Protocol Registration Receipt
01/16/2014

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

A 24-week Evaluation of GSK573719/Vilanterol (62.5/25mcg) and Components in COPD (DB2113373)

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT01313650

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: 62.5/25mcg Drug: 62.5mcg Drug: 25mcg Drug: Placebo	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 Once-Daily 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: 1538
Study Start Date: March 2011
Study Completion Date: March 2012
Primary Completion Date: March 2012

Arms	Assigned Interventions
Experimental: GSK573719/GW642444 62.5/25mcg	Drug: 62.5/25mcg GSK573719/GW64244
Experimental: GSK573719 62.5mcg	Drug: 62.5mcg GSK573719
Experimental: GW642444 25mcg	Drug: 25mcg GW642444

Arms	Assigned Interventions
Placebo Comparator: Placebo Placebo	Drug: Placebo 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 adequate controlled
- Significant allergy or hypersensitivity to anticholinergics, beta-agonist, 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 GW64244

Contacts and Locations

Locations

United States, Arizona

GSK Investigational Site

Tucson, Arizona, United States, 85723

United States, California

GSK Investigational Site

Los Angeles, California, United States, 90048

United States, Florida

GSK Investigational Site

Ormond Beach, Florida, United States, 32174

GSK Investigational Site

Tampa, Florida, United States, 33603

United States, Georgia

GSK Investigational Site

Atlanta, Georgia, United States, 30342

GSK Investigational Site

Lawrenceville, Georgia, United States, 30046

United States, Idaho

GSK Investigational Site

Coeur D'Alene, Idaho, United States, 83814

United States, Indiana

GSK Investigational Site

Lafayette, Indiana, United States, 47904

United States, Kansas

GSK Investigational Site

Olathe, Kansas, United States, 66061

GSK Investigational Site

Topeka, Kansas, United States, 66606

United States, Kentucky

GSK Investigational Site

Madisonville, Kentucky, United States, 42431

United States, Louisiana

GSK Investigational Site

New Orleans, Louisiana, United States, 70115

GSK Investigational Site

Sunset, Louisiana, United States, 70584

United States, Michigan

GSK Investigational Site

Cadillac, Michigan, United States, 49601

United States, Missouri

GSK Investigational Site

St. Louis, Missouri, United States, 63141

GSK Investigational Site

St. Louis, Missouri, United States, 63141

United States, Nebraska

GSK Investigational Site

Omaha, Nebraska, United States, 68134

United States, New Mexico

GSK Investigational Site

Albuquerque, New Mexico, United States, 87108

United States, New York

GSK Investigational Site

Larchmont, New York, United States, 10538

United States, Ohio

GSK Investigational Site

Cincinnati, Ohio, United States, 45245

GSK Investigational Site

Cincinnati, Ohio, United States, 45231

GSK Investigational Site

Columbus, Ohio, United States, 43215

GSK Investigational Site

Dayton, Ohio, United States, 45459

United States, Oregon

GSK Investigational Site

Medford, Oregon, United States, 97504

United States, Pennsylvania

GSK Investigational Site

Beaver, Pennsylvania, United States, 15009

GSK Investigational Site

Erie, Pennsylvania, United States, 16508

GSK Investigational Site

Phoenixville, Pennsylvania, United States, 19460

United States, South Carolina

GSK Investigational Site

Gaffney, South Carolina, United States, 29340

GSK Investigational Site

Greenville, South Carolina, United States, 29615

GSK Investigational Site

Pelzer, South Carolina, United States, 29669

GSK Investigational Site

Spartanburg, South Carolina, United States, 29303

United States, South Dakota

GSK Investigational Site

Rapid City, South Dakota, United States, 57702

United States, Tennessee

GSK Investigational Site

Johnson City, Tennessee, United States, 37601

United States, Texas

GSK Investigational Site

Houston, Texas, United States, 77030

GSK Investigational Site

Houston, Texas, United States, 77030

GSK Investigational Site

Kingwood, Texas, United States, 77339

United States, Virginia

GSK Investigational Site

Abingdon, Virginia, United States, 24210

GSK Investigational Site

Newport News, Virginia, United States, 23606

GSK Investigational Site

Richmond, Virginia, United States, 23249

Bulgaria

GSK Investigational Site

Dimitrovgrad, Bulgaria, 6400

GSK Investigational Site

Pleven, Bulgaria, 5800

GSK Investigational Site

Plovdiv, Bulgaria, 4000

GSK Investigational Site

Ruse, Bulgaria, 7000

GSK Investigational Site

Sofia, Bulgaria

GSK Investigational Site

Sofia, Bulgaria, 1202

GSK Investigational Site

Sofia, Bulgaria, 1431

GSK Investigational Site

Sofia, Bulgaria, 1000

GSK Investigational Site

Troyan, Bulgaria, 5600

GSK Investigational Site

Varna, Bulgaria, 9010

Canada, Alberta

GSK Investigational Site

Calgary, Alberta, Canada, T2N 4Z6

Canada, Manitoba

GSK Investigational Site

Winnipeg, Manitoba, Canada, R2K 3S8

Canada, Ontario

GSK Investigational Site

Burlington, Ontario, Canada, L7N 3V2

GSK Investigational Site

Grimsby, Ontario, Canada, L3M 1P3

GSK Investigational Site

Sarnia, Ontario, Canada, N7T 4X3

GSK Investigational Site

Toronto, Ontario, Canada, M5G 1N8

GSK Investigational Site

Toronto, Ontario, Canada, M9W 4L6

GSK Investigational Site

Toronto, Ontario, Canada, M3H 5S4

Canada, Quebec

GSK Investigational Site

Montreal, Quebec, Canada, H2R 1V6

GSK Investigational Site

Pointe-Claire, Quebec, Canada, H9R 3J1

GSK Investigational Site

Quebec, Quebec, Canada, G1V 4G5

GSK Investigational Site

Quebec, Quebec, Canada, G3K 2P8

GSK Investigational Site

St-Charles-Borromée, Quebec, Canada, J6E 6J2

GSK Investigational Site

Trois Rivières, Quebec, Canada, G8T 7A1

Chile

GSK Investigational Site

Talcahuano, Chile, 4270918

GSK Investigational Site

Viña del Mar, Chile, 2570017

GSK Investigational Site

Rancagua, Reg Del Libert Bern Ohiggins, Chile, 2841959

GSK Investigational Site

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

GSK Investigational Site

Santiago, Región Metro De Santiago, Chile

GSK Investigational Site

Santiago, Región Metro De Santiago, Chile

GSK Investigational Site

Santiago, Región Metro De Santiago, Chile, 8880465

GSK Investigational Site

Valparaiso, Valparaíso, Chile, 2341131

Czech Republic

GSK Investigational Site

Cesky Krumlov, Czech Republic, 381 01

GSK Investigational Site

Kralupy nad Vltavou, Czech Republic, 278 01

GSK Investigational Site

Kyjov, Czech Republic, 697 33

GSK Investigational Site

Lovosice, Czech Republic, 410 02

GSK Investigational Site

Novy Jicin, Czech Republic, 741 01

GSK Investigational Site

Olomouc, Czech Republic, 772 00

GSK Investigational Site

Plzen, Czech Republic, 301 00

GSK Investigational Site

Praha 5, Czech Republic, 150 00

GSK Investigational Site

Praha 5 - Radotin, Czech Republic, 153 00

GSK Investigational Site

Rokycany, Czech Republic, 337 01

GSK Investigational Site

Teplice, Czech Republic, 415 10

Greece

GSK Investigational Site

Athens, Greece, 115 27

GSK Investigational Site

Athens, Greece, 106 76

GSK Investigational Site
Athens, Greece, 151 26
GSK Investigational Site
Athens, Greece, 115 27
GSK Investigational Site
Haidari / Athens, Greece, 124 62
GSK Investigational Site
Heraklion, Crete, Greece, 71110
GSK Investigational Site
Larissa, Greece, 41110
GSK Investigational Site
Serres, Greece, 62100
GSK Investigational Site
Thessaloniki, Greece, 56429
GSK Investigational Site
Thessaloniki, Greece, 546 42

Japan

GSK Investigational Site
Fukushima, Japan, 963-8052
GSK Investigational Site
Hyogo, Japan, 672-8064
GSK Investigational Site
Ibaraki, Japan, 312-0057
GSK Investigational Site
Ibaraki, Japan, 311-3193
GSK Investigational Site
Kanagawa, Japan, 254-8502
GSK Investigational Site
Kumamoto, Japan, 861-1196
GSK Investigational Site
Kyoto, Japan, 602-8026
GSK Investigational Site
Osaka, Japan, 530-0001
GSK Investigational Site
Osaka, Japan, 558-8558

GSK Investigational Site
Saitama, Japan, 343-8555
GSK Investigational Site
Shimane, Japan, 690-8556
GSK Investigational Site
Shimane, Japan, 690-8506
GSK Investigational Site
Tokyo, Japan, 173-8610
GSK Investigational Site
Tokyo, Japan, 158-0083
GSK Investigational Site
Tokyo, Japan, 103-0027
GSK Investigational Site
Tokyo, Japan, 103-0028

Mexico

GSK Investigational Site
Guadalajara, Jalisco, Mexico, 44100
GSK Investigational Site
Zapopan, Jalisco, Mexico, 45040
GSK Investigational Site
Monterrey, Nuevo León, Mexico, 64020
GSK Investigational Site
Puebla, Pue, Puebla, Mexico, 72000

Poland

GSK Investigational Site
Bydgoszcz, Poland, 85-681
GSK Investigational Site
Gidle, Poland, 97-540
GSK Investigational Site
Grudziadz, Poland, 86-300
GSK Investigational Site
Ilawa, Poland, 14-200
GSK Investigational Site
Krakow, Poland, 31-023
GSK Investigational Site

Lomza, Poland, 18-400

GSK Investigational Site

Olsztyn, Poland, 10-357

GSK Investigational Site

Poznan, Poland, 60-569

GSK Investigational Site

Szczecin, Poland, 71-124

GSK Investigational Site

Warszawa, Poland, 01-456

Russian Federation

GSK Investigational Site

Arkhangelsk, Russian Federation, 153000

GSK Investigational Site

Barnaul, Russian Federation, 656 045

GSK Investigational Site

Blagoveshchensk, Russian Federation, 675000

GSK Investigational Site

Krasnoyarsk, Russian Federation, 660022

GSK Investigational Site

Moscow, Russian Federation, 105 229

GSK Investigational Site

Moscow, Russian Federation, 119620

GSK Investigational Site

Moscow, Russian Federation, 123182

GSK Investigational Site

Nizhniy Novgorod, Russian Federation, 603126

GSK Investigational Site

Novosibirsk, Russian Federation, 630087

GSK Investigational Site

Perm, Russian Federation, 614077

GSK Investigational Site

Pyatigorsk, Russian Federation, 357538

GSK Investigational Site

Saint-Petersburg, Russian Federation, 198260

GSK Investigational Site

Saint-Petersburg, Russian Federation, 194354

GSK Investigational Site

Saint-Petersburg, Russian Federation, 194354

GSK Investigational Site

Saratov, Russian Federation, 410028

GSK Investigational Site

Tomsk, Russian Federation, 634063

GSK Investigational Site

Ufa, Russian Federation, 450071

GSK Investigational Site

Yaroslavl, Russian Federation, 150062

South Africa

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

Newtown, South Africa, 2113

GSK Investigational Site

Somerset West, South Africa, 7130

GSK Investigational Site

Tygerberg, South Africa, 7505

GSK Investigational Site

Benoni, Gauteng, South Africa, 1501

GSK Investigational Site

Meyerspark, Gauteng, South Africa, 0184

Spain

GSK Investigational Site

Alicante, Spain, 03114

GSK Investigational Site

Badalona, Spain, 08916

GSK Investigational Site
Badalona / Barcelona, Spain
GSK Investigational Site
Barakaldo (Vizcaya), Spain, 48903
GSK Investigational Site
Centelles, Spain
GSK Investigational Site
Cáceres, Spain, 10003
GSK Investigational Site
Madrid, Spain, 28046
GSK Investigational Site
Palma de Mallorca, Spain, 07010
GSK Investigational Site
Pamplona, Spain, 31008
GSK Investigational Site
Pozuelo de Alarcón/Madrid, Spain, 28223
GSK Investigational Site
Salt (gerona), Spain, 17190
GSK Investigational Site
Sant Boi de Llobregat - Barcelona, Spain, 08830
GSK Investigational Site
Santander, Spain, 38008
GSK Investigational Site
Santiago de Compostela, Spain, 15706
GSK Investigational Site
Valencia, Spain, 46015

Thailand

GSK Investigational Site
Bangkok, Thailand, 10330
GSK Investigational Site
Bangkok, Thailand, 10400
GSK Investigational Site
Chiangmai, Thailand, 50200
GSK Investigational Site
Khon Kaen, Thailand, 40002

GSK Investigational Site
Nonthaburi, Thailand, 11000
GSK Investigational Site
Songkhla, Thailand, 90110

Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Responsible Party:	GlaxoSmithKline
Study ID Numbers:	113373
	2010-023349-32 [EudraCT Number]
Health Authority:	United States: Food and Drug Administration

---

Study Results

Participant Flow

Pre-Assignment Details

Participants (par.) who met eligibility criteria at Screening (Visit 1) completed a 7 to 10-day run-in period and were then randomized to a 24-week treatment (trt.) period. A total of 2210 participants were screened; 1536 participants were randomized and 1532 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 62.5 µg QD	Participants received umeclidinium bromide (UMEC) 62.5 micrograms (µg) QD via a DPI in the morning for 24 weeks.

	Description
VI 25 µg QD	Participants received vilanterol (VI) 25 µg QD via a DPI for 24 weeks.
UMEC/VI 62.5/25 µg QD	Participants received UMEC/VI 62.5/25 µg QD via a DPI in the morning for 24 weeks.

Overall Study

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
Started	280	418	421	413
Completed	204	324	318	332
Not Completed	76	94	103	81
Adverse Event	9	34	24	23
Lack of Efficacy	37	20	32	20
Lost to Follow-up	1	0	3	2
Withdrawal by Subject	16	20	15	15
Protocol Violation	4	7	5	6
Met Protocol-defined Stopping Criteria	9	13	24	15

Baseline Characteristics

Reporting Groups

	Description
Placebo	Participants received matching placebo QD via a DPI in the morning

	Description
	for 24 weeks.
UMEC 62.5 µg QD	Participants received UMEC 62.5 µg QD via a DPI in the morning for 24 weeks.
VI 25 µg QD	Participants received VI 25 µg QD via a DPI for 24 weeks.
UMEC/VI 62.5/25 µg QD	Participants received UMEC/VI 62.5/25 µg QD via a DPI in the morning for 24 weeks.

Baseline Measures

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	Total
Number of Participants	280	418	421	413	1532
Age, Continuous [units: Years] Mean (Standard Deviation)	62.2 (9.04)	64.0 (9.16)	62.7 (8.52)	63.1 (8.71)	63.1 (8.86)
Gender, Male/Female [units: Participants]					
Female	85	120	136	108	449
Male	195	298	285	305	1083
Race/Ethnicity, Customized [units: Participants]					
African American/African Heritage	9	14	9	15	47
American Indian or Alaska Native	1	3	5	0	9

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD	Total
Asian - Central/South Asian Heritage	0	0	1	1	2
Asian - East Asian Heritage	1	2	2	1	6
Asian - Japanese Heritage	12	18	18	20	68
Asian - South East Asian Heritage	9	15	13	13	50
Native Hawaiian or other Pacific Islander	0	0	0	1	1
White - White/Caucasian/European Heritage	237	354	363	348	1302
White - Mixed Race	0	0	1	0	1
Mixed Race	11	12	9	14	46

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 62.5 µg QD	Participants received UMEC 62.5 µg QD via a DPI in the morning for 24 weeks.
VI 25 µg QD	Participants received VI 25 µg QD via a DPI for 24 weeks.
UMEC/VI 62.5/25 µg QD	Participants received UMEC/VI 62.5/25 µg QD via a DPI in the morning for 24 weeks.

Measured Values

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
Number of Participants Analyzed	201	322	317	330
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)	0.004 (0.0158)	0.119 (0.0126)	0.076 (0.0127)	0.171 (0.0126)

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 62.5 µg QD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.115
95% Confidence Interval	0.076 to 0.155

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 62.5 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 QD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.072
95% Confidence Interval	0.032 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=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 62.5/25 µg QD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.167
95% Confidence Interval	0.128 to 0.207

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 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 62.5 µg QD, UMEC/VI 62.5/25 µg QD
Method	Mixed Models Analysis
P-Value	0.004
Other Estimated Parameter [Least squares mean difference]	0.052
95% Confidence Interval	0.017 to 0.087

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 minus UMEC 62.5 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 QD, UMEC/VI 62.5/25 µg QD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.095
95% Confidence Interval	0.060 to 0.130

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

[Not specified.]

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

[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 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 62.5 µg QD	Participants received UMEC 62.5 µg QD via a DPI in the morning for 24 weeks.
VI 25 µg QD	Participants received VI 25 µg QD via a DPI for 24 weeks.
UMEC/VI 62.5/25 µg QD	Participants received UMEC/VI 62.5/25 µg QD via a DPI in the morning for 24 weeks.

Measured Values

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
Number of Participants Analyzed	204	326	317	336

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
Mean Transition Dyspnea Index (TDI) Focal Score at Day 168 (Week 24) [units: Scores on a scale] Least Squares Mean (Standard Error)	1.2 (0.20)	2.2 (0.16)	2.1 (0.16)	2.4 (0.16)

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 62.5 µg QD	Participants received UMEC 62.5 µg QD via a DPI in the morning for 24 weeks.
VI 25 µg QD	Participants received VI 25 µg QD via a DPI for 24 weeks.
UMEC/VI 62.5/25 µg QD	Participants received UMEC/VI 62.5/25 µg QD via a DPI in the morning for 24 weeks.

Measured Values

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
Number of Participants Analyzed	206	319	311	333
Change From Baseline in Weighted Mean (WM) 0-6 Hour FEV1 Obtained Post-dose at Day 168 [units: Liters] Least Squares Mean (Standard Error)	0.001 (0.0158)	0.151 (0.0128)	0.123 (0.0128)	0.243 (0.0127)

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 62.5 µg QD	Participants received UMEC 62.5 µg QD via a DPI in the morning for 24 weeks.

	Description
VI 25 µg QD	Participants received VI 25 µg QD via a DPI for 24 weeks.
UMEC/VI 62.5/25 µg QD	Participants received UMEC/VI 62.5/25 µg QD via a DPI in the morning for 24 weeks.

Measured Values

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
Number of Participants Analyzed	125	209	202	230
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)	-0.06 (0.037)	-0.16 (0.029)	-0.21 (0.030)	-0.23 (0.029)

Reported Adverse Events

Reporting Groups

	Description
Placebo	Participants received matching placebo QD via a DPI in the morning for 24 weeks.
UMEC 62.5 µg QD	Participants received UMEC 62.5 µg QD via a DPI in the morning for 24 weeks.
VI 25 µg QD	Participants received VI 25 µg QD via a DPI for 24 weeks.
UMEC/VI 62.5/25 µg QD	Participants received UMEC/VI 62.5/25 µg QD via a DPI in the morning

	Description
	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 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
Total # participants affected/at risk	9/280 (3.21%)	27/418 (6.46%)	24/421 (5.7%)	21/413 (5.08%)
Blood and lymphatic system disorders				
Anaemia † [A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)
# events				
Lymph node pain † [A]				
# participants affected/at risk	1/280 (0.36%)	0/418 (0%)	0/421 (0%)	0/413 (0%)
# events				

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
Cardiac disorders				
Angina pectoris † [A]				
# participants affected/at risk	1/280 (0.36%)	0/418 (0%)	0/421 (0%)	0/413 (0%)
# events				
Angina unstable † [A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Atrial fibrillation † [A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	1/413 (0.24%)
# events				
Bradycardia † [A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Coronary artery disease † [A]				
# participants affected/at risk	0/280 (0%)	2/418 (0.48%)	1/421 (0.24%)	0/413 (0%)
# events				
Myocardial infarction † [A]				

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
# participants affected/at risk	0/280 (0%)	0/418 (0%)	0/421 (0%)	2/413 (0.48%)
# events				
Myocardial ischaemia † [A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	0/421 (0%)	1/413 (0.24%)
# events				
Supraventricular tachycardia † [A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)
# events				
Tachycardia † [A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Gastrointestinal disorders				
Appendix disorder † [A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
Diarrhoea † [A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Duodenal ulcer † [A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)
# events				
Gastric haemorrhage † [A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Gastric ulcer haemorrhage † [A]				
# participants affected/at risk	1/280 (0.36%)	0/418 (0%)	0/421 (0%)	0/413 (0%)
# events				
Gastrooesophageal reflux disease † [A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)
# events				
Inguinal hernia † [A]				

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
# participants affected/at risk	0/280 (0%)	0/418 (0%)	0/421 (0%)	1/413 (0.24%)
# events				
Irritable bowel syndrome †[A]				
# participants affected/at risk	1/280 (0.36%)	0/418 (0%)	0/421 (0%)	0/413 (0%)
# events				
Lower gastrointestinal haemorrhage †[A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)
# events				
Small intestinal obstruction †[A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	0/421 (0%)	1/413 (0.24%)
# events				
General disorders				
Sudden death †[A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)
# events				

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
Hepatobiliary disorders				
Biliary colic †[A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Cholecystitis acute †[A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)
# events				
Cholecystitis chronic †[A]				
# participants affected/at risk	0/280 (0%)	2/418 (0.48%)	0/421 (0%)	0/413 (0%)
# events				
Cholelithiasis †[A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Infections and infestations				
Bronchitis †[A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	2/413 (0.48%)

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
# events				
Bronchopneumonia † [A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)
# events				
Cellulitis † [A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Gangrene † [A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	0/421 (0%)	1/413 (0.24%)
# events				
Infective exacerbation of chronic obstructive airway disease † [A]				
# participants affected/at risk	0/280 (0%)	2/418 (0.48%)	0/421 (0%)	0/413 (0%)
# events				
Influenza † [A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)
# events				

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
Lung infection pseudomonal †[A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Pneumonia †[A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	2/413 (0.48%)
# events				
Staphylococcal infection †[A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Upper respiratory tract infection †[A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)
# events				
Injury, poisoning and procedural complications				
Alcohol poisoning †[A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
# events				
Ankle fracture † [A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Femur fracture † [A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	1/413 (0.24%)
# events				
Forearm fracture † [A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)
# events				
Hand fracture † [A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)
# events				
Joint dislocation † [A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)
# events				
Overdose † [A]				

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)
# events				
Investigations				
Electrocardiogram QT prolonged †[A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Troponin increased †[A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Musculoskeletal and connective tissue disorders				
Fracture nonunion †[A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Neoplasms benign, malignant and unspecified (incl cysts				

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
and polyps)				
Colon adenoma †[A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	0/421 (0%)	1/413 (0.24%)
# events				
Endometrial cancer stage III †[A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	0/421 (0%)	1/413 (0.24%)
# events				
Gastric cancer †[A]				
# participants affected/at risk	1/280 (0.36%)	0/418 (0%)	0/421 (0%)	0/413 (0%)
# events				
Lung neoplasm malignant †[A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	0/421 (0%)	1/413 (0.24%)
# events				
Nervous system disorders				
Cerebrovascular accident †[A]				

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
# participants affected/at risk	1/280 (0.36%)	0/418 (0%)	2/421 (0.48%)	0/413 (0%)
# events				
Encephalitis †[A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Syncope †[A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Psychiatric disorders				
Alcohol abuse †[A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)
# events				
Renal and urinary disorders				
Renal colic †[A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
Renal failure acute † [A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	1/421 (0.24%)	0/413 (0%)
# events				
Reproductive system and breast disorders				
Benign prostatic hyperplasia † [A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Menometrorrhagia † [A]				
# participants affected/at risk	1/280 (0.36%)	0/418 (0%)	0/421 (0%)	0/413 (0%)
# events				
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure † [A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	1/421 (0.24%)	0/413 (0%)
# events				
Chronic obstructive pulmonary				

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
disease † [A]				
# participants affected/at risk	3/280 (1.07%)	12/418 (2.87%)	8/421 (1.9%)	7/413 (1.69%)
# events				
Epistaxis † [A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Hypoventilation † [A]				
# participants affected/at risk	1/280 (0.36%)	0/418 (0%)	0/421 (0%)	0/413 (0%)
# events				
Pleurisy † [A]				
# participants affected/at risk	0/280 (0%)	0/418 (0%)	1/421 (0.24%)	0/413 (0%)
# events				
Respiratory acidosis † [A]				
# participants affected/at risk	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	0/413 (0%)
# events				
Respiratory failure † [A]				
# participants affected/at	0/280 (0%)	1/418 (0.24%)	0/421 (0%)	2/413 (0.48%)

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
risk				
# events				

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 3%

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
Total # participants affected/at risk	62/280 (22.14%)	96/418 (22.97%)	87/421 (20.67%)	93/413 (22.52%)
Infections and infestations				
Nasopharyngitis † [A]				
# participants affected/at risk	16/280 (5.71%)	29/418 (6.94%)	26/421 (6.18%)	39/413 (9.44%)
# events				
Upper respiratory tract infection † [A]				
# participants affected/at risk	14/280 (5%)	21/418 (5.02%)	17/421 (4.04%)	13/413 (3.15%)
# events				
Musculoskeletal and				

	Placebo	UMEC 62.5 µg QD	VI 25 µg QD	UMEC/VI 62.5/25 µg QD
connective tissue disorders				
Back pain †[A]				
# participants affected/at risk	7/280 (2.5%)	8/418 (1.91%)	7/421 (1.66%)	13/413 (3.15%)
# events				
Nervous system disorders				
Headache †[A]				
# participants affected/at risk	26/280 (9.29%)	32/418 (7.66%)	25/421 (5.94%)	35/413 (8.47%)
# events				
Respiratory, thoracic and mediastinal disorders				
Cough †[A]				
# participants affected/at risk	7/280 (2.5%)	16/418 (3.83%)	15/421 (3.56%)	6/413 (1.45%)
# events				
Oropharyngeal pain †[A]				
# participants affected/at risk	4/280 (1.43%)	6/418 (1.44%)	14/421 (3.33%)	13/413 (3.15%)
# 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: