Protocol Registration Receipt
05/08/2014

Grantor: CDER IND/IDE Number: 106616 Serial Number: 0111

A 52-Week, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Tolerability of GSK573719/GW642444 and GSK573719 in Subjects With Chronic Obstructive Pulmonary Disease (COPD) (COPD nDPI)

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT01316887

Purpose

The purpose of this 52-week study is to evaluate the long-term safety (in terms of adverse events, COPD exacerbations, laboratory, ECG, and Holter findings, vital signs, use of rescue medication and lung function) of GSK573719/GW642444 Inhalation Powder 125/25mcg in subjects with COPD. The long-term safety of GSK573719 Inhalation Powder 125mcg will also be evaluated. A placebo arm is included to evaluate these products compared to an inactive control.

Condition	Intervention	Phase
Pulmonary Disease, Chronic Obstructive	Drug: 125/25 mcg once-daily GSK573719/GW642444 Drug: 125mcg once-daily GSK573719 Drug: Placebo once-daily	Phase 3

Study Type: Interventional

Study Design: Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety Study

Official Title: A 52 Week Study to Evaluate the Safety and Tolerability of GSK573719/GW642444 125mcg Once-daily Alone and in Combination With GW642444 25mcg Once-daily Via Novel Dry Powder Inhaler (nDPI) in Subjects With Chronic Obstructive Pulmonary Disease

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Number of Participants With Any On-treatment Adverse Event (AE) or Any Serious Adverse Event (SAE) [Time Frame: From the start of study drug up to 52 weeks] [Designated as safety issue: No]

  An AE is defined as any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is an event of possible drug-induced liver injury with hyperbilirubinaemia. Medical or scientific judgment was to have been exercised in other important medical events. AEs with an onset on or after the date of the first dose of study drug and up to 1 day after the date of the last recorded dose of study drug were considered to be on-treatment AEs, Refer to the general AE/SAE module for a complete list of AEs and SAEs.

Secondary Outcome Measures:

- Number of Participants With at Least One Chronic Obstructive Pulmonary Disease (COPD) Exacerbation Over the Course of the 52-week Treatment Period [Time Frame: From the start of study drug up to 52 weeks] [Designated as safety issue: No]

  A COPD exacerbation is defined as worsening symptoms of COPD requiring a systemic corticosteroid, an antibiotic, and/or hospitalization.
- Time to the First On-treatment COPD Exacerbation [Time Frame: From the start of study drug up to 52 weeks] [Designated as safety issue: No]

  An on-treatment COPD exacerbation is defined as worsening symptoms of COPD requiring a systemic corticosteroid, an antibiotic, and/or hospitalization at any time during the 52-week Treatment Period. The time to the first on-treatment exacerbation was calculated as the exacerbation onset date of the first on-treatment exacerbation minus the date of the start of treatment + 1. The median time to the first on-treatment exacerbation was derived from the Kaplan-Meier analysis. A participant who did not experience an exacerbation prior to completing the study or withdrawal is considered censored; a time to first COPD exacerbation cannot be calculated for these participants.
- Change From Baseline in Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST), Creatine Kinase (CK), and Gamma Glutamyl Transferase (GGT) at Months 3, 6, 9, and 12 [Time Frame: Baseline; Months 3, 6, 9, and 12] [Designated as safety issue: No]

Blood samples were collected for the measurement of ALT, ALP, AST, CK, and GGT at Baseline and Months 3, 6, 9, and 12. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The value defined as the "Baseline" value is the most recent value collected prior to the start of treatment. For most participants, the Baseline value is the value collected at the Screening visit; however, for some participants, the Baseline value may have been collected at an unscheduled visit.

- Change From Baseline in Albumin, Total Protein, and Hemoglobin at Months 3, 6, 9, and 12 [Time Frame: Baseline; Months 3, 6, 9, and 12] [Designated as safety issue: No]

  Blood samples were collected for the measurement of albumin, total protein, and hemoglobin at Baseline and Months 3, 6, 9, and 12. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The value defined as the "Baseline" value is the most recent value collected prior to the start of treatment. For most participants, the Baseline value is the value collected at the Screening visit; however, for some participants, the Baseline value may have been collected at an unscheduled visit.
- Change From Baseline in Calcium, Carbon Dioxide (CO2) Content/Bicarbonate, Chloride, Glucose, Inorganic Phosphorus (IP), Potassium, Sodium, and Urea/Blood Urea Nitrogen (BUN) at Months 3, 6, 9, and 12 [Time Frame: Baseline; Months 3, 6, 9, and 12] [Designated as safety issue: No]

  Blood samples were collected for the measurement of calcium, CO2 content/bicarbonate, chloride, glucose, IP, potassium, sodium, and urea/BUN at Baseline and Months 3, 6, 9, and 12. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The value defined as the "Baseline" value is the most recent value collected prior to the start of treatment. For most participants, the Baseline value is the value collected at the Screening visit; however, for some participants, the Baseline value may have been collected at an unscheduled visit.
- Change From Baseline in Creatinine, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, and Uric Acid at Months 3, 6, 9, and 12 [Time Frame: Baseline; Months 3, 6, 9, and 12] [Designated as safety issue: No]

  Blood samples were collected for the measurement of creatinine, direct bilirubin, indirect bilirubin, total bilirubin, and uric acid at Baseline and Months 3, 6, 9, and 12. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The value defined as the "Baseline" value is the most recent value collected prior to the start of treatment. For most participants, the Baseline value is the value collected at the Screening visit; however, for some participants, the Baseline value may have been collected at an unscheduled visit.
- Change From Baseline in the Percentage of Basophils, Eosinophils, Lymphocytes, Monocytes, and Segmented Neutrophils in Blood at Months 3, 6, 9, and 12 [Time Frame: Baseline; Months 3, 6, 9, and 12] [Designated as safety issue: No]

  Blood samples were collected for the measurement of the percentage of basophils, eosinophils, lymphocytes, monocytes, and segmented neutrophils at Baseline and Months 3, 6, 9, and 12. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The value defined as the "Baseline" value is the most recent value collected prior to the start of treatment. For most participants, the Baseline value is the value collected at the Screening visit; however, for some participants, the Baseline value may have been collected at an unscheduled visit.
- Change From Baseline in Eosinophil Count, Platelet Count, and White Blood Cell (WBC) Count at Months 3, 6, 9, and 12 [Time Frame: Baseline; Months 3, 6, 9, and 12] [Designated as safety issue: No]

  Blood samples were collected for the measurement of eosinophils, platelets, and WBC count at Baseline and Months 3, 6, 9, and 12. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The value defined as the "Baseline" value is the most recent value collected prior to the start of treatment. For most participants, the Baseline value is the value collected at the Screening visit; however, for some participants, the Baseline value may have been collected at an unscheduled visit.
- Change From Baseline in Hematocrit at Months 3, 6, 9, and 12 [Time Frame: Baseline; Months 3, 6, 9, and 12] [Designated as safety issue: No]

Blood samples were collected for the measurement of hematocrit at Baseline and Months 3, 6, 9, and 12. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The value defined as the "Baseline" value is the most recent value collected prior to the start of treatment. For most participants, the Baseline value is the value collected at the Screening visit; however, for some participants, the Baseline value may have been collected at an unscheduled visit.

- Change From Baseline to Maximum Systolic Blood Pressure (SBP) and Change From Baseline to Minimum Diastolic Blood Pressure (DBP) Over the Course of the 52-week Treatment Period [Time Frame: Baseline; from the start of study drug up to 52 weeks] [Designated as safety issue: No]

  Baseline is defined as the most recent recorded value before dosing on Day 1. The maximum post-Baseline value for SBP and the minimum post-Basline value for DBP were derived using any scheduled, unscheduled, or early withdrawal visit made after the start of study treatment. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
- Maximum Change From Baseline in Pulse Rate Over the Course of the 52-week Treatment Period [Time Frame: Baseline; from the start of study drug up to 52 weeks] [Designated as safety issue: No]

  Baseline is defined as the most recent recorded value before dosing on Day 1. The maximum post-Baseline value for pulse rate was derived using any scheduled, unscheduled, or early withdrawal visit made after the start of study treatment. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
- Maximum Change From Baseline in the Electrocardiogram (ECG) Parameters of QT Interval Corrected for Heart Rate by Bazett's Formula (QTcB), QT Interval Corrected for Heart Rate by Fridericia's Formula (QTcF), and PR Interval Over the Course of the 52-week [Time Frame: Baseline; from the start of study drug up to 52 weeks] [Designated as safety issue: No]

  12-lead ECG measurements were obtained. Baseline is defined as the most recent recorded value before dosing on Day 1. The maximum post-Baseline values for QTcF, QTcB, and PR interval were derived using any scheduled, unscheduled, or early withdrawal visit made after the start of study treatment. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
- Maximum Change From Baseline in the ECG Parameter of Heart Rate Over the Course of the 52-week Treatment Period [Time Frame: Baseline; from the start of study drug up to 52 weeks] [Designated as safety issue: No]

  12-lead ECG measurements were obtained. Baseline is defined as the most recent recorded value before dosing on Day 1. The maximum post-Baseline value for heart rate was derived using any scheduled, unscheduled, or early withdrawal visit made after the start of study treatment. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
- Number of Participants With the Indicated ECG Result Interpretations at Any Time Post-Baseline [Time Frame: From the start of study drug up to 52 weeks] [Designated as safety issue: No]

  Post-Baseline visits include scheduled, unscheduled, and Early Withdrawal visits. Only the worst-case interpretation was counted for each participant. Clinical significance and abnormal/normal findings are based on the assessment of the independent cardiologists.
- Number of Participants With the Indicated Change From Screening to Any Time Post-Baseline in Holter ECG Interpretation [Time Frame: Screening; from the start of study drug up to 52 weeks] [Designated as safety issue: No]

  Twenty-four hour Holter monitor (12-lead) evaluations were obtained. Holter Baseline values were those recorded at Screening. An "any time post-Baseline" Holter evaluation was derived as the worst evaluation recorded at any scheduled, unscheduled, or early withdrawal visit made after the start of study treatment. Change from Screening was calculated as the post-Screening value minus the Screening value. The order of severity for change from Screening Holter evaluation from worst to best is: clinically significant change: unfavorable; no change or insignificant change; clinically significant

change: favorable, unable to compare, based on the assessment of the independent cardiologists.

- Change From Baseline in the Mean Number of Puffs of Rescue Medication (Salbutamol and/or Ipratropium Bromide) Per Day Over the Course of the 52-week Treatment Period [Time Frame: Baseline; from the start of study drug up to 52 weeks] [Designated as safety issue: No]

  Participants recorded the number of puffs and/or the number of nebules of rescue albuterol/salbutamol and/or ipratropium bromide used in the past 24 hours for the relief of COPD symptoms in the daily diary. The total puffs of rescue medication for each day was calculated as follows: (number of salbutamol puffs + number of ipratropium puffs + [2 * number of salbutamol nebules] + [2 * number of ipratropium nebules]). Baseline is the mean during the week prior to Day 1. Change from Baseline was calculated as the mean number of puffs/day over Weeks 1-52 minus the mean number of puffs/day at Baseline. Analysis was performed using an Analysis of Covariance (ANCOVA) model with covariates of treatment, Baseline (mean during the week prior to Day 1), smoking status, and center group.

- Change From Baseline in the Percentage of Rescue-free Days Over the Course of the 52-week Treatment Period [Time Frame: From the start of study drug up to 52 weeks] [Designated as safety issue: No]

  Rescue-free days are defined as days on which albuterol/salbutamol and/or ipratropium bromide was not used. Baseline is the percentage during the week prior to Day 1. Change from Baseline was calculated as the mean percentage of rescue-free days over Weeks 1-52 minus the mean percentage of rescue-free days at Baseline.

- Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) and Forced Vital Capacity (FVC) at Months 1, 3, 6, 9, and 12 [Time Frame: Baseline; Months 1, 3, 6, 9, and 12] [Designated as safety issue: No]

  FEV1 and FVC are measures of lung function. FEV1 is defined as the maximal amount of air that can be forcefully exhaled in one second. FVC is defined as the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible. Trough FEV1 and FVC were the values obtained approximately 24 hours after the previous morning's dose of study medication. Baseline is the value recorded pre-dose on Day 1. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Analysis was performed using a repeated measures model with covariates of treatment, Baseline (assessment made immediately pre-dose on Day 1), smoking status, center group, month, and month by Baseline and month by treatment interactions.

Enrollment: 563
Study Start Date: January 2011
Study Completion Date: July 2012
Primary Completion Date: July 2012

Arms	Assigned Interventions
Experimental: GSK573719/GW642444 125/25 mcg once-daily	Drug: 125/25 mcg once-daily GSK573719/GW642444 GSK573719/GW642444
Experimental: GSK573719 125 mcg once-daily	Drug: 125mcg once-daily GSK573719 GSK573719

Arms	Assigned Interventions
Placebo Comparator: Placebo inactive	Drug: Placebo once-daily inactive

Several studies have demonstrated the efficacy and safety of combining an individual LABA compound plus an individual LAMA compound in COPD. These studies have shown the combination of these two products to be superior to either agent alone on a variety of outcomes in COPD. The beneficial effects of this combination regimen are likely due to the different mechanisms of action of the two bronchodilators (smooth bronchial muscle relaxation from activation of beta2 receptors from the LABA product and inhibition of acetylcholine-mediated smooth bronchial muscle contraction via blockade of muscarinic receptors from the LAMA product). The availability of a LABA/LAMA combination in one product instead of two individual products is a technical and therapeutic advancement in the pharmacological armamentarium for COPD and may lead to increased patient compliance due to once-daily administration. The purpose of this 52-week study is to evaluate the long-term safety (in terms of adverse events, COPD exacerbations, laboratory, ECG, and Holter findings, vital signs, use of rescue medication, and lung function) of GSK573719/GW642444 Inhalation Powder 125/25mcg in subjects with COPD. The long-term safety of GSK573719 Inhalation Powder 125mcg will also be evaluated. A placebo arm is included to evaluate these products compared to an inactive control. All treatments will be delivered once-daily via the nDPI. This study will establish the long-term safety profile of GSK573719/GW642444 Inhalation Powder 125/25mcg once-daily in subjects with COPD. The safety profile of GSK573719 Inhalation Powder125mcg once-daily will also be evaluated.

Eligibility

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

Inclusion Criteria:

- outpatient
- signed and dated written informed consent
- 40 years of age or older
- male and female subjects
- COPD diagnosis
- at least 10 pack-year smoking history
- post-albuterol/salbutamol FEV1/FVC ratio of <0.70 and post-albuterol/salbutamol FEV1 greater than or equal to 35% and less than or equal to 80% of predicted normal

Exclusion Criteria:

- Pregant or lactating women or women planning to become pregnant during the study

- current diagnosis of asthma
- other respiratory disorders other than COPD
- other diseases/abnormalities that are uncontrolled including cancer not in remission for at least 5 years
- chest x-ray or CT scan with clinically significant abnormalities not believed to be due to COPD
- hypersensitivity to anticholinergics, beta-agonists, lactose/milk protein or magnesium stearate or medical conditions associated with inhaled anticholinergics
- hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1
- lung volume reduction surgery within 12 months prior to Visit 1
- abnormal and clinically significant ECG at Visit 1
- abnormal and clinically significant Holter monitor finding at Visit 1
- significantly abnormal finding from laboratory tests at Visit 1
- unable to withhold albuterol/salbutamol and/or ipratropium bromide at least 4 hours prior to spirometry at each visit
- use of depot corticosteroids within 12 weeks of Visit 1
- use of oral or parenteral corticosteroids within 6 weeks of Visit 1
- use of anitbiotics for lower respiratory tract infection within 6 weeks of Visit 1
- use of cytochrome P450 3A4 inhibitors within 6 weeks of Visit 1
- us of long-acting beta-agonist (LABA)/inhaled corticosteroid (ICS) products if LABA/ICS therapy is discontinued completely within 30 days of Visit 1
- use of ICS at a dose of >10000mcg/day of fluticasone propionate or equivalent within 30 days of Visit 1
- initiation or discontinuation of ICS within 30 days of Visit 1
- use of tiotropium within 14 days of Visit 1
- use of roflumilast within 14 days of Visit 1
- use of theophyllines within 48 hours of Visit 1
- use of oral leukotriene inhibitors within 48 hours prior to Visit 1
- use of long-acting oral beta-agonists within 48 hours of Visit 1
- use of short-acting oral beta-agonists within 12 hours of Visit 1
- use of inhaled long-acting beta-agonists within 48 hours prior to Visit 1
- use of LABA/ICS combination products only if discontinuing LABA therapy and switching to ICS monotherapy within 48 hours of Visit 1 for the LABA component
- use of sodium cromoglycate or nedocromil sodium within 24 hours of Visit 1
- use of inhaled short acting beta-agonists within 4 hours of Visit 1
- use of inhaled short-acting anticholinergics within 4 hours of Visit 1
- use of inhaled short-acting anticholinergic/short-acting beta2-agonist combination products within 4 hours of Visit 1
- use of any other investigational medication within 30 days or 5 drug half-lives (whichever is longer) of Visit 1
- long-term oxygen therapy prescribed for >12 hours per day
- regular use of short-acting bronchodilators
- use of CPAP or NIPPV

- participation in the maintenance phase of a pulmonary rehabilitation program
- known or suspected history of alcohol or drug abluse with 2 years prior to Visit 1
- anyone affiliated with the investigator site (e.g., investigator, study coordinator, etc.)
- previous use of GSK573719, GW642444 , GSK573719/GW642444 combination, GSK233705/GW642444 combination, or Fluticasone Furoate/GW642444 combination

Contacts and Locations

Locations

United States, Alabama

GSK Investigational Site

Mobile, Alabama, United States, 36608

United States, Louisiana

GSK Investigational Site

Sunset, Louisiana, United States, 70584

United States, Minnesota

GSK Investigational Site

Plymouth, Minnesota, United States, 55441

United States, Missouri

GSK Investigational Site

St. Louis, Missouri, United States, 63141

United States, North Carolina

GSK Investigational Site

Charlotte, North Carolina, United States, 28207

United States, Ohio

GSK Investigational Site

Columbus, Ohio, United States, 43215

United States, Oklahoma

GSK Investigational Site

Oklahoma City, Oklahoma, United States, 73103

United States, Pennsylvania

GSK Investigational Site

Erie, Pennsylvania, United States, 16508

United States, South Carolina

GSK Investigational Site

Charleston, South Carolina, United States, 29406-7108

GSK Investigational Site

Spartanburg, South Carolina, United States, 29303

GSK Investigational Site

Union, South Carolina, United States, 29379

United States, Texas

GSK Investigational Site

Corsicana, Texas, United States, 75110

GSK Investigational Site

San Antonio, Texas, United States, 78229

United States, Virginia

GSK Investigational Site

Richmond, Virginia, United States, 23229

United States, West Virginia

GSK Investigational Site

Morgantown, West Virginia, United States, 26505

Chile

GSK Investigational Site

Santiago, Chile, 8380453

GSK Investigational Site

Puente Alto - Santiago, Región Metro De Santiago, Chile, 8207257

GSK Investigational Site

Talca, Región Metro De Santiago, Chile, 3460001

Romania

GSK Investigational Site

Bacau, Romania, 600252

GSK Investigational Site

Brasov, Romania, 500283

GSK Investigational Site

Brasov, Romania, 500112

GSK Investigational Site

Bucuresti, Romania, 70000

GSK Investigational Site

Pitesti, Romania, 110084

GSK Investigational Site

Ploiesti, Romania, 100172

GSK Investigational Site

Ploiesti, Romania, 100379

GSK Investigational Site

Timisoara, Romania, 300310

Russian Federation

GSK Investigational Site

Ekaterinburg, Russian Federation, 620109

GSK Investigational Site

Ivanovo, Russian Federation, 153005

GSK Investigational Site

Moscow, Russian Federation, 119 048

GSK Investigational Site

Moscow, Russian Federation, 127018

GSK Investigational Site

Novgorod, Russian Federation, 173008

GSK Investigational Site

Penza, Russian Federation, 440067

GSK Investigational Site

Saint-Petersburg, Russian Federation, 194354

GSK Investigational Site

Saint-Petersburg, Russian Federation, 193231

GSK Investigational Site

Shakhty, Rostov region, Russian Federation, 346510

GSK Investigational Site

Sochi, Russian Federation, 354057

GSK Investigational Site

St'Petersburg, Russian Federation, 197706

GSK Investigational Site

Tomsk, Russian Federation, 634 050

GSK Investigational Site

Tumen, Russian Federation, 625023

GSK Investigational Site

Vladivostok, Russian Federation, 690950

Slovakia

GSK Investigational Site

Bratislava, Slovakia, 841 08

GSK Investigational Site

Bratislava, Slovakia, 826 06

GSK Investigational Site

Poprad, Slovakia, 058 01

GSK Investigational Site

Povazska Bystrica, Slovakia, 017 26

GSK Investigational Site

Sala, Slovakia, 927 01

GSK Investigational Site

Zilina, Slovakia, 012 07

South Africa

GSK Investigational Site

Bellville, South Africa, 7530

GSK Investigational Site

Bloemfontein, South Africa, 9301

GSK Investigational Site

Durban, South Africa, 4001

GSK Investigational Site

Gatesville, South Africa, 7764

GSK Investigational Site

Mowbray, South Africa, 7700

GSK Investigational Site

Somerset West, South Africa, 7130

GSK Investigational Site

Tygerberg, South Africa, 7505

GSK Investigational Site

Benoni, Gauteng, South Africa, 1501

Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Responsible Party: GlaxoSmithKline
Study ID Numbers: 113359
Health Authority: United States: Food and Drug Administration

---

Study Results

Participant Flow

Pre-Assignment Details

The study consisted of a Run-in Period of 7 to10 days, followed by a 52-week Treatment Period. A total of 893 participants were screened; of these, 312 were screen failures, 19 were Run-in failures, 563 were randomized, and 562 received at least one dose of study drug (one participant was randomized in error but did not receive study drug).

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Overall Study

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Started	109	227	226
Completed	66	133	143
Not Completed	43	94	83
Adverse Event	13	21	17
Lack of Efficacy	9	3	1
Protocol Violation	2	6	6
Protocol-defined Stopping Criteria	8	37	36
Study Closed/Terminated	2	4	3
Lost to Follow-up	1	7	5
Withdrawal by Subject	8	16	15

Baseline Characteristics

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Baseline Measures

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg	Total
Number of Participants	109	227	226	562
Age, Continuous [units: Years] Mean (Standard Deviation)	60.1 (8.28)	61.7 (9.10)	61.4 (9.01)	61.3 (8.92)
Gender, Customized [units: Participants]				
African American/African Heritage (HER)	3	13	14	30
Japanese/East Asian HER/South East Asian HER	2	0	1	3
White	104	214	211	529
Gender, Male/Female [units: Participants]				
Female	36	82	70	188
Male	73	145	156	374

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants With Any On-treatment Adverse Event (AE) or Any Serious Adverse Event (SAE)
Measure Description	An AE is defined as any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An SAE is defined as

	any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is an event of possible drug-induced liver injury with hyperbilirubinaemia. Medical or scientific judgment was to have been exercised in other important medical events. AEs with an onset on or after the date of the first dose of study drug and up to 1 day after the date of the last recorded dose of study drug were considered to be on-treatment AEs, Refer to the general AE/SAE module for a complete list of AEs and SAEs.
Time Frame	From the start of study drug up to 52 weeks
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all participants randomized to treatment who received at least one dose of randomized study drug

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	109	227	226

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants With Any On-treatment Adverse Event (AE) or Any Serious Adverse Event (SAE) [units: Participants]			
Any on-treatment AE	57	132	120
Any on-treatment SAE	7	17	14

2. Secondary Outcome Measure:

Measure Title	Number of Participants With at Least One Chronic Obstructive Pulmonary Disease (COPD) Exacerbation Over the Course of the 52-week Treatment Period
Measure Description	A COPD exacerbation is defined as worsening symptoms of COPD requiring a systemic corticosteroid, an antibiotic, and/or hospitalization.
Time Frame	From the start of study drug up to 52 weeks
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.

	Description
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	109	227	226
Number of Participants With at Least One Chronic Obstructive Pulmonary Disease (COPD) Exacerbation Over the Course of the 52-week Treatment Period [units: Participants]	26	33	29

3. Secondary Outcome Measure:

Measure Title	Time to the First On-treatment COPD Exacerbation
Measure Description	An on-treatment COPD exacerbation is defined as worsening symptoms of COPD requiring a systemic corticosteroid, an antibiotic, and/or hospitalization at any time during the 52-week Treatment Period. The time to the first on-treatment exacerbation was calculated as the exacerbation onset date of the first on-treatment exacerbation minus the date of the start of treatment + 1. The median time to the first on-treatment exacerbation was derived from the Kaplan-Meier analysis. A participant who did not experience an exacerbation prior to completing the study or withdrawal is considered censored; a time to first COPD exacerbation cannot be calculated for these participants.
Time Frame	From the start of study drug up to 52 weeks
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	109	227	226
Time to the First On-treatment COPD Exacerbation [units: Days] Median (Full Range)	NA (1 to 372) [1]	NA (1 to 372) [2]	NA (1 to 372) [3]

[1] Per Kaplan-Meier analysis, because 50% of the data were censored, the median could not be calculated.

[2] Per Kaplan-Meier analysis, because 50% of the data were censored, the median could not be calculated.

[3] Per Kaplan-Meier analysis, because 50% of the data were censored, the median could not be calculated.

4. Secondary Outcome Measure:

Measure Title	Change From Baseline in Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate Aminotransferase

	(AST), Creatine Kinase (CK), and Gamma Glutamyl Transferase (GGT) at Months 3, 6, 9, and 12
Measure Description	Blood samples were collected for the measurement of ALT, ALP, AST, CK, and GGT at Baseline and Months 3, 6, 9, and 12. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The value defined as the "Baseline" value is the most recent value collected prior to the start of treatment. For most participants, the Baseline value is the value collected at the Screening visit; however, for some participants, the Baseline value may have been collected at an unscheduled visit.
Time Frame	Baseline; Months 3, 6, 9, and 12
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants available at the specified time points were summarized (represented by n=X, X, X in the category titles). Different participants may have been summarized for different parameters/at different time points, so the overall number of participants summarized reflects everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	109	227	226
Change From Baseline in Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST), Creatine Kinase (CK), and Gamma Glutamyl Transferase (GGT) at Months 3, 6, 9, and 12 [units: International units per liter (IU/L)] Mean (Standard Deviation)			
ALT, Month 3, n=88, 190, 193	0.3 (12.53)	0.8 (9.40)	0.6 (15.27)
ALT, Month 6, n=73, 158, 172	-1.3 (14.03)	3.2 (22.35)	1.0 (16.83)
ALT, Month 9, n=69, 148, 149	-0.6 (12.81)	-0.2 (7.64)	-0.5 (14.68)
ALT, Month 12, n=65, 129, 140	-1.7 (14.92)	1.3 (15.63)	-1.7 (17.53)
ALP, Month 3, n=88, 190, 193	1.1 (21.90)	-1.6 (12.13)	0.3 (12.91)
ALP, Month 6, n=73, 158, 172	-0.4 (23.35)	-1.6 (17.15)	-0.9 (14.44)
ALP, Month 9, n=69, 148, 149	-1.5 (18.53)	-2.2 (12.68)	0.0 (16.51)
ALP, Month 12, n=65, 129, 140	-1.9 (18.09)	4.3 (61.45)	0.2 (15.93)
AST, Month 3, n=88, 190, 192	0.1 (19.27)	1.3 (10.87)	1.0 (14.75)
AST, Month 6, n=73, 158, 172	-2.8 (18.52)	3.8 (23.71)	1.3 (16.50)
AST, Month 9, n=69, 148, 148	-1.1 (10.79)	0.1 (6.53)	-1.1 (12.95)
AST, Month 12, n=65, 129, 140	-0.6 (12.06)	2.6 (15.71)	-0.8 (12.01)
CK, Month 3, n=88, 190, 193	2.4 (84.76)	-1.8 (97.44)	7.0 (63.51)
CK, Month 6, n=73, 158, 172	-8.3 (41.87)	3.6 (114.53)	10.8 (94.52)
CK, Month 9, n=69, 148, 149	3.8 (55.89)	-2.3 (113.58)	3.5 (58.82)

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
CK, Month 12, n=64, 129, 140	-1.8 (46.31)	0.9 (118.66)	16.7 (68.75)
GGT, Month 3, n=88, 190, 193	11.5 (95.98)	1.0 (24.07)	-2.1 (53.42)
GGT, Month 6, n=73, 158, 172	-5.6 (48.15)	9.8 (73.28)	1.5 (27.49)
GGT, Month 9, n=69, 148, 149	-1.3 (25.59)	-0.5 (22.45)	-2.5 (39.81)
GGT, Month 12, n=65, 129, 140	-6.9 (44.77)	7.8 (72.04)	-2.0 (30.93)

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in Albumin, Total Protein, and Hemoglobin at Months 3, 6, 9, and 12
Measure Description	Blood samples were collected for the measurement of albumin, total protein, and hemoglobin at Baseline and Months 3, 6, 9, and 12. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The value defined as the "Baseline" value is the most recent value collected prior to the start of treatment. For most participants, the Baseline value is the value collected at the Screening visit; however, for some participants, the Baseline value may have been collected at an unscheduled visit.
Time Frame	Baseline; Months 3, 6, 9, and 12
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants available at the specified time points were summarized (represented by n=X, X, X in the category titles). Different participants may have been summarized for different parameters/at different time points, so the overall number of participants summarized reflects everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25µg
Number of Participants Analyzed	109	227	226
Change From Baseline in Albumin, Total Protein, and Hemoglobin at Months 3, 6, 9, and 12 [units: Grams per liter (G/L)] Mean (Standard Deviation)			
Albumin, Month 3, n=88, 190, 193	-0.5 (2.44)	-0.8 (2.48)	-0.8 (2.67)
Albumin, Month 6, n=73, 158, 172	-0.6 (2.89)	-0.9 (2.59)	-0.4 (2.85)
Albumin, Month 9, n=69, 149, 149	-0.1 (3.19)	-0.8 (2.55)	-0.5 (3.31)
Albumin, Month 12, n=65, 129, 140	-1.2 (3.27)	-1.4 (2.35)	-0.9 (3.00)
Total protein, Month 3, n=88, 190, 193	-1.2 (3.99)	-1.3 (3.52)	-1.1 (3.91)
Total protein, Month 6, n=73, 158, 172	-1.1 (4.01)	-1.8 (3.57)	-0.7 (4.10)
Total protein, Month 9, n=69, 148, 149	-0.7 (4.50)	-1.8 (3.52)	-1.4 (4.56)
Total protein, Month 12, n=65, 129, 140	-2.1 (4.48)	-2.6 (3.48)	-1.9 (3.82)

	Placebo	UMEC 125 µg	UMEC/VI 125/25µg
Hemoglobin, Month 3, n=94, 198, 206	-1.2 (8.51)	-1.5 (8.05)	-2.0 (8.34)
Hemoglobin, Month 6, n=75, 159, 171	-1.6 (9.85)	-1.2 (7.31)	-1.4 (9.31)
Hemoglobin, Month 9, n=70, 152, 155	-1.4 (11.95)	-2.5 (10.35)	-2.2 (8.78)
Hemoglobin, Month 12, n=63, 130, 143	-2.7 (11.36)	-2.5 (7.04)	-2.1 (9.19)

6. Secondary Outcome Measure:

Measure Title	Change From Baseline in Calcium, Carbon Dioxide (CO2) Content/Bicarbonate, Chloride, Glucose, Inorganic Phosphorus (IP), Potassium, Sodium, and Urea/Blood Urea Nitrogen (BUN) at Months 3, 6, 9, and 12
Measure Description	Blood samples were collected for the measurement of calcium, CO2 content/bicarbonate, chloride, glucose, IP, potassium, sodium, and urea/BUN at Baseline and Months 3, 6, 9, and 12. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The value defined as the "Baseline" value is the most recent value collected prior to the start of treatment. For most participants, the Baseline value is the value collected at the Screening visit; however, for some participants, the Baseline value may have been collected at an unscheduled visit.
Time Frame	Baseline; Months 3, 6, 9, and 12
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants available at the specified time points were summarized (represented by n=X, X, X in the category titles). Different participants may have been summarized for different parameters/at different time points, so the overall number of participants summarized reflects

everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	109	227	226
Change From Baseline in Calcium, Carbon Dioxide (CO_2) Content/Bicarbonate, Chloride, Glucose, Inorganic Phosphorus (IP), Potassium, Sodium, and Urea/Blood Urea Nitrogen (BUN) at Months 3, 6, 9, and 12 [units: Millimoles per liter (mmol/L)] Mean (Standard Deviation)			
Calcium, Month 3, n=88, 189, 192	-0.004 (0.0957)	-0.006 (0.1178)	-0.016 (0.0990)
Calcium, Month 6, n=73, 157, 172	-0.027 (0.0893)	-0.011 (0.1058)	0.000 (0.1104)
Calcium, Month 9, n=69, 147, 148	-0.027 (0.1009)	-0.019 (0.1036)	-0.014 (0.1023)

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Calcium, Month 12, n=65, 129, 140	-0.023 (0.1070)	-0.007 (0.0959)	-0.009 (0.1059)
CO2 content/bicarbonate, Month 3, n=88, 190, 192	0.8 (2.99)	0.8 (2.70)	0.6 (2.87)
CO2 content/bicarbonate, Month 6, n=73, 158, 172	0.3 (3.03)	0.2 (2.84)	0.7 (3.14)
CO2 content/bicarbonate, Month 9, n=69, 149, 148	0.3 (3.21)	0.2 (2.78)	0.3 (2.87)
CO2 content/bicarbonate, Month 12, n=65, 129, 140	-0.6 (3.06)	-0.3 (2.70)	-0.4 (2.49)
Chloride, Month 3, n=88, 190, 193	0.0 (3.03)	-0.2 (3.33)	-0.1 (2.60)
Chloride, Month 6, n=73, 158, 172	-0.2 (2.84)	-0.2 (2.90)	-0.1 (3.23)
Chloride, Month 9, n=69, 149, 149	-0.7 (3.27)	-0.3 (2.93)	-0.5 (2.94)
Chloride, Month 12, n=64, 129, 140	-0.2 (3.08)	0.0 (2.56)	0.3 (2.86)
Glucose, Month 3, n=88, 190, 193	0.08 (1.269)	0.08 (1.315)	0.03 (1.419)
Glucose, Month 6, n=73, 158, 172	0.22 (1.412)	0.18 (1.645)	-0.01 (2.507)
Glucose, Month 9, n=69, 149, 149	0.18 (1.333)	0.16 (1.959)	0.05 (2.309)
Glucose, Month 12, n=65, 129, 140	0.19 (1.080)	0.00 (1.741)	0.01 (2.453)
IP, Month 3, n=87, 189, 193	0.022 (0.1844)	0.003 (0.1663)	-0.018 (0.1886)
IP, Month 6, n=72, 157, 171	0.016 (0.1880)	0.015 (0.1686)	0.027 (0.2125)
IP, Month 9, n=68, 147, 149	-0.026 (0.1773)	-0.002 (0.1850)	0.005 (0.1962)

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
IP, Month 12, n=64, 129, 140	-0.007 (0.1838)	0.022 (0.1821)	0.011 (0.1793)
Potassium, Month 3, n=88, 190, 192	0.04 (0.464)	0.05 (0.490)	0.08 (0.474)
Potassium, Month 6, n=73, 158, 171	-0.05 (0.462)	0.02 (0.468)	0.00 (0.428)
Potassium, Month 9, n=69, 149, 148	-0.14 (0.461)	-0.01 (0.494)	-0.05 (0.498)
Potassium, Month 12, n=65, 129, 140	-0.06 (0.489)	-0.01 (0.473)	-0.04 (0.510)
Sodium, Month 3, n=88, 190, 193	-0.1 (2.84)	-0.5 (2.50)	-0.8 (2.36)
Sodium, Month 6, n=73, 158, 172	-0.7 (2.31)	-0.8 (2.63)	-0.7 (2.48)
Sodium, Month 9, n=69, 149, 149	-0.7 (2.54)	-0.8 (2.72)	-1.0 (2.59)
Sodium, Month 12, n=64, 129, 140	-1.0 (2.11)	-0.7 (2.40)	-0.5 (2.75)
Urea/BUN, Month 3, n=88, 190, 193	-0.03 (1.961)	-0.18 (1.574)	-0.01 (1.814)
Urea/BUN, Month 6, n=73, 158, 172	-0.06 (2.734)	-0.12 (1.698)	0.00 (1.875)
Urea/BUN, Month 9, n=69, 149, 149	-0.12 (1.981)	-0.21 (1.692)	-0.11 (1.696)
Urea/BUN, Month 12, n=65, 129, 140	0.13 (2.591)	-0.29 (1.631)	0.16 (1.613)

7. Secondary Outcome Measure:

Measure Title	Change From Baseline in Creatinine, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, and Uric Acid at Months 3, 6, 9, and 12
Measure Description	Blood samples were collected for the measurement of creatinine, direct bilirubin, indirect bilirubin, total bilirubin, and uric acid at Baseline and Months 3, 6, 9, and 12. Change from Baseline was calculated as the

	post-Baseline value minus the Baseline value. The value defined as the "Baseline" value is the most recent value collected prior to the start of treatment. For most participants, the Baseline value is the value collected at the Screening visit; however, for some participants, the Baseline value may have been collected at an unscheduled visit.
Time Frame	Baseline; Months 3, 6, 9, and 12
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants available at the specified time points were summarized (represented by n=X, X, X in the category titles). Different participants may have been summarized for different parameters/at different time points, so the overall number of participants summarized reflects everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	109	227	226
Change From Baseline in Creatinine, Direct Bilirubin, Indirect Bilirubin, Total			

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Bilirubin, and Uric Acid at Months 3, 6, 9, and 12 [units: Micromoles per liter (µmol/L)] Mean (Standard Deviation)			
Creatinine, Month 3, n=88, 190, 193	-3.20 (16.221)	-1.63 (9.119)	-0.51 (10.034)
Creatinine, Month 6, n=73, 158, 171	-0.52 (19.828)	-1.14 (9.047)	0.13 (11.418)
Creatinine, Month 9, n=69, 148, 149	-1.17 (20.543)	-0.71 (9.780)	0.26 (11.057)
Creatinine, Month 12, n=65, 129, 140	-0.06 (20.259)	1.11 (12.375)	1.79 (11.571)
Direct bilirubin, Month 3, n=88, 190, 192	0.0 (1.08)	0.1 (1.13)	0.0 (1.05)
Direct Bilirubin, Month 6, n=73, 158, 172	-0.1 (1.02)	0.0 (1.20)	0.0 (0.91)
Direct bilirubin, Month 9, n=69, 149, 149	0.0 (1.06)	-0.2 (0.98)	-0.1 (0.93)
Direct bilirubin, Month 12, n=65, 129, 139	0.1 (0.88)	0.8 (8.77)	-0.2 (1.12)
Indirect bilirubin, Month 3, n=88, 190, 192	0.1 (3.30)	-0.2 (3.64)	-0.2 (3.03)
Indirect bilirubin, Month 6, n=73, 158, 172	-0.1 (3.21)	-0.3 (3.69)	-0.2 (2.94)
Indirect bilirubin, Month 9, n=69, 148, 149	0.2 (3.68)	-0.6 (3.28)	-0.3 (2.93)
Indirect bilirubin, Month 12, n=65, 129, 139	-0.2 (2.74)	0.4 (8.60)	-0.5 (3.51)
Total bilirubin, Month 3, n=88, 190, 193	0.1 (3.76)	0.0 (4.29)	-0.2 (3.52)
Total bilirubin, Month 6, n=73, 158, 172	-0.2 (3.61)	-0.3 (4.37)	-0.2 (3.51)

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Total bilirubin, Month 9, n=69, 148, 149	0.2 (4.13)	-0.8 (3.82)	-0.4 (3.41)
Total bilirubin, Month 12, n=65, 129, 140	-0.1 (3.06)	1.2 (17.09)	-0.7 (4.25)
Uric acid, Month 3, n=88, 189, 193	-3.4 (68.15)	-0.1 (53.93)	16.2 (72.11)
Uric acid, Month 6, n=73, 157, 172	2.5 (85.86)	0.3 (57.74)	1.9 (63.17)
Uric acid, Month 9, n=69, 147, 149	-2.9 (72.40)	-8.3 (61.57)	-1.9 (66.69)
Uric acid, Month 12, n=65, 129, 140	11.4 (80.09)	-2.8 (65.58)	0.9 (69.74)

8. Secondary Outcome Measure:

Measure Title	Change From Baseline in the Percentage of Basophils, Eosinophils, Lymphocytes, Monocytes, and Segmented Neutrophils in Blood at Months 3, 6, 9, and 12
Measure Description	Blood samples were collected for the measurement of the percentage of basophils, eosinophils, lymphocytes, monocytes, and segmented neutrophils at Baseline and Months 3, 6, 9, and 12. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The value defined as the "Baseline" value is the most recent value collected prior to the start of treatment. For most participants, the Baseline value is the value collected at the Screening visit; however, for some participants, the Baseline value may have been collected at an unscheduled visit.
Time Frame	Baseline; Months 3, 6, 9, and 12
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants available at the specified time points were summarized (represented by n=X, X, X in the category titles). Different participants may have been summarized for different parameters/at different time points, so the overall number of participants summarized reflects everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	109	227	226
Change From Baseline in the Percentage of Basophils, Eosinophils, Lymphocytes, Monocytes, and Segmented Neutrophils in Blood at Months 3, 6, 9, and 12 [units: Percentage in blood] Mean (Standard Deviation)			
Basophils, Month 3, n=93, 198, 206	-0.02 (0.244)	0.01 (0.290)	0.02 (0.302)
Basophils, Month 6, n=73, 156, 167	-0.03 (0.270)	0.03 (0.312)	0.01 (0.314)
Basophils, Month 9, n=70, 152, 154	-0.01 (0.265)	0.02 (0.276)	0.02 (0.300)
Basophils, Month 12, n=62, 130, 141	-0.05 (0.235)	0.00 (0.240)	0.02 (0.266)

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Eosinophils, Month 3, n=93, 198, 206	0.17 (1.569)	-0.01 (2.243)	-0.05 (1.791)
Eosinophils, Month 6, n=73, 156, 167	0.04 (1.720)	-0.08 (2.101)	0.27 (1.962)
Eosinophils, Month 9, n=70, 152, 154	0.18 (2.271)	-0.33 (2.232)	0.02 (1.678)
Eosinophils, Month 12, n=62, 130, 141	0.10 (1.698)	-0.19 (2.557)	0.09 (2.021)
Lymphocytes, Month 3, n=93, 198, 206	-1.02 (8.031)	-1.86 (7.912)	-0.92 (7.474)
Lymphocytes, Month 6, n=73, 156, 167	-1.14 (7.178)	-0.33 (10.319)	0.81 (9.211)
Lymphocytes, Month 9, n=70, 152, 154	-2.63 (6.977)	-1.32 (8.439)	-1.35 (8.265)
Lymphocytes, Month 12, n=62, 130, 141	-0.93 (6.654)	-0.55 (7.459)	-0.25 (7.138)
Monocytes, Month 3, n=93, 198, 206	-0.02 (2.544)	-0.06 (2.303)	0.13 (2.296)
Monocytes, Month 6, n=73, 156, 167	0.60 (2.929)	1.09 (3.170)	0.56 (2.935)
Monocytes, Month 9, n=70, 152, 154	0.14 (2.959)	0.62 (2.453)	0.24 (2.466)
Monocytes, Month 12, n=62, 130, 141	0.26 (2.563)	0.47 (2.632)	-0.16 (2.198)
Segmented neutrophils, Month 3, n=93, 198, 206	0.88 (9.494)	1.92 (9.714)	0.81 (9.002)
Segmented neutrophils, Month 6, n=73, 156, 167	0.53 (9.264)	-0.72 (12.744)	-1.65 (11.543)
Segmented neutrophils, Month 9, n=70, 152, 154	2.02 (8.225)	1.00 (10.311)	1.07 (9.472)
Segmented neutrophils, Month 12, n=62, 130, 141	0.63 (7.903)	0.27 (10.026)	0.29 (8.456)

9. Secondary Outcome Measure:

Measure Title	Change From Baseline in Eosinophil Count, Platelet Count, and White Blood Cell (WBC) Count at Months 3, 6, 9, and 12
Measure Description	Blood samples were collected for the measurement of eosinophils, platelets, and WBC count at Baseline and Months 3, 6, 9, and 12. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The value defined as the "Baseline" value is the most recent value collected prior to the start of treatment. For most participants, the Baseline value is the value collected at the Screening visit; however, for some participants, the Baseline value may have been collected at an unscheduled visit.
Time Frame	Baseline; Months 3, 6, 9, and 12
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants available at the specified time points were summarized (represented by n=X, X, X in the category titles). Different participants may have been summarized for different parameters/at different time points, so the overall number of participants summarized reflects everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	109	227	226
Change From Baseline in Eosinophil Count, Platelet Count, and White Blood Cell (WBC) Count at Months 3, 6, 9, and 12 [units: 10^9 cells per liter (GI/L)] Mean (Standard Deviation)			
Eosinophil count, Month 3, n=93, 198, 206	0.001 (0.1134)	-0.002 (0.1497)	-0.007 (0.1292)
Eosinophil count, Month 6, n=73, 156, 167	-0.005 (0.1246)	-0.007 (0.1277)	0.015 (0.1324)
Eosinophil count, Month 9, n=70, 152, 154	0.003 (0.1613)	-0.023 (0.1445)	0.001 (0.1227)
Eosinophil count, Month 12, n=62, 130, 141	-0.003 (0.1297)	-0.013 (0.1678)	0.010 (0.1496)
Platelet count, Month 3, n=93, 197, 204	2.2 (40.22)	-4.4 (38.28)	4.4 (34.39)
Platelet count, Month 6, n=73, 155, 169	-11.6 (39.11)	-5.4 (39.61)	-0.6 (33.65)
Platelet count, Month 9, n=68, 151, 154	-9.5 (39.36)	-3.0 (39.85)	0.7 (37.24)
Platelet count, Month 12, n=61, 128, 140	-11.8 (34.45)	-4.4 (33.09)	4.4 (37.68)
WBC count, Month 3, n=93, 198, 206	-0.20 (1.575)	-0.27 (1.781)	-0.21 (1.797)
WBC count, Month 6, n=73, 156, 167	-0.06 (1.666)	-0.13 (1.663)	-0.23 (2.065)
WBC count, Month 9, n=70, 152, 154	0.29 (2.820)	-0.09 (1.919)	-0.19 (1.850)
WBC count, Month 12, n=62, 130, 141	-0.19 (1.600)	-0.21 (2.114)	-0.09 (1.871)

10. Secondary Outcome Measure:

Measure Title	Change From Baseline in Hematocrit at Months 3, 6, 9, and 12
Measure Description	Blood samples were collected for the measurement of hematocrit at Baseline and Months 3, 6, 9, and 12. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The value defined as the "Baseline" value is the most recent value collected prior to the start of treatment. For most participants, the Baseline value is the value collected at the Screening visit; however, for some participants, the Baseline value may have been collected at an unscheduled visit.
Time Frame	Baseline; Months 3, 6, 9, and 12
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants available at the specified time points were summarized (represented by n=X, X, X in the category titles). Different participants may have been summarized at different time points, so the overall number of participants summarized reflects everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	109	227	226
Change From Baseline in Hematocrit at Months 3, 6, 9, and 12 [units: Proportion of red blood cells in blood] Mean (Standard Deviation)			
Month 3, n=94, 198, 206	-0.0140 (0.02757)	-0.0134 (0.02656)	-0.0131 (0.02699)
Month 6, n=75, 159, 171	-0.0195 (0.03320)	-0.0177 (0.02446)	-0.0170 (0.02871)
Month 9, n=70, 152, 155	-0.0133 (0.03785)	-0.0139 (0.03158)	-0.0146 (0.02829)
Month 12, n=63, 130, 143	-0.0072 (0.03336)	-0.0045 (0.02356)	-0.0040 (0.2959)

11. Secondary Outcome Measure:

Measure Title	Change From Baseline to Maximum Systolic Blood Pressure (SBP) and Change From Baseline to Minimum Diastolic Blood Pressure (DBP) Over the Course of the 52-week Treatment Period
Measure Description	Baseline is defined as the most recent recorded value before dosing on Day 1. The maximum post-Baseline value for SBP and the minimum post-Basline value for DBP were derived using any scheduled, unscheduled, or early withdrawal visit made after the start of study treatment. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

Time Frame	Baseline; from the start of study drug up to 52 weeks
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	109	227	226
Change From Baseline to Maximum Systolic Blood Pressure (SBP) and Change From Baseline to Minimum Diastolic Blood Pressure (DBP) Over the Course of the 52-week Treatment Period [units: Millimeters of mercury (mmHg)] Mean (Standard Deviation)			
Change from Baseline to maximum SBP	14.5 (15.28)	14.0 (14.05)	13.5 (13.02)
Change from Baseline to minimum DBP	-11.0 (8.87)	-9.5 (7.86)	-10.8 (8.89)

12. Secondary Outcome Measure:

Measure Title	Maximum Change From Baseline in Pulse Rate Over the Course of the 52-week Treatment Period
Measure Description	Baseline is defined as the most recent recorded value before dosing on Day 1. The maximum post-Baseline value for pulse rate was derived using any scheduled, unscheduled, or early withdrawal visit made after the start of study treatment. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
Time Frame	Baseline; from the start of study drug up to 52 weeks
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	109	227	226
Maximum Change From Baseline in Pulse Rate Over the Course of the 52-week Treatment Period [units: Beats per minute] Mean (Standard Deviation)	9.1 (9.30)	9.8 (10.16)	9.0 (9.04)

13. Secondary Outcome Measure:

Measure Title	Maximum Change From Baseline in the Electrocardiogram (ECG) Parameters of QT Interval Corrected for Heart Rate by Bazett's Formula (QTcB), QT Interval Corrected for Heart Rate by Fridericia's Formula (QTcF), and PR Interval Over the Course of the 52-week
Measure Description	12-lead ECG measurements were obtained. Baseline is defined as the most recent recorded value before dosing on Day 1. The maximum post-Baseline values for QTcF, QTcB, and PR interval were derived using any scheduled, unscheduled, or early withdrawal visit made after the start of study treatment. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
Time Frame	Baseline; from the start of study drug up to 52 weeks
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	109	227	226
Maximum Change From Baseline in the Electrocardiogram (ECG) Parameters of QT Interval Corrected for Heart Rate by Bazett's Formula (QTcB), QT Interval Corrected for Heart Rate by Fridericia's Formula (QTcF), and PR Interval Over the Course of the 52-week [units: Milliseconds] Mean (Standard Deviation)			
Maximum change from Baseline in QTcF	15.6 (13.67)	16.9 (14.20)	18.4 (14.42)
Maximum change from Baseline in QTcB	17.1 (16.90)	19.0 (17.62)	20.7 (17.14)
Maximum change from Baseline in PR interval	12.4 (11.03)	13.5 (10.26)	12.0 (9.79)

14. Secondary Outcome Measure:

Measure Title	Maximum Change From Baseline in the ECG Parameter of Heart Rate Over the Course of the 52-week Treatment Period
Measure Description	12-lead ECG measurements were obtained. Baseline is defined as the most recent recorded value before dosing on Day 1. The maximum post-Baseline value for heart rate was derived using any scheduled, unscheduled, or early withdrawal visit made after the start of study treatment. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
Time Frame	Baseline; from the start of study drug up to 52 weeks
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	109	227	226
Maximum Change From Baseline in the ECG Parameter of Heart Rate Over the Course of the 52-week Treatment Period [units: Beats per minute] Mean (Standard Deviation)	7.8 (8.67)	9.9 (13.66)	9.3 (9.43)

15. Secondary Outcome Measure:

Measure Title	Number of Participants With the Indicated ECG Result Interpretations at Any Time Post-Baseline
Measure Description	Post-Baseline visits include scheduled, unscheduled, and Early Withdrawal visits. Only the worst-case interpretation was counted for each participant. Clinical significance and abnormal/normal findings are based on the assessment of the independent cardiologists.
Time Frame	From the start of study drug up to 52 weeks
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.

	Description
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	109	227	226
Number of Participants With the Indicated ECG Result Interpretations at Any Time Post-Baseline [units: participants]			
Normal	32	64	71
Abnormal - Not Clinically Significant	52	105	101
Abnormal - Clinically Significant	25	58	54
Unable to Evaluate	0	0	0

16. Secondary Outcome Measure:

Measure Title	Number of Participants With the Indicated Change From Screening to Any Time Post-Baseline in Holter ECG Interpretation
Measure Description	Twenty-four hour Holter monitor (12-lead) evaluations were obtained. Holter Baseline values were those recorded at Screening. An "any time post-Baseline" Holter evaluation was derived as the worst evaluation recorded at any scheduled, unscheduled, or early withdrawal visit made after the start of study treatment. Change from Screening was calculated as the post-Screening value minus the Screening value. The

	order of severity for change from Screening Holter evaluation from worst to best is: clinically significant change: unfavorable; no change or insignificant change; clinically significant change: favorable, unable to compare, based on the assessment of the independent cardiologists.
Time Frame	Screening; from the start of study drug up to 52 weeks
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants providing at least one post-Baseline interpretation were summarized.

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	90	198	207
Number of Participants With the Indicated Change From Screening to Any Time Post-Baseline in Holter ECG Interpretation [units: Participants]			
Clinically significant change:	39	86	87

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
unfavorable			
No change or insignificant change	46	98	110
Clinically significant change: favorable	3	6	4
Unable to compare	2	8	6

17. Secondary Outcome Measure:

Measure Title	Change From Baseline in the Mean Number of Puffs of Rescue Medication (Salbutamol and/or Ipratropium Bromide) Per Day Over the Course of the 52-week Treatment Period
Measure Description	Participants recorded the number of puffs and/or the number of nebules of rescue albuterol/salbutamol and/or ipratropium bromide used in the past 24 hours for the relief of COPD symptoms in the daily diary. The total puffs of rescue medication for each day was calculated as follows: (number of salbutamol puffs + number of ipratropium puffs + [2 * number of salbutamol nebules] + [2 * number of ipratropium nebules]). Baseline is the mean during the week prior to Day 1. Change from Baseline was calculated as the mean number of puffs/day over Weeks 1-52 minus the mean number of puffs/day at Baseline. Analysis was performed using an Analysis of Covariance (ANCOVA) model with covariates of treatment, Baseline (mean during the week prior to Day 1), smoking status, and center group.
Time Frame	Baseline; from the start of study drug up to 52 weeks
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants who had rescue data available on at least 50% of the days in the 52-week treatment period were included in the analysis.

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	75	158	168
Change From Baseline in the Mean Number of Puffs of Rescue Medication (Salbutamol and/or Ipratropium Bromide) Per Day Over the Course of the 52-week Treatment Period [units: Number of puffs per day] Least Squares Mean (Standard Error)	-0.4 (0.20)	-0.8 (0.14)	-1.4 (0.13)

18. Secondary Outcome Measure:

Measure Title	Change From Baseline in the Percentage of Rescue-free Days Over the Course of the 52-week Treatment Period

Measure Description	Rescue-free days are defined as days on which albuterol/salbutamol and/or ipratropium bromide was not used. Baseline is the percentage during the week prior to Day 1. Change from Baseline was calculated as the mean percentage of rescue-free days over Weeks 1-52 minus the mean percentage of rescue-free days at Baseline.
Time Frame	From the start of study drug up to 52 weeks
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants who had rescue data available on at least 50% of the days in the 52-week treatment period were included in the summary.

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	75	158	168
Change From Baseline in the Percentage of Rescue-free Days Over the Course of the 52-week Treatment Period	11.1 (30.06)	13.1 (37.35)	23.2 (39.27)

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
[units: Percentage of rescue-free days] Mean (Standard Deviation)			

19. Secondary Outcome Measure:

Measure Title	Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) and Forced Vital Capacity (FVC) at Months 1, 3, 6, 9, and 12
Measure Description	FEV1 and FVC are measures of lung function. FEV1 is defined as the maximal amount of air that can be forcefully exhaled in one second. FVC is defined as the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible. Trough FEV1 and FVC were the values obtained approximately 24 hours after the previous morning's dose of study medication. Baseline is the value recorded pre-dose on Day 1. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Analysis was performed using a repeated measures model with covariates of treatment, Baseline (assessment made immediately pre-dose on Day 1), smoking status, center group, month, and month by Baseline and month by treatment interactions.
Time Frame	Baseline; Months 1, 3, 6, 9, and 12
Safety Issue?	No

Analysis Population Description

ITT Population. The overall number of participants reflects all participants who provided at least one post-treatment assessment. Participants who provided data the specified time points are represented by n=X, X, X in the category titles.

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Measured Values

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	103	215	216
Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) and Forced Vital Capacity (FVC) at Months 1, 3, 6, 9, and 12 [units: Liters] Least Squares Mean (Standard Error)			
FEV1: Month 1, n=103, 215, 215	-0.030 (0.0253)	0.138 (0.0175)	0.161 (0.0174)
FEV1: Month 3, n=90, 197, 208	-0.036 (0.0289)	0.140 (0.0197)	0.189 (0.0192)
FEV1: Month 6, n=79, 163, 178	-0.015 (0.0320)	0.144 (0.0221)	0.181 (0.0214)
FEV1: Month 9, n=71, 142, 153	-0.050 (0.0314)	0.104 (0.0219)	0.180 (0.0213)
FEV1: Month 12, n=66, 132, 143	-0.045 (0.0332)	0.133 (0.0232)	0.186 (0.0224)

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
FVC: Month 1, n=103, 215, 215	-0.035 (0.0386)	0.197 (0.0267)	0.237 (0.0267)
FVC: Month 3, n=90, 197, 208	-0.044 (0.0442)	0.189 (0.0301)	0.244 (0.0295)
FVC: Month 6, n=79, 163, 178	-0.002 (0.0478)	0.206 (0.0330)	0.237 (0.0320)
FVC: Month 9, n=71, 142, 153	-0.076 (0.0510)	0.088 (0.0356)	0.200 (0.0345)
FVC: Month 12, n=66, 132, 143	-0.039 (0.0491)	0.155 (0.0343)	0.213 (0.0333)

Reported Adverse Events

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 52 weeks.ve
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 52 weeks.
UMEC/VI 125/25 µg	Participants received umeclidinium bromide/vilanterol (UMEC/VI) 125/25 µg QD in the morning via a DPI for 52 weeks.

Time Frame

On-treatment serious adverse events (SAEs) and non-serious AEs were collected from on or after the date of the first dose of

study drug to up to 1 day after the date of the last recorded dose of study drug (up to Study Week 52).

Additional Description

On-treatment AEs and SAEs were collected in members of the Intent-to-Treat (ITT) Population, comprised of all participants randomized to treatment who received at least one dose of randomized study drug.

Serious Adverse Events

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Total # participants affected/at risk	7/109 (6.42%)	17/227 (7.49%)	14/226 (6.19%)
Blood and lymphatic system disorders			
Anaemia †[A]			
# participants affected/at risk	1/109 (0.92%)	0/227 (0%)	0/226 (0%)
# events			
Cardiac disorders			
Acute coronary syndrome †[A]			
# participants affected/at risk	0/109 (0%)	0/227 (0%)	1/226 (0.44%)
# events			
Acute myocardial infarction †[A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	1/226 (0.44%)
# events			

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Angina unstable †[A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	0/226 (0%)
# events			
Cardiac failure †[A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	0/226 (0%)
# events			
Cardiac failure chronic †[A]			
# participants affected/at risk	0/109 (0%)	0/227 (0%)	1/226 (0.44%)
# events			
Cardiac failure congestive †[A]			
# participants affected/at risk	1/109 (0.92%)	1/227 (0.44%)	0/226 (0%)
# events			
Coronary artery disease †[A]			
# participants affected/at risk	1/109 (0.92%)	1/227 (0.44%)	2/226 (0.88%)
# events			
Myocardial fibrosis †[A]			
# participants affected/at	0/109 (0%)	0/227 (0%)	1/226 (0.44%)

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
risk			
# events			
Myocardial infarction † [A]			
# participants affected/at risk	1/109 (0.92%)	0/227 (0%)	0/226 (0%)
# events			
Rhythm idioventricular † [A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	0/226 (0%)
# events			
Ventricular extrasystoles † [A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	0/226 (0%)
# events			
Gastrointestinal disorders			
Peptic ulcer † [A]			
# participants affected/at risk	1/109 (0.92%)	0/227 (0%)	0/226 (0%)
# events			
Peptic ulcer haemorrhage † [A]			
# participants affected/at	0/109 (0%)	0/227 (0%)	1/226 (0.44%)

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
risk			
# events			
General disorders			
Chest pain †[A]			
# participants affected/at risk	1/109 (0.92%)	0/227 (0%)	0/226 (0%)
# events			
Infections and infestations			
Gastroenteritis †[A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	0/226 (0%)
# events			
Infection †[A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	0/226 (0%)
# events			
Lobar pneumonia †[A]			
# participants affected/at risk	0/109 (0%)	0/227 (0%)	1/226 (0.44%)
# events			
Pneumonia †[A]			

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
# participants affected/at risk	0/109 (0%)	3/227 (1.32%)	0/226 (0%)
# events			
Urinary tract infection † [A]			
# participants affected/at risk	0/109 (0%)	2/227 (0.88%)	0/226 (0%)
# events			
Injury, poisoning and procedural complications			
Ankle fracture † [A]			
# participants affected/at risk	0/109 (0%)	0/227 (0%)	1/226 (0.44%)
# events			
Femur fracture † [A]			
# participants affected/at risk	0/109 (0%)	0/227 (0%)	1/226 (0.44%)
# events			
Fibula fracture † [A]			
# participants affected/at risk	1/109 (0.92%)	0/227 (0%)	0/226 (0%)
# events			
Rib fracture † [A]			
# participants affected/at	0/109 (0%)	0/227 (0%)	1/226 (0.44%)

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
risk			
# events			
Tibia fracture † [A]			
# participants affected/at risk	1/109 (0.92%)	0/227 (0%)	0/226 (0%)
# events			
Traumatic lung injury † [A]			
# participants affected/at risk	0/109 (0%)	0/227 (0%)	1/226 (0.44%)
# events			
Investigations			
Clostridium test positive † [A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	0/226 (0%)
# events			
Musculoskeletal and connective tissue disorders			
Plantar fasciitis † [A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	0/226 (0%)
# events			

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer † [A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	0/226 (0%)
# events			
Bladder neoplasm † [A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	0/226 (0%)
# events			
Brain neoplasm † [A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	0/226 (0%)
# events			
Breast cancer † [A]			
# participants affected/at risk	0/109 (0%)	0/227 (0%)	1/226 (0.44%)
# events			
Metastases to spine † [A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	0/226 (0%)

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
# events			
Nervous system disorders			
Cerebrovascular accident † [A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	0/226 (0%)
# events			
Epilepsy † [A]			
# participants affected/at risk	0/109 (0%)	0/227 (0%)	1/226 (0.44%)
# events			
Migraine † [A]			
# participants affected/at risk	0/109 (0%)	0/227 (0%)	1/226 (0.44%)
# events			
Psychomotor hyperactivity † [A]			
# participants affected/at risk	0/109 (0%)	0/227 (0%)	1/226 (0.44%)
# events			
Psychiatric disorders			
Depression † [A]			

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
# participants affected/at risk	0/109 (0%)	0/227 (0%)	1/226 (0.44%)
# events			
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease †[A]			
# participants affected/at risk	3/109 (2.75%)	4/227 (1.76%)	2/226 (0.88%)
# events			
Epistaxis †[A]			
# participants affected/at risk	0/109 (0%)	0/227 (0%)	1/226 (0.44%)
# events			
Pneumothorax †[A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	0/226 (0%)
# events			
Respiratory failure †[A]			
# participants affected/at risk	1/109 (0.92%)	0/227 (0%)	0/226 (0%)
# events			
Surgical and medical			

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
procedures			
Skin graft † [A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	0/226 (0%)
# events			
Vascular disorders			
Hypertension † [A]			
# participants affected/at risk	0/109 (0%)	1/227 (0.44%)	1/226 (0.44%)
# 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 125 µg	UMEC/VI 125/25 µg
Total # participants affected/at risk	34/109 (31.19%)	78/227 (34.36%)	65/226 (28.76%)
Cardiac disorders			
Extrasystoles † [A]			
# participants affected/at risk	4/109 (3.67%)	10/227 (4.41%)	10/226 (4.42%)
# events			

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
Ventricular extrasystoles † [A]			
# participants affected/at risk	5/109 (4.59%)	11/227 (4.85%)	11/226 (4.87%)
# events			
Ventricular tachycardia † [A]			
# participants affected/at risk	4/109 (3.67%)	3/227 (1.32%)	4/226 (1.77%)
# events			
Infections and infestations			
Influenza † [A]			
# participants affected/at risk	5/109 (4.59%)	5/227 (2.2%)	6/226 (2.65%)
# events			
Nasopharyngitis † [A]			
# participants affected/at risk	5/109 (4.59%)	20/227 (8.81%)	11/226 (4.87%)
# events			
Sinusitis † [A]			
# participants affected/at risk	3/109 (2.75%)	6/227 (2.64%)	8/226 (3.54%)
# events			
Upper respiratory tract			

	Placebo	UMEC 125 µg	UMEC/VI 125/25 µg
infection † [A]			
# participants affected/at risk	3/109 (2.75%)	8/227 (3.52%)	2/226 (0.88%)
# events			
Musculoskeletal and connective tissue disorders			
Back pain † [A]			
# participants affected/at risk	3/109 (2.75%)	9/227 (3.96%)	10/226 (4.42%)
# events			
Nervous system disorders			
Headache † [A]			
# participants affected/at risk	9/109 (8.26%)	25/227 (11.01%)	20/226 (8.85%)
# events			
Vascular disorders			
Hypertension † [A]			
# participants affected/at risk	5/109 (4.59%)	3/227 (1.32%)	7/226 (3.1%)
# 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: