participants were assigned to a different treatment arm in each period.

[5] By crossover design, participants were assigned to a different treatment arm in each period.

[6] By crossover design, participants were assigned to a different treatment arm in each period.

Baseline Characteristics

Reporting Groups

	Description
All Study Treatments	Participants were randomized to receive a sequence consisting of 2 of the following treatments: UMEC/VI 125/25 µg , UMEC/VI 62.5/25 µg , UMEC 125 µg , UMEC 62.5 µg , VI 25 µg , or placebo QD via a DPI. Each treatment was administered in the morning for 12 weeks. The treatment periods were seperated by 14-day washout period.

Baseline Measures

	All Study Treatments
Number of Participants	348
Age, Continuous [units: Years] Mean (Standard Deviation)	61.6 (8.25)
Gender, Male/Female [units: Participants]	
Female	153
Male	195
Race/Ethnicity, Customized [units: Participants]	
African American/African Heritage	11
White - White/Caucasian/European Heritage	336
Mixed Race	1

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Change From Baseline in Exercise Endurance Time Post-dose at Week 12 of Each Treatment Period
Measure Description	Exercise endurance time (EET) post-dose at Week 12 is defined as the EET obtained 3 hours after dosing at Week 12. EET was measured using the externally paced field walking test called the endurance shuttle walk test (ESWT). Analysis performed using a repeated

	measures model with covariates of period walking speed, mean walking speed, period, treatment, visit, smoking status, center group, visit by period walking speed, visit by mean walking speed and visit by treatment interactions. The model used all available 3-hour post-dose change from baseline EET values recorded on Day 2, Week 6 and Week 12. Baseline was the EET assessment obtained prior to dosing on Day 1 of each period. The mean walking speed for each participant is the mean of the levels used for the ESWT in each of the two treatment periods. The period walking speed for each participant and treatment period is the difference between the level for that participant and period and the mean walking speed for that participant.
Time Frame	Week 12 of each treatment period (up to Study Week 29)
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all par. randomized to treatment who received at least one dose of study drug in either treatment period. Number of par. represent those with data available at the time point; however, all par. in the ITT population without missing covariate information and with at least one post Baseline measurement are included.

Reporting Groups

	Description
Placebo	Participants received matching placebo QD via a DPI in the morning for 12 weeks.
UMEC 62.5 µg QD	Participants received UMEC 62.5 µg QD via a DPI in the morning for 12 weeks.
UMEC 125 µg QD	Participants received UMEC 125 µg QD via a DPI in the morning for 12 weeks.
VI 25 µg QD	Participants received vilanterol (VI) 25 µg QD via a DPI for 12 weeks.

	Description
UMEC/VI 62.5/25 µg QD	Participants received UMEC/VI 62.5/25 µg QD via a DPI in the morning for 12 weeks.
UMEC/VI 125/25 µg QD	Participants received UMEC/VI 125/25 µg QD via a DPI in the morning for 12 weeks.

Measured Values

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC/VI 125/25 µg QD
Number of Participants Analyzed	145	43	44	63	131	130
Change From Baseline in Exercise Endurance Time Post-dose at Week 12 of Each Treatment Period [units: Seconds] Least Squares Mean (Standard Error)	36.7 (13.17)	63.2 (23.93)	49.8 (23.77)	26.7 (19.72)	58.6 (13.82)	69.1 (13.99)

Statistical Analysis 1 for Change From Baseline in Exercise Endurance Time Post-dose at Week 12 of Each Treatment Period

Groups	Placebo, UMEC 62.5 µg QD
Method	Mixed Models Analysis
P-Value	0.321
Other Estimated Parameter [Least squares mean difference]	26.5
95% Confidence Interval	-25.9 to 78.9

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=UMEC 62.5 µg minus Placebo.

Statistical Analysis 2 for Change From Baseline in Exercise Endurance Time Post-dose at Week 12 of Each Treatment Period

Groups	Placebo, UMEC 125 µg QD
Method	Mixed Models Analysis
P-Value	0.620
Other Estimated Parameter [Least squares mean difference]	13.1
95% Confidence Interval	-38.9 to 65.1

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=UMEC 125 µg minus Placebo.

Statistical Analysis 3 for Change From Baseline in Exercise Endurance Time Post-dose at Week 12 of Each Treatment Period

Groups	Placebo, VI 25 µg QD
Method	Mixed Models Analysis

P-Value	0.665
Other Estimated Parameter [Least squares mean difference]	-10.0
95% Confidence Interval	-55.5 to 35.4

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=VI 25 µg minus Placebo.

Statistical Analysis 4 for Change From Baseline in Exercise Endurance Time Post-dose at Week 12 of Each Treatment Period

Groups	UMEC 62.5 µg QD, UMEC/VI 62.5/25 µg QD
Method	Mixed Models Analysis
P-Value	0.865
Other Estimated Parameter [Least squares mean difference]	-4.6
95% Confidence Interval	-57.6 to 48.4

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=UMEC/VI 62.5/25 µg minus UMEC 62.5 µg.

Statistical Analysis 5 for Change From Baseline in Exercise Endurance Time Post-dose at Week 12 of Each Treatment Period

Groups	VI 25 µg QD, UMEC/VI 62.5/25 µg QD
Method	Mixed Models Analysis
P-Value	0.174
Other Estimated Parameter [Least squares mean difference]	31.9
95% Confidence Interval	-14.1 to 77.9

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=UMEC/VI 62.5/25 µg minus VI 25 µg.

Statistical Analysis 6 for Change From Baseline in Exercise Endurance Time Post-dose at Week 12 of Each Treatment Period

Groups	UMEC 125 µg QD, UMEC/VI 125/25 µg QD
Method	Mixed Models Analysis
P-Value	0.472

Other Estimated Parameter [Least squares mean difference]	19.3
95% Confidence Interval	-33.4 to 71.9

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=UMEC/VI 125/25 µg minus UMEC 125 µg.

Statistical Analysis 7 for Change From Baseline in Exercise Endurance Time Post-dose at Week 12 of Each Treatment Period

Groups	VI 25 µg QD, UMEC/VI 125/25 µg QD
Method	Mixed Models Analysis
P-Value	0.072
Other Estimated Parameter [Least squares mean difference]	42.4
95% Confidence Interval	-3.8 to 88.7

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=UMEC/VI 125/25 µg minus VI 25 µg.

Statistical Analysis 8 for Change From Baseline in Exercise Endurance Time Post-dose at Week 12 of Each Treatment Period

Groups	Placebo, UMEC/VI 62.5/25 µg QD
Method	Mixed Models Analysis
P-Value	0.234
Other Estimated Parameter [Least squares mean difference]	21.9
95% Confidence Interval	-14.2 to 58.0

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=UMEC/VI 62.5/25 µg minus Placebo.

Statistical Analysis 9 for Change From Baseline in Exercise Endurance Time Post-dose at Week 12 of Each Treatment Period

Groups	Placebo, UMEC/VI 125/25 µg QD
Method	Mixed Models Analysis
P-Value	0.080
Other Estimated Parameter [Least squares mean difference]	32.4

95% Confidence Interval	-3.9 to 68.8

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=UMEC/VI 125/25 µg minus Placebo.

2. Primary Outcome Measure:

Measure Title	Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Week 12 of Each Treatment Period
Measure Description	FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. Trough FEV1 measurements were taken electronically by spirometry on Day 2, Week 6 and Week 12. Baseline is the FEV1 value recorded 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. Clinic visit trough (pre-bronchodilator and pre-dose) FEV1 at Week 12 (Treatment Day 85) is defined as the FEV1 value obtained 24 hours after dosing on Treatment Day 84. Analysis performed using a repeated measures model with covariates of period Baseline, mean Baseline, period, treatment, visit, smoking status, center group, visit by period Baseline, visit by mean Baseline and visit by treatment interactions.

Time Frame	Week 12 of each treatment period (up to Study Week 29)
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all par. randomized to treatment who received at least one dose of study drug in either treatment period. Number of par. represent those with data available at the time point; however, all par. in the ITT population without missing covariate information and with at least one post Baseline measurement are included.

Reporting Groups

	Description
Placebo	Participants received matching placebo QD via a DPI in the morning for 12 weeks.
UMEC 62.5 µg QD	Participants received UMEC 62.5 µg QD via a DPI in the morning for 12 weeks.
UMEC 125 µg QD	Participants received UMEC 125 µg QD via a DPI in the morning for 12 weeks.
VI 25 µg QD	Participants received vilanterol (VI) 25 µg QD via a DPI for 12 weeks.
UMEC/VI 62.5/25 µg QD	Participants received UMEC/VI 62.5/25 µg QD via a DPI in the morning for 12 weeks.
UMEC/VI 125/25 µg QD	Participants received UMEC/VI 125/25 µg QD via a DPI in the morning for 12 weeks.

Measured Values

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC/VI 125/25 µg QD
Number of Participants Analyzed	148	43	44	64	130	132

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC/VI 125/25 µg QD
Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Week 12 of Each Treatment Period [units: Liters] Least Squares Mean (Standard Error)	-0.032 (0.0149)	0.054 (0.0264)	0.108 (0.0263)	0.067 (0.0218)	0.178 (0.0156)	0.136 (0.0158)

Statistical Analysis 1 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Week 12 of Each Treatment Period

Groups	Placebo, UMEC 62.5 µg QD
Method	Mixed Models Analysis
P-Value	0.003
Other Estimated Parameter [Least squares mean difference]	0.087
95% Confidence Interval	0.030 to 0.143

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=UMEC 62.5 µg minus Placebo.

Statistical Analysis 2 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Week 12 of Each

Treatment Period

Groups	Placebo, UMEC 125 µg QD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.140
95% Confidence Interval	0.084 to 0.196

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=UMEC 125 µg minus Placebo.

Statistical Analysis 3 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Week 12 of Each Treatment Period

Groups	Placebo, VI 25 µg QD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.099
95% Confidence Interval	0.050 to 0.148

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=VI 25 µg minus Placebo.

Statistical Analysis 4 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Week 12 of Each Treatment Period

Groups	UMEC 62.5 µg QD, UMEC/VI 62.5/25 µg QD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.124
95% Confidence Interval	0.067 to 0.181

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=UMEC/VI 62.5/25 µg minus UMEC 62.5 µg.

Statistical Analysis 5 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Week 12 of Each Treatment Period

Groups	VI 25 µg QD, UMEC/VI 62.5/25 µg QD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.111
95% Confidence Interval	0.062 to 0.161

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=UMEC/VI 62.5/25 µg minus VI 25 µg.

Statistical Analysis 6 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Week 12 of Each Treatment Period

Groups	UMEC 125 µg QD, UMEC/VI 125/25 µg QD
Method	Mixed Models Analysis
P-Value	0.320
Other Estimated Parameter [Least squares mean difference]	0.029

95% Confidence Interval	-0.028 to 0.086

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=UMEC/VI 125/25 µg minus UMEC 125 µg.

Statistical Analysis 7 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Week 12 of Each Treatment Period

Groups	VI 25 µg QD, UMEC/VI 125/25 µg QD
Method	Mixed Models Analysis
P-Value	0.007
Other Estimated Parameter [Least squares mean difference]	0.070
95% Confidence Interval	0.019 to 0.120

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=UMEC/VI 125/25 µg minus VI 25 µg.

Statistical Analysis 8 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Week 12 of Each Treatment Period

Groups	Placebo, UMEC/VI 62.5/25 µg QD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.211
95% Confidence Interval	0.172 to 0.249

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=UMEC/VI 62.5/25 µg minus Placebo.

Statistical Analysis 9 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Week 12 of Each Treatment Period

Groups	Placebo, UMEC/VI 125/25 µg QD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least	0.169

squares mean difference]	
95% Confidence Interval	0.129 to 0.209

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:

Nominal p-value

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

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Other relevant estimation information:

Least square mean change difference=UMEC/VI 125/25 µg minus Placebo.

3. Secondary Outcome Measure:

Measure Title	Change From Baseline in Inspiratory Capacity (Trough and 3-hours Post-dose) at Week 12 of Each Treatment Period
Measure Description	Inspiratory capacity (IC) is defined as the maximum amount of air that can be inhaled into the lungs from the normal resting position after breathing out normally. Baseline is the IC value recorded 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. Trough IC is measured pre-dose on Treatment Week 12 of each treatment period. IC 3-hours post-dose is measured from the value obtained 3 hours after dosing on Treatment Week 12 of each treatment period. Analysis performed using a repeated measures model with covariates of period Baseline, mean Baseline, period, treatment, visit, smoking status, center group, visit by period Baseline, visit by mean Baseline and visit by treatment interactions. IC

	measurements were taken electronically by plethysmography on Day 2, Week 6 and Week 12.
Time Frame	Week 12 of each treatment period (up to Study Week 29)
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) population: all par. randomized to treatment who received at least one dose of study drug in either treatment period. Number of par. represent those with data available at the time point; however, all par. in the ITT population without missing covariate information and with at least one post Baseline measurement are included.

Reporting Groups

	Description
Placebo	Participants received matching placebo QD via a DPI in the morning for 12 weeks.
UMEC 62.5 µg QD	Participants received UMEC 62.5 µg QD via a DPI in the morning for 12 weeks.
UMEC 125 µg QD	Participants received UMEC 125 µg QD via a DPI in the morning for 12 weeks.
VI 25 µg QD	Participants received vilanterol (VI) 25 µg QD via a DPI for 12 weeks.
UMEC/VI 62.5/25 µg QD	Participants received UMEC/VI 62.5/25 µg QD via a DPI in the morning for 12 weeks.
UMEC/VI 125/25 µg QD	Participants received UMEC/VI 125/25 µg QD via a DPI in the morning for 12 weeks.

Measured Values

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC/VI 125/25 µg QD
Number of Participants Analyzed	148	43	44	64	131	132
Change From Baseline in Inspiratory Capacity (Trough and 3-hours Post-dose) at Week 12 of Each Treatment Period [units: Liters] Least Squares Mean (Standard Error)						
Trough	-0.002 (0.0255)	0.025 (0.0457)	0.187 (0.0457)	0.067 (0.0377)	0.196 (0.0269)	0.168 (0.0270)
3-hours post-dose	0.028 (0.0259)	0.142 (0.0463)	0.249 (0.0462)	0.160 (0.0382)	0.267 (0.0274)	0.250 (0.0275)

4. Secondary Outcome Measure:

Measure Title	Change From Baseline in Functional Residual Capacity (Trough and 3-hours Post-dose) at Week 12 of Each Treatment Period
Measure Description	Functional Residual Capacity (FRC) is defined as the amount of air still left in the lungs after breathing out normally. Baseline is the FRC value recorded 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. Trough FRC is measured pre-dose on Treatment Week 12. FRC 3-hours post-dose is measured from the value obtained 3 hours after dosing on Treatment Week 12. Analysis performed using a repeated measures model with covariates of period Baseline, mean Baseline, period, treatment, visit, smoking status, center group, visit by period Baseline, visit by mean Baseline and visit by treatment interactions. FRC measurements were taken

	electronically by plethysmography on Day 2, Week 6 and Week 12.
Time Frame	Week 12 of each treatment period (up to Study Week 29)
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) population: all par. randomized to treatment who received at least one dose of study drug in either treatment period. Number of par. represent those with data available at the time point; however, all par. in the ITT population without missing covariate information and with at least one post Baseline measurement are included.

Reporting Groups

	Description
Placebo	Participants received matching placebo QD via a DPI in the morning for 12 weeks.
UMEC 62.5 µg QD	Participants received UMEC 62.5 µg QD via a DPI in the morning for 12 weeks.
UMEC 125 µg QD	Participants received UMEC 125 µg QD via a DPI in the morning for 12 weeks.
VI 25 µg QD	Participants received vilanterol (VI) 25 µg QD via a DPI for 12 weeks.
UMEC/VI 62.5/25 µg QD	Participants received UMEC/VI 62.5/25 µg QD via a DPI in the morning for 12 weeks.
UMEC/VI 125/25 µg QD	Participants received UMEC/VI 125/25 µg QD via a DPI in the morning for 12 weeks.

Measured Values

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC/VI 125/25 µg QD
Number of Participants Analyzed	148	43	44	64	131	132
Change From Baseline in Functional Residual Capacity (Trough and 3-hours Post-dose) at Week 12 of Each Treatment Period [units: Liters] Least Squares Mean (Standard Error)						
Trough	0.020 (0.0494)	-0.262 (0.0899)	-0.241 (0.0890)	-0.109 (0.0738)	-0.219 (0.0523)	-0.350 (0.0524)
3-hours post-dose	-0.081 (0.0495)	-0.358 (0.0893)	-0.456 (0.0885)	-0.229 (0.0734)	-0.384 (0.0523)	-0.548 (0.0526)

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in Residual Volume (Trough and 3-hours Post-dose) at Week 12 of Each Treatment Period
Measure Description	Residual Volume (RV) is defined as the air that remains in the lungs after breathing out as fully as possible. Baseline is the RV value recorded 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. Trough RV is measured pre-dose on Treatment Week 12. RV 3-hours post-dose is measured from the value obtained 3 hours after dosing on Treatment Week 12. Analysis performed using a repeated measures model with covariates of period Baseline, mean Baseline, period, treatment, visit, smoking status, center group, visit by period Baseline, visit by mean Baseline and visit by treatment interactions. RV measurements were taken electronically

	by plethysmography on Day 2, Week 6 and Week 12.
Time Frame	Week 12 of each treatment period (up to Study Week 29)
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) population: all par. randomized to treatment who received at least one dose of study drug in either treatment period. Number of par. represent those with data available at the time point; however, all par. in the ITT population without missing covariate information and with at least one post Baseline measurement are included.

Reporting Groups

	Description
Placebo	Participants received matching placebo QD via a DPI in the morning for 12 weeks.
UMEC 62.5 µg QD	Participants received UMEC 62.5 µg QD via a DPI in the morning for 12 weeks.
UMEC 125 µg QD	Participants received UMEC 125 µg QD via a DPI in the morning for 12 weeks.
VI 25 µg QD	Participants received vilanterol (VI) 25 µg QD via a DPI for 12 weeks.
UMEC/VI 62.5/25 µg QD	Participants received UMEC/VI 62.5/25 µg QD via a DPI in the morning for 12 weeks.
UMEC/VI 125/25 µg QD	Participants received UMEC/VI 125/25 µg QD via a DPI in the morning for 12 weeks.

Measured Values

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC/VI 125/25 µg QD
Number of Participants Analyzed	148	43	44	64	131	132
Change From Baseline in Residual Volume (Trough and 3-hours Post-dose) at Week 12 of Each Treatment Period [units: Liters] Least Squares Mean (Standard Error)						
Trough	0.039 (0.0521)	-0.337 (0.0948)	-0.249 (0.0940)	-0.138 (0.0779)	-0.255 (0.0552)	-0.432 (0.0553)
3-hours post-dose	-0.086 (0.0526)	-0.375 (0.0955)	-0.451 (0.0945)	-0.253 (0.0784)	-0.437 (0.0556)	-0.625 (0.0560)

6. Secondary Outcome Measure:

Measure Title	Change From Baseline in 3-hours Post-dose FEV1 at Week 12 of Each Treatment Period
Measure Description	FEVI is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. Baseline is the FEV1 value recorded 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. Clinic visit post-dose FEV1 at Week 12 (Treatment Day 85) is defined as the FEV1 value obtained 3 hours after dosing on Treatment Day 85. Analysis performed using a repeated measures model with covariates of period Baseline, mean Baseline, period, treatment, visit, smoking status, center group, visit by period Baseline, visit by mean Baseline and visit by treatment interactions 3 hour post-dose FEV1 measurements were taken electronically by spirometry on Day 2, Week

	6 and Week 12.
Time Frame	Week 12 of each treatment period (up to Study Week 29)
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) population: all par. randomized to treatment who received at least one dose of study drug in either treatment period. Number of par. represent those with data available at the time point; however, all par. in the ITT population without missing covariate information and with at least one post Baseline measurement are included.

Reporting Groups

	Description
Placebo	Participants received matching placebo QD via a DPI in the morning for 12 weeks.
UMEC 62.5 µg QD	Participants received UMEC 62.5 µg QD via a DPI in the morning for 12 weeks.
UMEC 125 µg QD	Participants received UMEC 125 µg QD via a DPI in the morning for 12 weeks.
VI 25 µg QD	Participants received vilanterol (VI) 25 µg QD via a DPI for 12 weeks.
UMEC/VI 62.5/25 µg QD	Participants received UMEC/VI 62.5/25 µg QD via a DPI in the morning for 12 weeks.
UMEC/VI 125/25 µg QD	Participants received UMEC/VI 125/25 µg QD via a DPI in the morning for 12 weeks.

Measured Values

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC/VI 125/25 µg QD
Number of Participants Analyzed	147	43	44	64	130	130
Change From Baseline in 3-hours Post-dose FEV1 at Week 12 of Each Treatment Period [units: Liters] Least Squares Mean (Standard Error)	-0.007 (0.0159)	0.122 (0.0277)	0.156 (0.0275)	0.115 (0.0229)	0.254 (0.0166)	0.217 (0.0169)

Reported Adverse Events

Reporting Groups

	Description
Placebo	Participants received matching placebo QD via a DPI in the morning for 12 weeks.
UMEC 62.5 µg QD	Participants received UMEC 62.5 µg QD via a DPI in the morning for 12 weeks.
UMEC 125 µg QD	Participants received UMEC 125 µg QD via a DPI in the morning for 12 weeks.
VI 25 µg QD	Participants received vilanterol (VI) 25 µg QD via a DPI for 12 weeks.
UMEC/VI 62.5/25 µg QD	Participants received UMEC/VI 62.5/25 µg QD via a DPI in the morning for 12 weeks.
UMEC/VI 125/25 µg QD	Participants received UMEC/VI 125/25 µg QD via a DPI in the morning for 12 weeks.

Time Frame

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs), defined as those events occuring while participants were on treatment up until one day after the last dose (up to Week 33), are reported.

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

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC/VI 125/25 µg QD
Total # participants affected/at risk	6/170 (3.53%)	0/49 (0%)	3/50 (6%)	7/76 (9.21%)	4/152 (2.63%)	4/144 (2.78%)
Cardiac disorders						
Angina pectoris †[A]						
# participants affected/at risk	1/170 (0.59%)	0/49 (0%)	0/50 (0%)	0/76 (0%)	0/152 (0%)	0/144 (0%)
# events						
Bundle branch block left †[A]						
# participants affected/at risk	0/170 (0%)	0/49 (0%)	0/50 (0%)	1/76 (1.32%)	0/152 (0%)	0/144 (0%)
# events						
Myocardial infarction †[A]						
# participants affected/at risk	0/170 (0%)	0/49 (0%)	0/50 (0%)	0/76 (0%)	1/152 (0.66%)	0/144 (0%)
# events						

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC/VI 125/25 µg QD
Eye disorders						
Cataract † [A]						
# participants affected/at risk	0/170 (0%)	0/49 (0%)	0/50 (0%)	1/76 (1.32%)	0/152 (0%)	0/144 (0%)
# events						
Gastrointestinal disorders						
Abdominal pain † [A]						
# participants affected/at risk	0/170 (0%)	0/49 (0%)	0/50 (0%)	0/76 (0%)	0/152 (0%)	1/144 (0.69%)
# events						
General disorders						
Death † [A]						
# participants affected/at risk	0/170 (0%)	0/49 (0%)	1/50 (2%)	0/76 (0%)	0/152 (0%)	0/144 (0%)
# events						
Non-cardiac chest pain † [A]						
# participants affected/at risk	1/170 (0.59%)	0/49 (0%)	0/50 (0%)	1/76 (1.32%)	0/152 (0%)	0/144 (0%)
# events						
Infections and infestations						

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC/VI 125/25 µg QD
Bronchitis † [A]						
# participants affected/at risk	1/170 (0.59%)	0/49 (0%)	0/50 (0%)	0/76 (0%)	0/152 (0%)	0/144 (0%)
# events						
Perirectal abscess † [A]						
# participants affected/at risk	1/170 (0.59%)	0/49 (0%)	0/50 (0%)	0/76 (0%)	0/152 (0%)	0/144 (0%)
# events						
Pneumonia † [A]						
# participants affected/at risk	0/170 (0%)	0/49 (0%)	0/50 (0%)	1/76 (1.32%)	0/152 (0%)	1/144 (0.69%)
# events						
Injury, poisoning and procedural complications						
Ankle fracture † [A]						
# participants affected/at risk	0/170 (0%)	0/49 (0%)	0/50 (0%)	1/76 (1.32%)	0/152 (0%)	0/144 (0%)
# events						
Spinal compression fracture † [A]						
# participants affected/at risk	0/170 (0%)	0/49 (0%)	0/50 (0%)	0/76 (0%)	1/152 (0.66%)	0/144 (0%)

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC/VI 125/25 µg QD
# events						
Metabolism and nutrition disorders						
Type 2 diabetes mellitus † [A]						
# participants affected/at risk	0/170 (0%)	0/49 (0%)	1/50 (2%)	0/76 (0%)	0/152 (0%)	0/144 (0%)
# events						
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Bladder cancer † [A]						
# participants affected/at risk	0/170 (0%)	0/49 (0%)	0/50 (0%)	0/76 (0%)	1/152 (0.66%)	0/144 (0%)
# events						
Breast cancer † [A]						
# participants affected/at risk	0/170 (0%)	0/49 (0%)	0/50 (0%)	0/76 (0%)	1/152 (0.66%)	0/144 (0%)
# events						
Lung neoplasm malignant † [A]						
# participants affected/at risk	0/170 (0%)	0/49 (0%)	1/50 (2%)	0/76 (0%)	0/152 (0%)	0/144 (0%)

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC/VI 125/25 µg QD
# events						
Oropharyngeal cancer stage III † [A]						
# participants affected/at risk	0/170 (0%)	0/49 (0%)	0/50 (0%)	0/76 (0%)	0/152 (0%)	1/144 (0.69%)
# events						
Rectal cancer † [A]						
# participants affected/at risk	0/170 (0%)	0/49 (0%)	0/50 (0%)	1/76 (1.32%)	0/152 (0%)	0/144 (0%)
# events						
Nervous system disorders						
Carotid artery stenosis † [A]						
# participants affected/at risk	1/170 (0.59%)	0/49 (0%)	0/50 (0%)	0/76 (0%)	0/152 (0%)	0/144 (0%)
# events						
Cerebrovascular accident † [A]						
# participants affected/at risk	1/170 (0.59%)	0/49 (0%)	0/50 (0%)	0/76 (0%)	0/152 (0%)	0/144 (0%)
# events						
Renal and urinary disorders						

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC/VI 125/25 µg QD
Renal failure † [A]						
# participants affected/at risk	1/170 (0.59%)	0/49 (0%)	0/50 (0%)	0/76 (0%)	0/152 (0%)	0/144 (0%)
# events						
Respiratory, thoracic and mediastinal disorders						
Acute respiratory failure † [A]						
# participants affected/at risk	0/170 (0%)	0/49 (0%)	0/50 (0%)	1/76 (1.32%)	0/152 (0%)	0/144 (0%)
# events						
Chronic obstructive pulmonary disease † [A]						
# participants affected/at risk	1/170 (0.59%)	0/49 (0%)	0/50 (0%)	0/76 (0%)	0/152 (0%)	1/144 (0.69%)
# events						
Vascular disorders						
Hypertension † [A]						
# participants affected/at risk	1/170 (0.59%)	0/49 (0%)	0/50 (0%)	0/76 (0%)	0/152 (0%)	0/144 (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%

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC/VI 125/25 µg QD
Total # participants affected/at risk	18/170 (10.59%)	1/49 (2.04%)	5/50 (10%)	7/76 (9.21%)	8/152 (5.26%)	8/144 (5.56%)
Gastrointestinal disorders						
Dry mouth † [A]						
# participants affected/at risk	0/170 (0%)	0/49 (0%)	2/50 (4%)	0/76 (0%)	0/152 (0%)	0/144 (0%)
# events						
Infections and infestations						
Nasopharyngitis † [A]						
# participants affected/at risk	10/170 (5.88%)	1/49 (2.04%)	1/50 (2%)	3/76 (3.95%)	5/152 (3.29%)	8/144 (5.56%)
# events						
Sinusitis † [A]						
# participants affected/at risk	3/170 (1.76%)	0/49 (0%)	2/50 (4%)	0/76 (0%)	0/152 (0%)	4/144 (2.78%)
# events						
Nervous system disorders						

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	UMEC/VI 125/25 µg QD
Headache † [A]						
# participants affected/at risk	7/170 (4.12%)	0/49 (0%)	1/50 (2%)	4/76 (5.26%)	3/152 (1.97%)	2/144 (1.39%)
# 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

Email: