Protocol Registration Receipt
02/20/2014

Grantor: CDER IND/IDE Number: 106,616 Serial Number: SN 0135

A 24-week Evaluation of GSK573719/Vilanterol (125/25mcg) and Components in COPD (DB2113361)

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT01313637

Purpose

This is a phase III multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of GSK573719/GW642444 Inhalation Powder, GSK573719 Inhalation Powder, GW642444 Inhalation Powder and Placebo when administered once-daily via a Novel Dry Powder Inhaler over a 24-week treatment period in subjects with COPD. Subjects who meet eligibility criteria at Screening (Visit 1) will complete a 7 to14 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 27 weeks. A subset of subjects at selected sites will also perform 24-hour serial spirometry and Holter monitoring during the study and provide serial blood samples for pharmacokinetic analysis. Sparse pharmacokinetic sampling for population pharmacokinetic analyses will be obtained from

non-subset subjects. The primary measure of efficacy is clinic visit trough (pre-bronchodilator and pre-dose) FEV1 on Treatment Day 169. Safety will be assessed by adverse events, 12-lead ECGs, vital signs, clinical laboratory tests, and 24 hour Holter monitoring (subset only).

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

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Randomized, Safety/Efficacy Study
Official Title: A 24-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of GSK573719/GW642444 Inhalation Powder and the Individual Components Delivered Once-Daily Via a Novel Dry Powder Inhaler in Subjects With Chronic Obstructive Pulmonary Disease

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:

- Mean Transition Dyspnea Index (TDI) Focal Score at Day 168 (Week 24) [Time Frame: Day 168 (Week 24)] [Designated as safety issue: No]

  Considered an 'other' endpoint by the FDA. The TDI is an interviewer-administered instrument which measures the changes in the participant's dyspnea from Baseline. This questionnaire was collected on Days 28, 84 and 168. The scores in the TDI evaluate ratings for 3 different categories (functional impairment, magnitude of task in exertional capacity, and magnitude of effort). TDI scores ranged from -3 (major deterioration) to +3 (major improvement); total score = -9 to 9. Analysis was performed using a repeated measures model with covariates of treatment, Baseline dyspnea index (BDI) focal score,smoking status, center group, day, day by BDI focal score and day by treatment interactions.

- Change From Baseline 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, 28, 84, and 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 min, 30 min, 1 hour, 3 hours, and 6 hours. Change from Baseline at a particular visit was calculated as the WM at that visit minus Baseline. Analysis was performed using a repeated measures model with covariates of treatment, Baseline (mean of the two assessments made 30 min and 5 min pre-dose on Day 1), smoking status, center group, day, and day by Baseline and day by treatment interactions.

Other Pre-specified Outcome Measures:

- Change From Baseline 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: 1493
Study Start Date: March 2011
Study Completion Date: March 2012
Primary Completion Date: March 2012

Arms	Assigned Interventions
Experimental: GSK573719/GW642444 125/25mcg	Drug: GSK573719/GW642444 125/25mcg 125/25mcg Other Names: umeclidinium bromide/vilanterol trifenatate
Experimental: GSK573719 125mcg	Drug: GSK573719 125mcg 125mcg

Arms	Assigned Interventions
	Other Names: umeclidinium bromide
Experimental: GW642444 25mcg	Drug: GW642444 25mcg 25mcg Other Names: vilanterol trifenatate
Placebo Comparator: Placebo Placebo	Drug: Placebo only Placebo Other Names: placebo

This is a 24-week, phase III multicenter, randomized, double-blind, placebo-controlled, parallel-group study.

Eligible subjects will be randomized to GSK573719/GW642444 125/25mcg, GSK573719 125mcg, GW642444 25mcg, and placebo treatment groups in a 3:3:3:2 ratio such that of the planned 1463 total number of randomized subjects approximately 399 subjects will be randomized to each active treatment group and 266 subjects will be randomized to placebo. All treatments will be administered once-daily in the morning by inhalation using a Novel Dry Powder Inhaler (Novel DPI).

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 14 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 27 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/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, 4, 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 evening throughout the run-in and treatment periods. Subjects will use the eDiary to record 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. Disease specific health status will be evaluated using the subject-completed St. George's Respiratory Questionnaire (SGRQ). The SGRQ will be completed at Visits 2, 4, 6, and 8. Administration of the SGRQ and BDI/TDI should be done prior to spirometry testing.

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. Blood samples for population pharmacokinetic analyses will be obtained.

At selected study sites, a subset of approximately 198 subjects will perform 24-hour serial spirometry during the study for evaluation of lung function over the dosing period. In conjunction with the serial spirometry, this subset of subjects will also perform 24 hour Holter monitoring and provide blood samples for PK analysis.

Eligibility

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

Inclusion Criteria:

- Diagnosis of COPD
- 10 pack-year or greater history of cigarette smoking
- Post-bronchodilator FEV1/FVC of <0.7
- Predicted FEV1 of 70% of normal or less
- Modified Medical Research Council (mMRC) dyspnea score of 2 or greater

Exclusion Criteria:

- Women who are pregnant, lactating, or planning to become pregnant
- Respiratory disorders other than COPD, including a current diagnosis of asthma
- Clinically significant non-respiratory diseases or abnormalities that are not adequately controlled
- Significant allergy or hypersensitivity to anticholinergics, beta2-agonists, or the excipients of magnesium stereate or lactose used in the inhaler delivery device
- Hospitalization for COPD or pneumonia within 12 weeks prior to screening

- Lung volume reduction surgery within 12 weeks prior to screening
- Abnormal and clinically significant ECG findings at screening
- Clinically significant laboratory findings at screening
- Use of systemic corticosteroids, antibiotics for respiratory tract infections, strong cytochrome P450 3A4 inhibitors, high dose inhaled steroids (>1000mcg fluticasone propionate or equivalent), PDE4 inhibitors, tiotropium, oral beta2-agoinists, short- and long-acting inhaled beta2-agonists, ipratropium, inhaled sodium cromoglycate or nedocromil sodium, or investigational medicines for defined time periods prior to the screening visit
- Use of long-term oxygen therapy (12 hours or greater per day)
- Regular use of nebulized treatment with short-acting bronchodilators
- Participation in the acute phase of a pulmonary rehabilitation program
- A know or suspected history of alcohol or drug abuse
- Affiliation with the investigational site
- Previous use of GSK573719 or GW642444 alone or in combination, including the combination of fluticasone furoate and GW642444

Contacts and Locations

Locations

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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:	113361
	2010-023348-33 [EudraCT Number]
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- to14-day run-in period and were then randomized to a 24-week treatment (trt.) period. A total of 2114 participants were screened; 1493 participants were randomized, and 1489

participants took at least one dose of randomized medication.

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) via a dry powder inhaler (DPI) in the morning for 24 weeks.
UMEC 125 µg QD	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD via a DPI in the morning for 24 weeks.
VI 25 µg QD	Participants received vilanterol (VI) 25 µg QD via a DPI for 24 weeks.
UMEC/VI 125/25 µg QD	Participants received UMEC/VI 125/25 µg QD via a DPI in the morning for 24 weeks.

Overall Study

	Placebo	UMEC 125 µg QD	VI 25 µg QD	UMEC/VI 125/25 µg QD
Started	275	407	404	403
Completed	183	312	298	325
Not Completed	92	95	106	78
Adverse Event	17	24	25	18
Lack of Efficacy	44	38	37	24
Protocol Violation	4	3	11	5
Met Protocol- Defined Stopping Criteria	16	15	14	13
Lost to Follow-up	0	2	1	3
Withdrawal by Subject	11	13	18	15

Baseline Characteristics

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) via a dry powder inhaler (DPI) in the morning for 24 weeks.
UMEC 125 µg	Participants received UMEC 125 µg QD via a DPI in the morning for 24 weeks.
VI 25 µg	Participants received VI 25 µg QD via a DPI for 24 weeks.
UMEC/VI 125/25 µg	Participants received UMEC/VI 125/25 µg QD via a DPI in the morning for 24 weeks.

Baseline Measures

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg	Total
Number of Participants	275	407	404	403	1489
Age, Continuous [units: Years] Mean (Standard Deviation)	62.2 (8.53)	63.1 (8.48)	62.8 (8.80)	63.4 (8.08)	62.9 (8.47)
Gender, Male/Female [units: Participants]					
Female	100	137	139	139	515
Male	175	270	265	264	974
Race/Ethnicity, Customized [units: Participants]					
African American/African	9	4	7	4	24

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg	Total
Heritage					
American Indian or Alaska Native	0	0	1	1	2
Asian - Central/South Asian Heritage	0	0	1	0	1
Asian - Japanese Heritage	13	21	21	19	74
Asian - South East Asian Heritage	14	19	20	20	73
White - Arabic/North African Heritage	1	2	1	0	4
White - White/Caucasian/European Heritage	237	361	353	359	1310
Mixed Race	1	0	0	0	1

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

Intent-to-Treat (ITT) Population: all par. randomized to trt. who received at least one dose of randomized study drug. Par. represents those with data available at the time point being presented; however, all par. in the ITT population without missing covariate information and with at least one post BL measurement are included in the analysis.

Reporting Groups

	Description
Placebo	Participants received matching placebo QD via a DPI in the morning for 24 weeks.
UMEC 125 µg	Participants received UMEC 125 µg QD via a DPI in the morning for 24 weeks.
VI 25 µg	Participants received VI 25 µg QD via a DPI for 24 weeks.
UMEC/VI 125/25 µg	Participants received UMEC/VI 125/25 µg QD via a DPI in the morning for 24 weeks.

Measured Values

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	182	312	299	323
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)	-0.031 (0.0153)	0.129 (0.0119)	0.093 (0.0121)	0.207 (0.0119)

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

Groups	Placebo, UMEC 125 µg
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.160
95% Confidence Interval	0.122 to 0.198

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 125 µg minus Placebo.

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

(Week 24)

Groups	Placebo, VI 25 µg
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.124
95% Confidence Interval	0.086 to 0.162

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=VI 25 µg minus Placebo.

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

Groups	Placebo, UMEC/VI 125/25 µg
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.238
95% Confidence Interval	0.200 to 0.276

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 Placebo.

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

Groups	UMEC 125 µg, UMEC/VI 125/25 µg
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.079
95% Confidence Interval	0.046 to 0.112

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 minus UMEC 125 µg.

Statistical Analysis 5 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]	0.114
95% Confidence Interval	0.081 to 0.148

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

[Not specified.]

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

[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 minus VI 25 µg.

2. Secondary Outcome Measure:

Measure Title	Mean Transition Dyspnea Index (TDI) Focal Score at Day 168 (Week 24)
Measure Description	Considered an 'other' endpoint by the FDA. The TDI is an interviewer-administered instrument which measures the changes in the participant's dyspnea from Baseline. This questionnaire was collected on Days 28, 84 and 168. The scores in the TDI evaluate ratings for 3 different categories (functional impairment, magnitude of task in exertional capacity, and magnitude of effort). TDI scores ranged

	from -3 (major deterioration) to +3 (major improvement); total score = -9 to 9. Analysis was performed using a repeated measures model with covariates of treatment, Baseline dyspnea index (BDI) focal score,smoking status, center group, day, day by BDI focal score and day by treatment interactions.
Time Frame	Day 168 (Week 24)
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all par. randomized to trt. who received at least one dose of randomized study drug. Par. represents those with data available at the time point being presented; however, all par. in the ITT population without missing covariate information and with at least one post BL measurement are included in the analysis.

Reporting Groups

	Description
Placebo	Participants received matching placebo QD via a DPI in the morning for 24 weeks.
UMEC 125 µg	Participants received UMEC 125 µg QD via a DPI in the morning for 24 weeks.
VI 25 µg	Participants received VI 25 µg QD via a DPI for 24 weeks.
UMEC/VI 125/25 µg	Participants received UMEC/VI 125/25 µg QD via a DPI in the morning for 24 weeks.

Measured Values

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	186	313	294	324

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
Mean Transition Dyspnea Index (TDI) Focal Score at Day 168 (Week 24) [units: Scores on a scale] Least Squares Mean (Standard Error)	0.8 (0.20)	1.2 (0.16)	1.3 (0.16)	1.8 (0.15)

3. Secondary Outcome Measure:

Measure Title	Change From Baseline 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, 28, 84, and 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 min, 30 min, 1 hour, 3 hours, and 6 hours. Change from Baseline at a particular visit was calculated as the WM at that visit minus Baseline. Analysis was performed using a repeated measures model with covariates of treatment, Baseline (mean of the two assessments made 30 min and 5 min pre-dose on Day 1), smoking status, center group, day, and day by Baseline and day by treatment interactions.
Time Frame	Baseline and Day 168
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all par. randomized to trt. who received at least one dose of randomized study drug. Par. represents those with data

available at the time point being presented; however, all par. in the ITT population without missing covariate information and with at least one post BL measurement are included in the analysis.

Reporting Groups

	Description
Placebo	Participants received matching placebo QD via a DPI in the morning for 24 weeks.
UMEC 125 µg	Participants received UMEC 125 µg QD via a DPI in the morning for 24 weeks.
VI 25 µg	Participants received VI 25 µg QD via a DPI for 24 weeks.
UMEC/VI 125/25 µg	Participants received UMEC/VI 125/25 µg QD via a DPI in the morning for 24 weeks.

Measured Values

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	180	311	298	316
Change From Baseline in Weighted Mean (WM) 0-6 Hour FEV1 Obtained Post-dose at Day 168 [units: Liters] Least Squares Mean (Standard Error)	-0.018 (0.0150)	0.160 (0.0118)	0.127 (0.0119)	0.269 (0.0118)

4. Other Pre-specified Outcome Measure:

Measure Title	Change From Baseline 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

Intent-to-Treat (ITT) Population: all par. randomized to trt. who received at least one dose of randomized study drug. Par. represents those with data available at the time point being presented; however, all par. in the ITT population without missing covariate information and with at least one post BL measurement are included in the analysis.

Reporting Groups

	Description
Placebo	Participants received matching placebo QD via a DPI in the morning for 24 weeks.
UMEC 125 µg	Participants received UMEC 125 µg QD via a DPI in the morning for 24 weeks.
VI 25 µg	Participants received VI 25 µg QD via a DPI for 24 weeks.

	Description
UMEC/VI 125/25 µg	Participants received UMEC/VI 125/25 µg QD via a DPI in the morning for 24 weeks.

Measured Values

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
Number of Participants Analyzed	118	215	212	234
Change From Baseline in the Mean Shortness of Breath With Daily Activities (SOBDA) Score for Week 24 [units: Scores on a scale] Least Squares Mean (Standard Error)	-0.07 (0.038)	-0.15 (0.029)	-0.10 (0.029)	-0.22 (0.029)

Reported Adverse Events

Reporting Groups

	Description
Placebo	Participants received matching placebo QD via a DPI in the morning for 24 weeks.
UMEC 125 µg	Participants received UMEC 125 µg QD via a DPI in the morning for 24 weeks.
VI 25 µg	Participants received VI 25 µg QD via a DPI for 24 weeks.
UMEC/VI 125/25 µg	Participants received UMEC/VI 125/25 µg QD via a DPI in the morning for 24 weeks.

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

SAEs and non-serious AEs were collected in members of the ITT Population, comprised of all participants who had received at least one dose of randomized study medication during treatment period.

Serious Adverse Events

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
Total # participants affected/at risk	17/275 (6.18%)	22/407 (5.41%)	20/404 (4.95%)	23/403 (5.71%)
Cardiac disorders				
Acute myocardial infarction † [A]				
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	2/404 (0.5%)	0/403 (0%)
# events				
Angina unstable † [A]				
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	0/404 (0%)	0/403 (0%)
# events				
Atrial fibrillation † [A]				
# participants affected/at risk	0/275 (0%)	2/407 (0.49%)	1/404 (0.25%)	0/403 (0%)
# events				
Myocardial infarction † [A]				

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	0/404 (0%)	1/403 (0.25%)
# events				
Supraventricular tachycardia † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	0/404 (0%)	1/403 (0.25%)
# events				
Ventricular extrasystoles † [A]				
# participants affected/at risk	0/275 (0%)	2/407 (0.49%)	0/404 (0%)	0/403 (0%)
# events				
Eye disorders				
Retinal detachment † [A]				
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	0/404 (0%)	0/403 (0%)
# events				
Gastrointestinal disorders				
Abdominal pain lower † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)
# events				

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
Colitis ischaemic † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)
# events				
Colitis ulcerative † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)
# events				
Crohn's disease † [A]				
# participants affected/at risk	1/275 (0.36%)	0/407 (0%)	0/404 (0%)	0/403 (0%)
# events				
Gastrooesophageal reflux disease † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	0/404 (0%)	1/403 (0.25%)
# events				
Ileus † [A]				
# participants affected/at risk	1/275 (0.36%)	0/407 (0%)	0/404 (0%)	0/403 (0%)
# events				
Inguinal hernia † [A]				
# participants affected/at	0/275 (0%)	1/407 (0.25%)	0/404 (0%)	0/403 (0%)

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
risk				
# events				
Lower gastrointestinal haemorrhage †[A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)
# events				
Pancreatic atrophy †[A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)
# events				
Small intestinal obstruction †[A]				
# participants affected/at risk	1/275 (0.36%)	0/407 (0%)	0/404 (0%)	0/403 (0%)
# events				
General disorders				
Chest pain †[A]				
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	0/404 (0%)	0/403 (0%)
# events				
Oedema peripheral †[A]				
# participants affected/at	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
risk				
# events				
Polyp † [A]				
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	0/404 (0%)	0/403 (0%)
# events				
Hepatobiliary disorders				
Hepatic steatosis † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)
# events				
Immune system disorders				
Hypersensitivity † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	0/404 (0%)	1/403 (0.25%)
# events				
Infections and infestations				
Cellulitis † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	0/404 (0%)	1/403 (0.25%)

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
# events				
Cystitis †[A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	0/404 (0%)	1/403 (0.25%)
# events				
Epstein-Barr virus infection †[A]				
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	0/404 (0%)	0/403 (0%)
# events				
Lobar pneumonia †[A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)
# events				
Pneumonia †[A]				
# participants affected/at risk	4/275 (1.45%)	2/407 (0.49%)	0/404 (0%)	3/403 (0.74%)
# events				
Post procedural sepsis †[A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)
# events				
Injury, poisoning and				

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
procedural complications				
Bladder injury † [A]				
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	0/404 (0%)	0/403 (0%)
# events				
Femoral neck fracture † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	0/404 (0%)	1/403 (0.25%)
# events				
Rib fracture † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	0/404 (0%)	1/403 (0.25%)
# events				
Upper limb fracture † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	0/404 (0%)	1/403 (0.25%)
# events				
Vascular pseudoaneurysm † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	0/404 (0%)	1/403 (0.25%)
# events				
Investigations				

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
Cardiac enzymes increased †[A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)
# events				
Metabolism and nutrition disorders				
Starvation †[A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)
# events				
Musculoskeletal and connective tissue disorders				
Back pain †[A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	0/404 (0%)	1/403 (0.25%)
# events				
Intervertebral disc protrusion †[A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)
# events				

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
Spinal column stenosis † [A]				
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	0/404 (0%)	0/403 (0%)
# events				
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Breast cancer † [A]				
# participants affected/at risk	1/275 (0.36%)	0/407 (0%)	0/404 (0%)	0/403 (0%)
# events				
Lung neoplasm malignant † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	2/403 (0.5%)
# events				
Metastases to bone † [A]				
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	1/404 (0.25%)	0/403 (0%)
# events				
Metastases to central nervous system † [A]				

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	0/404 (0%)	0/403 (0%)
# events				
Non-small cell lung cancer † [A]				
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	0/404 (0%)	0/403 (0%)
# events				
Oesophageal squamous cell carcinoma stage II † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	0/404 (0%)	1/403 (0.25%)
# events				
Pancreatic carcinoma metastatic † [A]				
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	0/404 (0%)	0/403 (0%)
# events				
Prostate cancer † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	0/404 (0%)	1/403 (0.25%)
# events				
Ureteric cancer † [A]				
# participants affected/at	1/275 (0.36%)	0/407 (0%)	0/404 (0%)	0/403 (0%)

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
risk				
# events				
Nervous system disorders				
Epilepsy † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	0/404 (0%)	1/403 (0.25%)
# events				
Headache † [A]				
# participants affected/at risk	1/275 (0.36%)	0/407 (0%)	0/404 (0%)	0/403 (0%)
# events				
Lumbar radiculopathy † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)
# events				
Syncope † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)
# events				
Transient ischemic attack † [A]				
# participants affected/at	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
risk				
# events				
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease †[A]				
# participants affected/at risk	8/275 (2.91%)	4/407 (0.98%)	3/404 (0.74%)	5/403 (1.24%)
# events				
Pneumothorax †[A]				
# participants affected/at risk	1/275 (0.36%)	0/407 (0%)	0/404 (0%)	0/403 (0%)
# events				
Pulmonary embolism †[A]				
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	0/404 (0%)	0/403 (0%)
# events				
Pulmonary haemorrhage †[A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	0/404 (0%)	1/403 (0.25%)
# events				
Pulmonary oedema †[A]				
# participants affected/at	0/275 (0%)	0/407 (0%)	0/404 (0%)	1/403 (0.25%)

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
risk				
# events				
Sleep apnoea syndrome † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)
# events				
Vascular disorders				
Accelerated hypertension † [A]				
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	0/404 (0%)	0/403 (0%)
# events				
Arterial occlusive disease † [A]				
# participants affected/at risk	0/275 (0%)	0/407 (0%)	0/404 (0%)	1/403 (0.25%)
# events				
Arteriosclerosis † [A]				
# participants affected/at risk	1/275 (0.36%)	0/407 (0%)	0/404 (0%)	0/403 (0%)
# events				
Embolism † [A]				
# participants affected/at	0/275 (0%)	0/407 (0%)	1/404 (0.25%)	0/403 (0%)

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
risk				
# events				
Peripheral arterial occlusive disease † [A]				
# participants affected/at risk	1/275 (0.36%)	1/407 (0.25%)	0/404 (0%)	1/403 (0.25%)
# events				
Thromboangiitis obliterans † [A]				
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	0/404 (0%)	0/403 (0%)
# events				
Thrombosis † [A]				
# participants affected/at risk	0/275 (0%)	1/407 (0.25%)	0/404 (0%)	1/403 (0.25%)
# 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	VI 25 µg	UMEC/VI 125/25 µg
Total # participants affected/at risk	63/275 (22.91%)	97/407 (23.83%)	113/404 (27.97%)	102/403 (25.31%)

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
General disorders				
Pyrexia †[A]				
# participants affected/at risk	7/275 (2.55%)	9/407 (2.21%)	9/404 (2.23%)	13/403 (3.23%)
# events				
Infections and infestations				
Nasopharyngitis †[A]				
# participants affected/at risk	32/275 (11.64%)	37/407 (9.09%)	55/404 (13.61%)	47/403 (11.66%)
# events				
Musculoskeletal and connective tissue disorders				
Back pain †[A]				
# participants affected/at risk	13/275 (4.73%)	17/407 (4.18%)	10/404 (2.48%)	10/403 (2.48%)
# events				
Nervous system disorders				
Headache †[A]				
# participants affected/at risk	31/275 (11.27%)	37/407 (9.09%)	41/404 (10.15%)	41/403 (10.17%)

	Placebo	UMEC 125 µg	VI 25 µg	UMEC/VI 125/25 µg
# events				
Respiratory, thoracic and mediastinal disorders				
Cough † [A]				
# participants affected/at risk	16/275 (5.82%)	15/407 (3.69%)	18/404 (4.46%)	29/403 (7.2%)
# events				
Dyspnoea † [A]				
# participants affected/at risk	9/275 (3.27%)	5/407 (1.23%)	10/404 (2.48%)	4/403 (0.99%)
# 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

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