Protocol Registration Receipt
12/19/2013

Grantor: CDER IND/IDE Number: 106,616 Serial Number: 0137

24-week Trial Comparing GSK573719/GW642444 With GW642444 and With Tiotropium in Chronic Obstructive Pulmonary Disease

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT01316900

Purpose

This is a Phase III multicenter, randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of two doses of GSK573719/GW642444 Inhalation Powder and GW642444 Inhalation Powder via a Novel Dry Powder Inhaler and tiotropium via HandiHaler when administered once-daily over a 24-week treatment period in subjects with chronic obstructive pulmonary disease (COPD). Subjects who meet eligibility criteria at Screening (Visit 1) will complete a 7 to10 day run-in period followed by a randomization visit (Visit 2) then a 24-week treatment period. There will be a total of 9 clinic study visits. A follow-up phone contact for adverse event assessment will be conducted approximately one week after the last study visit (Visit 9 or Early Withdrawal). The total duration of subject participation in the study will be approximately 26 weeks. The primary measure of efficacy is clinic visit trough (pre-bronchodilator

and pre-dose) forced expiratory volume in one second (FEV1) on Treatment Day 169. Safety will be assessed by adverse events, 12-lead ECGs, vital signs, and clinical laboratory tests.

Condition	Intervention	Phase
Pulmonary Disease, Chronic Obstructive	Drug: GSK573719/GW642444 125/25 Drug: GSK573719/GW642444 62.5/25 Drug: GW642444 Drug: tiotropium bromide	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Randomized, Safety/Efficacy Study
Official Title: DB2113360: A Multicenter Trial Comparing the Efficacy and Safety of GSK573719/GW642444 With GW642444 and With Tiotropium Over 24 Weeks in Subjects With COPD

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Change From Baseline (BL) in Trough Forced Expiratory Volume in One Second (FEV1) on Day 169 (Week 24) [Time Frame: Baseline and Day 169] [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 Days 2, 28, 56, 84, 112, 168, and 169. Baseline is defined as the mean of the assessments made 30 minutes pre-dose and 5 minutes pre-dose on Treatment Day 1. Trough FEV1 is defined as the mean of the FEV1 values obtained at 23 and 24 hours after the previous morning's dosing (ie., trough FEV1 on Day 169 is the mean of the FEV1 values obtained 23 and 24 hours after the morning dosing on Day 168). Change from Baseline at a particular visit was calculated as the trough FEV1 at that visit minus Baseline. Analysis was performed using a repeated measures model with covariates of treatment, Baseline , smoking status, center group, day, and day by Baseline and day by treatment interactions. ITT=Intent-to-Treat; par.=participants. .

Secondary Outcome Measures:

- Change From Baseline (BL) in Weighted Mean (WM) 0-6 Hour FEV1 Obtained Post-dose at Day 168 [Time Frame: Baseline and Day 168] [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. The WM FEV1 was derived by calculating the area under the FEV1/time curve (AUC) using the trapezoidal rule, and then dividing the value by the time interval over which the AUC was calculated. The WM was calculated at Days 1, 84, and Day 168 using the 0-6-hour post-dose FEV1 measurements collected on that day, which included pre-dose (Day 1: 30 minutes [min] and 5 min prior to dosing; other serial visits: 23 and 24 hours after the previous morning dose) and post-dose at 15 minutes, 30 minutes, 1 hour, 3 hours, and 6 hours. Change from BL at a particular visit was calculated as WM at that visit minus BL. Analysis was

performed using a repeated measures model with covariates of treatment, BL (mean of the two assessments made 30 minutes and 5 minutes pre-dose on Day 1), smoking status, center group, day, and day by BL and day by treatment interactions.

Other Pre-specified Outcome Measures:

- Change From Baseline (BL) in the Mean Shortness of Breath With Daily Activities (SOBDA) Score for Week 24 [Time Frame: Baseline and Week 24] [Designated as safety issue: No]

  The newly developed SOBDA questionnaire assesses dyspnea or shortness of breath (SOB) with daily activities. The SOBDA questionnaire is made up of 13 items completed by the participant (par.) each evening prior to bedtime, when the par. is instructed to reflect on the current day's activities. The daily score is computed as the mean of the scores on the 13 items (>=7 items must have non-missing responses for this to be calculated). The par. is assigned a weekly mean SOBDA score ranging from 1 to 4 (greater scores indicate more severe breathlessness with daily activities) based on the mean of 7 days of data (>=4 of 7 days must be completed for a weekly mean to be calculated). Change from BL is the mean weekly SOBDA score minus BL. Analysis was performed using MMRM with covariates of treatment, BL (mean score in the week prior to treatment), smoking status, center group, week, week by BL and week by treatment interactions. This MMRM analysis only included Weeks 4, 8, 12, and 24.

Enrollment: 846
Study Start Date: March 2011
Study Completion Date: April 2012
Primary Completion Date: April 2012

Arms	Assigned Interventions
Experimental: GSK573719/GW642444 125/25 125/25 mcg once-daily	Drug: GSK573719/GW642444 125/25 125/25 mcg once-daily Other Names: GSK573719/vilanterol trifenatate
Experimental: GSK573719/GW642444 62.5/25 62.5/25 mcg once-daily	Drug: GSK573719/GW642444 62.5/25 62.5/26 mcg once-daily Other Names: GSK573719/vilanterol trifenatate
Experimental: GW642444 25 mcg once-daily	Drug: GW642444 25 mcg once-daily Other Names: vilanterol trifenatate

Arms	Assigned Interventions
Active Comparator: tiotropium bromide 18 mcg once-daily	Drug: tiotropium bromide 18 mcg once-daily Other Names: tiotropium bromide

This is a 24-week, Phase III multicenter, randomized, double-blind, double-dummy, parallel-group study. Eligible subjects will be randomized to GSK573719/GW642444 125/25mcg, GSK573719/GW642444 62.5/25mcg, GW642444 25mcg, or tiotropium treatment groups in a 1:1:1:1 ratio. Treatments will be administered once-daily in the morning by inhalation using a Novel Dry Powder Inhaler (Novel DPI) and HandiHaler. There will be a total of 9 study clinic visits conducted on an outpatient basis. Subjects who meet the eligibility criteria at Screening (Visit 1) will complete a 7 to 10 day run-in period followed by a 24-week treatment period. Clinic visits will be at Screening, Randomization (Day 1), Day 2, after 4, 8, 12, 16, and 24-weeks of treatment, and 1 day after the Week 24 Visit (also referred as Treatment Day 169). A follow-up contact for adverse assessment will be conducted by telephone approximately 7 days after Visit 9 or the Early Withdrawal Visit. The total duration of subject participation, including follow-up will be approximately 26 weeks. All subjects will be provided with albuterol/salbutamol for use on an “as-needed” basis throughout the run-in and study treatment periods. At screening, pre-bronchodilator spirometry testing will be followed by post-albuterol/salbutamol spirometry testing. Post-albuterol/salbutamol FEV1 and FEV1/forced vital capacity (FVC) values will be used to determine subject eligibility. To further characterize bronchodilator responsiveness, post-ipratropium testing will be conducted following completion of post-albuterol/salbutamol spirometry. Spirometry will be conducted at each post-randomization clinic visit. Six hour post-dose serial spirometry will be conducted at Visits 2, 6, and 8. Trough spirometry will be obtained 23 and 24 hours after the previous day’s dose of blinded study medication at Visits 3 to 9. All subjects will be provided with an electronic diary (eDiary) for completion daily in the morning and the evening throughout the run-in and treatment periods. Subjects will use the eDiary to record peak expiratory flow (PEF) each morning, dyspnea scores using the Shortness of Breath with Daily Activities instrument (SOBDA), daily use of supplemental albuterol/salbutamol as either puffs/day from a metered-dose inhaler (MDI) and/or nebules used per day, and any healthcare contacts related to COPD. Additional assessments of dyspnea will be obtained using the Baseline and Transition Dyspnea Index (BDI/TDI) which is an interviewer based instrument. At Visit 2, the severity of dyspnea at baseline will be assessed using the BDI. At subsequent visits (Visits 4, 6, and 8) change from baseline will be assessed using the TDI. General health status will be evaluated using the subject-completed EQ-5D questionnaire at Visits 2, 4, 6, and 8. Disease specific health status will be evaluated using the subject-completed St. George’s Respiratory Questionnaire (SGRQ) at Visits 2, 4, 6, and 8, and the subject-completed COPD Assessment Test (CAT) at Visits 2, 6, and 8. The occurrence of adverse events will be evaluated throughout the study beginning at Visit 2. SAEs will be collected over the same time period as for AEs. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. Additional safety assessments of vital signs (blood pressure and pulse rate), 12-lead ECGs and standard clinical laboratory tests (hematology and chemistry) will be obtained at selected clinic visits.

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 of less than or equal to 70% predicted normal values
- score of greater than or equal to 2 on the Modified Medical Resarch Council Dyspnea Scale (mMRC)

Exclusion Criteria:

- women who are pregnant or lactating or are planning on becoming 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
- significantly abnormal finding from laboratory tests at Visit 1
- unable to withhold albuterol/salbutamol 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, antibiotics for lower respiratory tract infection, or cytochrome P450 3A4 inhibitors, within 6 weeks of Visit 1
- use of long-acting beta-agonist (LABA)/inhaled corticosteroid (ICS) product if LABA/ICS therapy is discontinued withing 30 days of Visit 1
- use of ICS at a dose of >1000mcg/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 or roflumilast within 14 days of Visit 1
- use of theophyllines, oral leukotriene inhibitors, long-acting oral beta-agonists, or inhaled long-acting beta-agonists within 48 hours of Visit 1
- short-acting oral beta-agonists within 12 hours of 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, inhaled short-acting anticholinergics, or inhaled short-acting anticholinergic/short-acting beta-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)
- long-term oxygen therapy prescribed for >12 hours per day
- regular use of nebulized short-acting bronchodilators
- participation in acute phase of pulmonary rehabilitation program
- known or suspected history of alcohol or drug abse within 2 years prior to Visit 1
- anyone affiliated with the investigator site (e.g., investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member)
- previous exposure to GSK573719, GSK573719/GW642444 combination, GW642444 (vilanterol), or fluticasone furoate/GW642444 combination

Contacts and Locations

Locations

United States, Alabama

GSK Investigational Site

Birmingham, Alabama, United States, 35216

United States, California

GSK Investigational Site

San Diego, California, United States, 92117

United States, Florida

GSK Investigational Site

DeLand, Florida, United States, 32720

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Orlando, Florida, United States, 32822

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Tampa, Florida, United States, 33603

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Lima 27, Lima, Peru, Lima 27

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San Borja, Lima, Peru, Lima 41

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San Isidro, Lima, Peru, Lima 27

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San Miguel, Lima, Peru, Lima 32

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Santiago de Surco, Lima, Peru, Lima 33

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Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline
Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Responsible Party: GlaxoSmithKline
Study ID Numbers: 113360
Health Authority: United States: Food and Drug Administration

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Study Results

Participant Flow

Pre-Assignment Details

Participants (par.) who met eligibility criteria at Screening (Visit 1) completed a 7- to10-day run-in period and were then randomized to a 24-week treatment period. A total of 1141 par. were screened; 846 par. were randomized (3 par. were randomized [2 in error] and received no study drug) and 843 par. received at least one dose of study drug.

Reporting Groups

	Description
VI 25 µg	Participants received vilanterol (VI) 25 micrograms (µg) once daily (QD) via a dry powder inhaler (DPI). All participants also received placebo QD via a HandiHaler.
UMEC/VI 62.5/25 µg	Participants received umeclidinium bromide (UMEC)/VI 62.5/25 µg QD via a DPI. All participants also received placebo QD via a HandiHaler.
UMEC/VI 125/25 µg	Participants received UMEC/VI 125/25 µg QD via a DPI. All participants also received placebo QD via a HandiHaler.

	Description
TIO 18 µg	Participants received tiotropium (TIO) 18 µg QD via a HandiHaler. All participants also received placebo QD via a DPI.

Overall Study

	VI 25 µg	UMEC/VI 62.5/25 µg	UMEC/VI 125/25 µg	TIO 18 µg
Started	209	212	214	208
Completed	165	181	173	177
Not Completed	44	31	41	31
Adverse Event	10	10	15	9
Lack of Efficacy	17	9	5	7
Protocol Violation	7	1	4	0
Protocol-defined Stopping Criteria	2	3	10	5
Lost to Follow-up	1	0	1	1
Withdrawal by Subject	7	8	6	9

Baseline Characteristics

Reporting Groups

	Description
VI 25 µg	Participants received vilanterol (VI) 25 micrograms (µg) once daily (QD) via a dry powder inhaler (DPI). All participants also received placebo QD via a HandiHaler.

	Description
UMEC/VI 62.5/25 µg	Participants received umeclidinium bromide (UMEC)/VI 62.5/25 µg QD via a DPI. All participants also received placebo QD via a HandiHaler.
UMEC/VI 125/25 µg	Participants received UMEC/VI 125/25 µg QD via a DPI. All participants also received placebo QD via a HandiHaler.
Tiotropium 18 µg	Participants received tiotropium (TIO) 18 µg QD via a HandiHaler. All participants also received placebo QD via a DPI.

Baseline Measures

	VI 25 µg	UMEC/VI 62.5/25 µg	UMEC/VI 125/25 µg	Tiotropium 18 µg	Total
Number of Participants	209	212	214	208	843
Age, Continuous [units: Years] Mean (Standard Deviation)	63.2 (9.10)	63.0 (8.67)	62.9 (8.87)	62.6 (9.39)	62.9 (9.00)
Gender, Male/Female [units: Participants]					
Female	66	64	63	68	261
Male	143	148	151	140	582
Race/Ethnicity, Customized [units: participants]					
African American/African Heritage	3	7	9	6	25
American Indian or Alaska Native	19	16	21	20	76
Asian - Central/South Asian Heritage	0	0	1	0	1

	VI 25 µg	UMEC/VI 62.5/25 µg	UMEC/VI 125/25 µg	Tiotropium 18 µg	Total
Asian - Japanese Heritage	0	3	0	2	5
White - White/Caucasian/European Heritage	184	182	180	177	723
Mixed Race	3	4	3	3	13

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Change From Baseline (BL) in Trough Forced Expiratory Volume in One Second (FEV1) on Day 169 (Week 24)
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 Days 2, 28, 56, 84, 112, 168, and 169. Baseline is defined as the mean of the assessments made 30 minutes pre-dose and 5 minutes pre-dose on Treatment Day 1. Trough FEV1 is defined as the mean of the FEV1 values obtained at 23 and 24 hours after the previous morning's dosing (ie., trough FEV1 on Day 169 is the mean of the FEV1 values obtained 23 and 24 hours after the morning dosing on Day 168). Change from Baseline at a particular visit was calculated as the trough FEV1 at that visit minus Baseline. Analysis was performed using a repeated measures model with covariates of treatment, Baseline , smoking status, center group, day, and day by Baseline and day by treatment interactions. ITT=Intent-to-Treat; par.=participants. .
Time Frame	Baseline and Day 169
Safety Issue?	No

Analysis Population Description

ITT Population excluding par. from Investigator 040688: all randomized par. who received >=1 dose of study drug, except for those from Investigator 040688. Par. analyzed are those with data available at the presented time point; but, all par. without missing covariate information and with >=1 post-BL measurement were included in the analysis.

Reporting Groups

	Description
VI 25 µg	Participants received vilanterol (VI) 25 micrograms (µg) once daily (QD) via a dry powder inhaler (DPI). All participants also received placebo QD via a HandiHaler.
UMEC/VI 62.5/25 µg	Participants received umeclidinium bromide (UMEC)/VI 62.5/25 µg QD via a DPI. All participants also received placebo QD via a HandiHaler.
UMEC/VI 125/25 µg	Participants received UMEC/VI 125/25 µg QD via a DPI. All participants also received placebo QD via a HandiHaler.
TIO 18 µg	Participants received tiotropium (TIO) 18 µg QD via a HandiHaler. All participants also received placebo QD via a DPI.

Measured Values

	VI 25 µg	UMEC/VI 62.5/25 µg	UMEC/VI 125/25 µg	TIO 18 µg
Number of Participants Analyzed	162	177	167	173
Change From Baseline (BL) in Trough Forced Expiratory Volume in One Second (FEV1) on Day 169 (Week 24) [units: Liters] Least Squares Mean (Standard Error)	0.121 (0.0189)	0.211 (0.0183)	0.209 (0.0187)	0.121 (0.0186)

Statistical Analysis 1 for Change From Baseline (BL) in Trough Forced Expiratory Volume in One Second (FEV1) on Day 169 (Week 24)

Groups	VI 25 µg, UMEC/VI 62.5/25 µg
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.090
95% Confidence Interval	0.039 to 0.142

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:

[Not specified.]

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

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

Other relevant estimation information:

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

Statistical Analysis 2 for Change From Baseline (BL) in Trough Forced Expiratory Volume in One Second (FEV1) on Day 169 (Week 24)

Groups	UMEC/VI 62.5/25 µg, TIO 18 µg
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.090
95% Confidence Interval	0.039 to 0.141

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 squares mean difference=UMEC/VI 62.5/25 µg minus Tio 18 µg.

Statistical Analysis 3 for Change From Baseline (BL) in Trough Forced Expiratory Volume in One Second (FEV1) on Day 169 (Week 24)

Groups	VI 25 µg, UMEC/VI 125/25 µg
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.088
95% Confidence Interval	0.036 to 0.140

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:

[Not specified.]

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

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

Other relevant estimation information:

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

Statistical Analysis 4 for Change From Baseline (BL) in Trough Forced Expiratory Volume in One Second (FEV1) on Day 169 (Week 24)

Groups	UMEC/VI 125/25 µg, TIO 18 µg
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.088
95% Confidence Interval	0.036 to 0.140

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:

[Not specified.]

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

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

Other relevant estimation information:

Least squares mean difference=UMEC/VI 125/25 µg minus TIO 18 µg.

2. Secondary Outcome Measure:

Measure Title	Change From Baseline (BL) in Weighted Mean (WM) 0-6 Hour FEV1 Obtained Post-dose at Day 168
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. The WM FEV1 was derived by calculating the area under the FEV1/time curve (AUC) using the trapezoidal rule, and then dividing the value by the time interval over which the AUC was calculated. The WM was calculated at Days 1, 84, and Day 168 using the 0-6-hour post-dose

	FEV1 measurements collected on that day, which included pre-dose (Day 1: 30 minutes [min] and 5 min prior to dosing; other serial visits: 23 and 24 hours after the previous morning dose) and post-dose at 15 minutes, 30 minutes, 1 hour, 3 hours, and 6 hours. Change from BL at a particular visit was calculated as WM at that visit minus BL. Analysis was performed using a repeated measures model with covariates of treatment, BL (mean of the two assessments made 30 minutes and 5 minutes pre-dose on Day 1), smoking status, center group, day, and day by BL and day by treatment interactions.
Time Frame	Baseline and Day 168
Safety Issue?	No

Analysis Population Description

ITT Population excluding participants from Investigator 040688. Par. analyzed are those with data available at the presented time point; but, all par. without missing covariate information and with >=1 post-Baseline measurement were included in the analysis.

Reporting Groups

	Description
VI 25 µg	Participants received vilanterol (VI) 25 micrograms (µg) once daily (QD) via a dry powder inhaler (DPI). All participants also received placebo QD via a HandiHaler.
UMEC/VI 62.5/25 µg	Participants received umeclidinium bromide (UMEC)/VI 62.5/25 µg QD via a DPI. All participants also received placebo QD via a HandiHaler.
UMEC/VI 125/25 µg	Participants received UMEC/VI 125/25 µg QD via a DPI. All participants also received placebo QD via a HandiHaler.
TIO 18 µg	Participants received tiotropium (TIO) 18 µg QD via a HandiHaler. All participants also received placebo QD via a DPI.

Measured Values

	VI 25 µg	UMEC/VI 62.5/25 µg	UMEC/VI 125/25 µg	TIO 18 µg
Number of Participants Analyzed	161	173	166	168
Change From Baseline (BL) in Weighted Mean (WM) 0-6 Hour FEV1 Obtained Post-dose at Day 168 [units: Liters] Least Squares Mean (Standard Error)	0.178 (0.0189)	0.254 (0.0183)	0.263 (0.0187)	0.181 (0.0187)

3. Other Pre-specified Outcome Measure:

Measure Title	Change From Baseline (BL) in the Mean Shortness of Breath With Daily Activities (SOBDA) Score for Week 24
Measure Description	The newly developed SOBDA questionnaire assesses dyspnea or shortness of breath (SOB) with daily activities. The SOBDA questionnaire is made up of 13 items completed by the participant (par.) each evening prior to bedtime, when the par. is instructed to reflect on the current day's activities. The daily score is computed as the mean of the scores on the 13 items (>=7 items must have non-missing responses for this to be calculated). The par. is assigned a weekly mean SOBDA score ranging from 1 to 4 (greater scores indicate more severe breathlessness with daily activities) based on the mean of 7 days of data (>=4 of 7 days must be completed for a weekly mean to be calculated). Change from BL is the mean weekly SOBDA score minus BL. Analysis was performed using MMRM with covariates of treatment, BL (mean score in the week prior to treatment), smoking status, center group, week, week by BL and week by treatment interactions. This MMRM analysis only included Weeks 4, 8, 12, and 24.
Time Frame	Baseline and Week 24

Safety Issue?	No

Analysis Population Description

ITT Population excluding participants from Investigator 040688. Participants analyzed are those with data available at the presented time point; but, all participants without missing covariate information and with >=1 post-Baseline measurement were included in the analysis.

Reporting Groups

	Description
VI 25 µg	Participants received vilanterol (VI) 25 micrograms (µg) once daily (QD) via a dry powder inhaler (DPI). All participants also received placebo QD via a HandiHaler.
UMEC/VI 62.5/25 µg	Participants received umeclidinium bromide (UMEC)/VI 62.5/25 µg QD via a DPI. All participants also received placebo QD via a HandiHaler.
UMEC/VI 125/25 µg	Participants received UMEC/VI 125/25 µg QD via a DPI. All participants also received placebo QD via a HandiHaler.
TIO 18 µg	Participants received tiotropium (TIO) 18 µg QD via a HandiHaler. All participants also received placebo QD via a DPI.

Measured Values

	VI 25 µg	UMEC/VI 62.5/25 µg	UMEC/VI 125/25 µg	TIO 18 µg
Number of Participants Analyzed	110	118	107	105
Change From Baseline (BL) in the Mean Shortness of Breath With Daily Activities (SOBDA) Score for Week 24 [units: Scores on a scale] Least Squares Mean (Standard Error)	-0.16 (0.043)	-0.18 (0.042)	-0.18 (0.044)	-0.18 (0.044)

Reported Adverse Events

Reporting Groups

	Description
VI 25 µg	Participants received vilanterol (VI) 25 micrograms (µg) once daily (QD) via a dry powder inhaler (DPI). All participants also received placebo QD via a HandiHaler.
UMEC/VI 62.5/25 µg	Participants received umeclidinium bromide (UMEC)/VI 62.5/25 µg QD via a DPI. All participants also received placebo QD via a HandiHaler.
UMEC/VI 125/25 µg	Participants received UMEC/VI 125/25 µg QD via a DPI. All participants also received placebo QD via a HandiHaler.
TIO 18 µg	Participants received tiotropium (TIO) 18 µg QD via a HandiHaler. All participants also received placebo QD via a DPI.

Time Frame

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of study medication until the end of treatment (up to 24 weeks).

Additional Description

On-treatment 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

	VI 25 µg	UMEC/VI 62.5/25 µg	UMEC/VI 125/25 µg	TIO 18 µg
Total # participants affected/at risk	15/209 (7.18%)	7/212 (3.3%)	5/214 (2.34%)	13/208 (6.25%)
Cardiac disorders				

	VI 25 µg	UMEC/VI 62.5/25 µg	UMEC/VI 125/25 µg	TIO 18 µg
Acute myocardial infarction † [A]				
# participants affected/at risk	1/209 (0.48%)	0/212 (0%)	0/214 (0%)	0/208 (0%)
# events				
Angina pectoris † [A]				
# participants affected/at risk	1/209 (0.48%)	0/212 (0%)	0/214 (0%)	0/208 (0%)
# events				
Cardiac failure acute † [A]				
# participants affected/at risk	1/209 (0.48%)	0/212 (0%)	0/214 (0%)	0/208 (0%)
# events				
Cardiac failure congestive † [A]				
# participants affected/at risk	1/209 (0.48%)	0/212 (0%)	0/214 (0%)	0/208 (0%)
# events				
Supraventricular extrasystoles † [A]				
# participants affected/at risk	1/209 (0.48%)	0/212 (0%)	0/214 (0%)	0/208 (0%)
# events				
Gastrointestinal				

	VI 25 µg	UMEC/VI 62.5/25 µg	UMEC/VI 125/25 µg	TIO 18 µg
disorders				
Abdominal pain †[A]				
# participants affected/at risk	1/209 (0.48%)	0/212 (0%)	0/214 (0%)	0/208 (0%)
# events				
Abdominal pain upper †[A]				
# participants affected/at risk	1/209 (0.48%)	0/212 (0%)	0/214 (0%)	0/208 (0%)
# events				
Gastrointestinal haemorrhage †[A]				
# participants affected/at risk	1/209 (0.48%)	0/212 (0%)	0/214 (0%)	0/208 (0%)
# events				
Mallory-Weiss syndrome †[A]				
# participants affected/at risk	0/209 (0%)	0/212 (0%)	0/214 (0%)	1/208 (0.48%)
# events				
General disorders				
Non-cardiac chest pain †[A]				
# participants affected/at risk	0/209 (0%)	0/212 (0%)	0/214 (0%)	2/208 (0.96%)
# events				

	VI 25 µg	UMEC/VI 62.5/25 µg	UMEC/VI 125/25 µg	TIO 18 µg
Infections and infestations				
Appendicitis † [A]				
# participants affected/at risk	1/209 (0.48%)	0/212 (0%)	0/214 (0%)	0/208 (0%)
# events				
Gastroenteritis † [A]				
# participants affected/at risk	0/209 (0%)	0/212 (0%)	0/214 (0%)	1/208 (0.48%)
# events				
Infective exacerbation of chronic obstructive airways diseas † [A]				
# participants affected/at risk	1/209 (0.48%)	0/212 (0%)	0/214 (0%)	0/208 (0%)
# events				
Osteomyelitis † [A]				
# participants affected/at risk	0/209 (0%)	0/212 (0%)	0/214 (0%)	1/208 (0.48%)
# events				
Pneumonia † [A]				
# participants affected/at risk	1/209 (0.48%)	0/212 (0%)	0/214 (0%)	2/208 (0.96%)

	VI 25 µg	UMEC/VI 62.5/25 µg	UMEC/VI 125/25 µg	TIO 18 µg
# events				
Urinary tract infection † [A]				
# participants affected/at risk	0/209 (0%)	0/212 (0%)	0/214 (0%)	1/208 (0.48%)
# events				
Injury, poisoning and procedural complications				
Craniocerebral injury † [A]				
# participants affected/at risk	0/209 (0%)	0/212 (0%)	0/214 (0%)	1/208 (0.48%)
# events				
Foot fracture † [A]				
# participants affected/at risk	1/209 (0.48%)	0/212 (0%)	0/214 (0%)	0/208 (0%)
# events				
Lower limb fracture † [A]				
# participants affected/at risk	0/209 (0%)	0/212 (0%)	1/214 (0.47%)	0/208 (0%)
# events				
Lumbar vertebral fracture † [A]				
# participants affected/at risk	0/209 (0%)	0/212 (0%)	0/214 (0%)	1/208 (0.48%)

	VI 25 µg	UMEC/VI 62.5/25 µg	UMEC/VI 125/25 µg	TIO 18 µg
# events				
Meniscus lesion † [A]				
# participants affected/at risk	0/209 (0%)	1/212 (0.47%)	0/214 (0%)	0/208 (0%)
# events				
Vascular graft occlusion † [A]				
# participants affected/at risk	0/209 (0%)	0/212 (0%)	0/214 (0%)	1/208 (0.48%)
# events				
Wound † [A]				
# participants affected/at risk	0/209 (0%)	0/212 (0%)	0/214 (0%)	1/208 (0.48%)
# events				
Metabolism and nutrition disorders				
Hyperglycaemia † [A]				
# participants affected/at risk	0/209 (0%)	0/212 (0%)	0/214 (0%)	1/208 (0.48%)
# events				
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				

	VI 25 µg	UMEC/VI 62.5/25 µg	UMEC/VI 125/25 µg	TIO 18 µg
Adenoma benign † [A]				
# participants affected/at risk	0/209 (0%)	0/212 (0%)	0/214 (0%)	1/208 (0.48%)
# events				
Bladder cancer stage III † [A]				
# participants affected/at risk	1/209 (0.48%)	0/212 (0%)	0/214 (0%)	0/208 (0%)
# events				
Hepatic neoplasm malignant † [A]				
# participants affected/at risk	0/209 (0%)	1/212 (0.47%)	0/214 (0%)	0/208 (0%)
# events				
Lung neoplasm † [A]				
# participants affected/at risk	0/209 (0%)	0/212 (0%)	0/214 (0%)	1/208 (0.48%)
# events				
Nervous system disorders				
Syncope † [A]				
# participants affected/at risk	1/209 (0.48%)	0/212 (0%)	1/214 (0.47%)	0/208 (0%)
# events				

	VI 25 µg	UMEC/VI 62.5/25 µg	UMEC/VI 125/25 µg	TIO 18 µg
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure † [A]				
# participants affected/at risk	0/209 (0%)	1/212 (0.47%)	0/214 (0%)	0/208 (0%)
# events				
Chronic obstructive pulmonary disease † [A]				
# participants affected/at risk	2/209 (0.96%)	5/212 (2.36%)	3/214 (1.4%)	3/208 (1.44%)
# events				
Pleurisy † [A]				
# participants affected/at risk	1/209 (0.48%)	0/212 (0%)	0/214 (0%)	0/208 (0%)
# events				
Vascular disorders				
Hypertension † [A]				
# participants affected/at risk	1/209 (0.48%)	0/212 (0%)	0/214 (0%)	0/208 (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%

	VI 25 µg	UMEC/VI 62.5/25 µg	UMEC/VI 125/25 µg	TIO 18 µg
Total # participants affected/at risk	44/209 (21.05%)	54/212 (25.47%)	40/214 (18.69%)	37/208 (17.79%)
Infections and infestations				
Nasopharyngitis † [A]				
# participants affected/at risk	17/209 (8.13%)	21/212 (9.91%)	14/214 (6.54%)	16/208 (7.69%)
# events				
Upper respiratory tract infection † [A]				
# participants affected/at risk	5/209 (2.39%)	8/212 (3.77%)	7/214 (3.27%)	8/208 (3.85%)
# events				
Musculoskeletal and connective tissue disorders				
Back pain † [A]				
# participants affected/at risk	3/209 (1.44%)	10/212 (4.72%)	7/214 (3.27%)	4/208 (1.92%)
# events				
Nervous system disorders				

	VI 25 µg	UMEC/VI 62.5/25 µg	UMEC/VI 125/25 µg	TIO 18 µg
Headache † [A]				
# participants affected/at risk	21/209 (10.05%)	20/212 (9.43%)	14/214 (6.54%)	9/208 (4.33%)
# events				
Respiratory, thoracic and mediastinal disorders				
Cough † [A]				
# participants affected/at risk	4/209 (1.91%)	7/212 (3.3%)	7/214 (3.27%)	5/208 (2.4%)
# 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

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