Protocol Registration Receipt
01/16/2014

Grantor: CDER IND/IDE Number: 104,479 Serial Number:

GSK573719 Dose Ranging Study in Chronic Obstructive Pulmonary Disease

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	GlaxoSmithKline
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT00950807

Purpose

The study will evaluate the dose response, safety, and pharmacokinetics of GSK573719 compared with placebo in subjects with COPD.

Condition	Intervention	Phase
Pulmonary Disease, Chronic Obstructive	Drug: Tiotropium Drug: Placebo Drug: GSK573179	Phase 2

Study Type: Interventional

Study Design: Treatment, Crossover Assignment, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Randomized, Safety/Efficacy Study

Official Title: A Randomized, Double-Blind, Placebo-Controlled, 3-Way Cross-Over Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of GSK573719 Administered Once- and Twice-Daily in Subjects With COPD

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 15 of Each Treatment Period [Time Frame: Baseline and Day 15 of each treatment period (up to Study Day 71)] [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 on Treatment Day 15 is defined as the value obtained 24 hours after the morning dose administered on Day 14. Analysis were performed using a mixed model with covariates of mean Baseline, period Baseline, treatment and period as fixed effects and participant as a random effect. Baseline is the FEV1 value recorded pre-dose on Day 1 of each treatment period; mean Baseline is the mean of the Baselines for each participant and period Baseline is the difference between the Baseline and the mean Baseline in each treatment period for each participant. Change from Baseline for each treatment period is the trough FEV1 at Day 15 minus the Baseline value for that treatment period.

Secondary Outcome Measures:

- Change From Baseline (BL) in Weighted Mean FEV1 Over 0 to 24 Hours Obtained Post-dose on Day 14 of Each Treatment Period [Time Frame: Baseline and Day 14 of each treatment period (TP; up to Study Day 70)] [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 weighted mean 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 weighted mean FEV1 was calculated using 0-24 hour (h) post-dose measurements at Day 14 of each treatment period, which included pre-dose and post-dose 1, 3, 6, 9, 12, 13, 15, 18, 21 and 24 hours. Analysis performed using a mixed model with covariates mean BL, period BL, treatment and period as fixed effects and participant as a random effect. BL is the FEV1 value recorded pre-dose on Day 1 of each TP; mean BL is the mean of the BLs for each participant and period BL is the difference between the BL and the mean BL in each TP for each participant. Change from BL for each TP is the trough FEV1 at Day 15 minus the BL value for that TP.
- Change From Baseline (BL) in Serial FEV1 Over 0-28 Hours After the Morning Dose at Day 14 of Each Treatment Period [Time Frame: Baseline and Day (D) 14 of each treatment period (TP; up to Study Day 70)] [Designated as safety issue: No]

  Serial FEV1 for OQ dosing is recorded at the pre-AM dose (time 0 h) and at 1, 3, 6, 9, 12,13, 15, 18, 21, 24 and 28 hs after the AM dose on D 14. For BID dosing, the 12 h AM dose corresponds to the pre-PM dose, 13 h AM dose corresponds to the 1 h PM dose, 15 h AM dose corresponds to the 3 h PM dose, 18 h AM corresponds to the 6 h PM dose, 21 h AM dose corresponds to 9 h PM dose, 24 h AM dose corresponds to the 12 h PM dose and 28 h AM dose corresponds to the 16 h PM dose in the table. Analysis performed using a mixed model with covariates of mean BL, period BL, trt, period, time, time by period BL interaction, time by mean BL interaction and time by trt interaction as fixed effects and par. as a random effect. BL is the FEV1 value recorded pre-dose on D 1 of each TP; mean BL is the mean of the BLs for each par. and period BL is the difference between the BL and the mean BL in each TP for each par. Change from BL for each TP is the trough FEV1 at Day 15 minus the BL value for that TP.

Enrollment: 176
Study Start Date: September 2009
Study Completion Date: March 2010
Primary Completion Date: March 2010

Arms	Assigned Interventions
Placebo Comparator: Placebo Placebo	Drug: Placebo Inactive/ excipients only
Active Comparator: Tiotropium Tiotropium	Drug: Tiotropium long-acting muscarinic receptor antagonist; 18mcg once-daily
Experimental: Arm 1 GSK573719 1000mcg once daily	Drug: GSK573179 GSK573179 investigational drug
Experimental: Arm 2 GSK573719 500mcg once daily	Drug: GSK573179 GSK573179 investigational drug
Experimental: Arm 3 GSK573719 250mcg once daily	Drug: GSK573179 GSK573179 investigational drug
Experimental: Arm 4 GSK573719 125mcg once daily	Drug: GSK573179 GSK573179 investigational drug
Experimental: Arm 5 GSK573719 62.5 mcg once daily	Drug: GSK573179 GSK573179 investigational drug
Experimental: Arm 6 GSK573719 250mcg twice daily	Drug: GSK573179 GSK573179 investigational drug
Experimental: Arm 7	Drug: GSK573179

Arms	Assigned Interventions
GSK573719 125mcg twice daily	GSK573179 investigational drug
Experimental: Arm 8 GSK573719 62.5mcg twice daily	Drug: GSK573179 GSK573179 investigational drug

This is multicenter, randomized, double-blind, double-dummy, placebo-controlled, three-way cross-over, incomplete block design study to evaluation of 5 doses of GSK573719 administered once-daily and 3 doses of GSK573719 administered twice-daily over 14 days in subjects with COPD and will include tiotropium as an open-label active control. The pharmacokinetic profile of GSK573719 will also be evaluated.

Eligibility

Ages Eligible for Study: 40 Years to 80 Years
Genders Eligible for Study: Both

Inclusion Criteria:

- A signed and dated written informed consent prior to study participation
- Males or females of non-childbearing potential
- 40 to 80 years of age
- COPD diagnosis
- 10 pack-years history or greater of cigarette smoking
- Post-bronchodilator FEV1/FVC ratio of 0.70 or less
- Post-bronchodilator FEV1 of 35 to 70% of predicted normal

Exclusion Criteria:

- Asthma
- Other significant respiratory disorders besides COPD, including alpha-1 deficiency
- Previous lung resection surgery
- Use of oral steroids or antibiotics for a COPD exacerbation within 6 weeks of screening
- Hospitalization for COPD or pneumonia within 3 months of screening
- Any significant disease that would put subject at risk through study participation
- BMI greater than 35
- Pacemaker

- Significantly abnormal ECG, Holter, or clinical lab finding (including Hepatitis B or C)
- Cancer
- Allergy or hypersensitivity to anticholinergics or inhaler excipients
- Diseases that would contra-indicate the use of anticholinergics
- Use of oral corticosteroids within 6 weeks of screening
- Use of long-acting beta-agonists within 48 hours of screening
- Use of tiotropium within 14 days of screening
- Use of theophyllines or anti-leukotrienes within 48 hours of screening
- Use of short-acting bronchodilators within 4 to 6 hours of screening
- Use of investigational medicines within 30 days of screening
- Use of high dose inhaled corticosteroids
- Use of long-term oxygen therapy, CPAP or NIPPV
- Previous use of GSK573719

Contacts and Locations

Locations

United States, Arizona

GSK Investigational Site

Phoenix, Arizona, United States, 85013

United States, California

GSK Investigational Site

San Diego, California, United States, 92117

GSK Investigational Site

Upland, California, United States, 91786

United States, Ohio

GSK Investigational Site

Cincinnati, Ohio, United States, 45231

United States, South Carolina

GSK Investigational Site

Easley, South Carolina, United States, 29640

GSK Investigational Site

Gaffney, South Carolina, United States, 29340

GSK Investigational Site

Greenville, South Carolina, United States, 29615

GSK Investigational Site

Greenville, South Carolina, United States, 29615

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Seneca, South Carolina, United States, 29678

GSK Investigational Site

Spartanburg, South Carolina, United States, 29303

GSK Investigational Site

Union, South Carolina, United States, 29379

Germany

GSK Investigational Site

Berlin, Berlin, Germany, 10787

GSK Investigational Site

Berlin, Berlin, Germany, 13125

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Hamburg, Hamburg, Germany, 20253

GSK Investigational Site

Frankfurt, Hessen, Germany, 60596

GSK Investigational Site

Wiesbaden, Hessen, Germany, 65187

GSK Investigational Site

Hannover, Niedersachsen, Germany, 30159

GSK Investigational Site

Mainz, Rheinland-Pfalz, Germany, 55131

GSK Investigational Site

Magdeburg, Sachsen-Anhalt, Germany, 39112

GSK Investigational Site

Grosshansdorf, Schleswig-Holstein, Germany, 22927

Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Publications:

Donohue JF, Anzueto A, Brooks J, Crater G, Mehta R, Kalberg C. A randomized, double-blind, dose-ranging study of the novel LAMA GSK573719 in patients with COPD. [Respir Med]. 2012;106(7):970-979.

Responsible Party: GlaxoSmithKline
Study ID Numbers: 113073
Health Authority: Germany: Bundesinstitut für Arzneimittel und Medizinprodukte
United States: Food and Drug Administration
Europe: European Medicines Agency

Study Results

Participant Flow

Pre-Assignment Details

Participants (par.) who were eligible completed a 4- to 7-day Run-in period prior to randomization. The treatment (trt) phase was comprised of three 14-day trt periods. Par. were randomly assigned to receive a sequence of placebo and 2 of the 9 active trts over the trt phase. Participant Flow data are presented by treatment rather than sequence.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via dry powder inhaler (DPI) A and in the evening via DPI B for 14 days.
UMEC 62.5 µg QD	Participants received umeclidinium bromide (UMEC) 62.5 micrograms (µg) in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 125 µg QD	Participants received UMEC 125 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 250 µg QD	Participants received UMEC 250 µg in the morning via DPI A and

	Description
	placebo in the evening via DPI B for 14 days.
UMEC 500 µg QD	Participants received UMEC 500 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 1000 µg QD	Participants received UMEC 1000 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 62.5 µg BID	Participants received UMEC 62.5 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 125 µg BID	Participants received UMEC 125 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 250 µg BID	Participants received UMEC 250 µg in the morning via DPI A and in the evening via DPI B for 14 days.
Tiotropium 18 µg QD	Participants received tiotropium bromide 18 µg in the morning via the HandiHaler and placebo in the evening via DPI B for 14 days.

Treatment Period 1

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
Started	59	13	14	12	13	13
Completed	56	13	13	12	12	11
Not Completed	3	0	1	0	1	2
Lack of Efficacy	1	0	0	0	0	1
Protocol Violation	1	0	0	0	0	0

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
Lost to Follow-up	0	0	1	0	0	0
Withdrawal by Subject	1	0	0	0	1	0
Adverse Event	0	0	0	0	0	1

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tiotropium 18 µg QD
Started	12	14	13	13
Completed	12	14	12	13
Not Completed	0	0	1	0
Lack of Efficacy	0	0	0	0
Protocol Violation	0	0	0	0
Lost to Follow-up	0	0	0	0
Withdrawal by Subject	0	0	1	0
Adverse Event	0	0	0	0

Washout Period 1

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
Started	56	13	13	12	12	11
Completed	51 [1]	13 [2]	13 [3]	11 [4]	11 [5]	11 [6]
Not Completed	5	0	0	1	1	0
Lack of Efficacy	0	0	0	0	0	0
Withdrawal by Subject	0	0	0	0	0	0

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
Protocol-defined Stopping Criteria	3	0	0	0	0	0
Adverse Event	2	0	0	1	1	0

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

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

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

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

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

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

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tiotropium 18 µg QD
Started	12	14	12	13
Completed	10 [1]	13 [2]	11 [3]	13 [4]
Not Completed	2	1	1	0
Lack of Efficacy	1	0	0	0
Withdrawal by Subject	0	0	1	0
Protocol-defined Stopping Criteria	1	1	0	0
Adverse Event	0	0	0	0

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

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

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

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

Treatment Period 2

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
Started	53 [1]	13 [2]	10 [3]	13 [4]	13 [5]	10 [6]
Completed	51	12	10	12	13	9
Not Completed	2	1	0	1	0	1
Lack of Efficacy	1	0	0	0	0	0
Withdrawal by Subject	0	0	0	0	0	0
Protocol-defined Stopping Criteria	1	0	0	0	0	0
Adverse Event	0	1	0	1	0	1

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

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

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

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

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

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

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tiotropium 18 µg QD
Started	10 [1]	13 [2]	11 [3]	11 [4]
Completed	9	10	11	11
Not Completed	1	3	0	0

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tiotropium 18 µg QD
Lack of Efficacy	0	0	0	0
Withdrawal by Subject	1	2	0	0
Protocol-defined Stopping Criteria	0	0	0	0
Adverse Event	0	1	0	0

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

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

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

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

Washout Period 2

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
Started	51	12	10	12	13	9
Completed	47 [1]	11 [2]	10 [3]	11 [4]	12 [5]	9 [6]
Not Completed	4	1	0	1	1	0
Lack of Efficacy	1	0	0	0	0	0
Protocol-defined Stopping Criteria	0	1	0	0	1	0
Adverse Event	3	0	0	1	0	0

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

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

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

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

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

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

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tiotropium 18 µg QD
Started	9	10	11	11
Completed	8 [1]	9 [2]	11 [3]	11 [4]
Not Completed	1	1	0	0
Lack of Efficacy	0	0	0	0
Protocol-defined Stopping Criteria	1	1	0	0
Adverse Event	0	0	0	0

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

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

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

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

Treatment Period 3

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
Started	46 [1]	9 [2]	10 [3]	11 [4]	12 [5]	9 [6]
Completed	45	9	10	11	12	9
Not Completed	1	0	0	0	0	0
Withdrawal by Subject	0	0	0	0	0	0
Protocol-defined Stopping	1	0	0	0	0	0

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
Criteria						
Adverse Event	0	0	0	0	0	0

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

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

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

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

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

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

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tiotropium 18 µg QD
Started	12 [1]	10 [2]	9 [3]	11 [4]
Completed	11	9	9	10
Not Completed	1	1	0	1
Withdrawal by Subject	0	0	0	1
Protocol-defined Stopping Criteria	0	1	0	0
Adverse Event	1	0	0	0

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

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

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

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

Baseline Characteristics

Reporting Groups

	Description
All Study Treatments	The treatment phase was comprised of three 14-day treatment periods, each separated by a 10-14 day washout period. Participants were randomly assigned to receive a sequence of placebo and 2 of the 9 active treatments : UMEC 62.5, 125, 250, 500, and 1000 µg QD, UMEC 62.5, 125, and 250 µg BID, tiotropium 18 µg QD.

Baseline Measures

	All Study Treatments
Number of Participants	176
Age, Continuous [units: Years] Mean (Standard Deviation)	59.7 (8.12)
Gender, Male/Female [units: Participants]	
Female	75
Male	101
Race/Ethnicity, Customized [units: Participants]	
African American/African Heritage	4
White	172

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 15 of Each Treatment Period
Measure Description	FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. Trough FEV1 on Treatment Day 15 is defined as the value obtained 24 hours after the morning dose administered on Day 14. Analysis were performed using a mixed model with covariates of mean Baseline, period Baseline, treatment and period as fixed effects and participant as a random effect. Baseline is the FEV1 value recorded pre-dose on Day 1 of each treatment period; mean Baseline is the mean of the Baselines for each participant and period Baseline is the difference between the Baseline and the mean Baseline in each treatment period for each participant. Change from Baseline for each treatment period is the trough FEV1 at Day 15 minus the Baseline value for that treatment period.
Time Frame	Baseline and Day 15 of each treatment period (up to Study Day 71)
Safety Issue?	No

Analysis Population Description

Modified Intent-To-Treat (mITT) Population: all participants randomized to treatment who received at least one dose of study medication. All participants with >=1 post-baseline assessment and non-missing covariate data are included in the analysis. The number of participants represents participants who provided data at Day 15.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via dry powder

	Description
	inhaler (DPI) A and in the evening via DPI B for 14 days.
UMEC 62.5 µg QD	Participants received UMEC 62.5 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 125 µg QD	Participants received UMEC 125 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 250 µg QD	Participants received UMEC 250 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 500 µg QD	Participants received UMEC 500 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 1000 µg QD	Participants received UMEC 1000 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 62.5 µg BID	Participants received UMEC 62.5 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 125 µg BID	Participants received UMEC 125 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 250 µg BID	Participants received UMEC 250 µg in the morning via DPI A and in the evening via DPI B for 14 days.
Tio 18 µg QD	Participants received tiotropium bromide 18 µg in the morning via the HandiHaler and placebo in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
Number of Participants Analyzed	150	34	33	35	37	29
Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 15 of Each Treatment Period [units: Liters] Least Squares Mean (Standard Error)	-0.047 (0.017)	0.081 (0.033)	0.099 (0.034)	0.048 (0.033)	0.092 (0.032)	0.138 (0.036)

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tio 18 µg QD
Number of Participants Analyzed	31	33	32	34
Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 15 of Each Treatment Period [units: Liters] Least Squares Mean (Standard Error)	0.032 (0.035)	0.087 (0.034)	0.124 (0.034)	0.058 (0.033)

Statistical Analysis 1 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 15 of Each Treatment Period

Groups	Placebo, UMEC 62.5 µg QD
Method	Mixed Models Analysis
P-Value	<0.001
Mean Difference (Final Values)	0.128
95% Confidence Interval	0.060 to 0.196

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

[Not specified.]

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

statistical significance:

[Not specified.]

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

[Not specified.]

Statistical Analysis 2 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 15 of Each Treatment Period

Groups	Placebo, UMEC 125 µg QD
Method	Mixed Models Analysis
P-Value	<0.001
Mean Difference (Final Values)	0.147
95% Confidence Interval	0.077 to 0.216

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:

[Not specified.]

Statistical Analysis 3 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 15 of Each Treatment Period

Groups	Placebo, UMEC 250 µg QD
Method	Mixed Models Analysis
P-Value	0.006
Mean Difference (Final Values)	0.095
95% Confidence Interval	0.027 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:

[Not specified.]

Statistical Analysis 4 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 15 of Each Treatment Period

Groups	Placebo, UMEC 500 µg QD
Method	Mixed Models Analysis
P-Value	<0.001
Mean Difference (Final Values)	0.140
95% Confidence Interval	0.074 to 0.205

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:

[Not specified.]

Statistical Analysis 5 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 15 of Each Treatment Period

Groups	Placebo, UMEC 1000 µg QD
Method	Mixed Models Analysis
P-Value	<0.001

Mean Difference (Final Values)	0.186
95% Confidence Interval	0.113 to 0.259

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:

[Not specified.]

Statistical Analysis 6 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 15 of Each Treatment Period

Groups	Placebo, UMEC 62.5 µg BID
Method	Mixed Models Analysis
P-Value	0.030
Mean Difference (Final Values)	0.079
95% Confidence Interval	0.008 to 0.151

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:

[Not specified.]

Statistical Analysis 7 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 15 of Each Treatment Period

Groups	Placebo, UMEC 125 µg BID

Method	Mixed Models Analysis
P-Value	<0.001
Mean Difference (Final Values)	0.134
95% Confidence Interval	0.064 to 0.204

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:

[Not specified.]

Statistical Analysis 8 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 15 of Each Treatment Period

Groups	Placebo, UMEC 250 µg BID
Method	Mixed Models Analysis
P-Value	<0.001
Mean Difference (Final Values)	0.172
95% Confidence Interval	0.101 to 0.242

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:

[Not specified.]

Statistical Analysis 9 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 15 of Each Treatment Period

Groups	Placebo, Tio 18 µg QD
Method	Mixed Models Analysis
P-Value	0.003
Mean Difference (Final Values)	0.105
95% Confidence Interval	0.037 to 0.173

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:

[Not specified.]

2. Secondary Outcome Measure:

Measure Title	Change From Baseline (BL) in Weighted Mean FEV1 Over 0 to 24 Hours Obtained Post-dose on Day 14 of Each Treatment Period
Measure Description	FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. The weighted mean 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 weighted mean FEV1 was calculated using 0-24 hour (h) post-dose measurements at Day 14 of each treatment period, which included pre-dose and post-dose 1, 3, 6, 9, 12, 13, 15, 18, 21 and 24 hours. Analysis performed using a mixed model with covariates mean BL,

	period BL, treatment and period as fixed effects and participant as a random effect. BL is the FEV1 value recorded pre-dose on Day 1 of each TP; mean BL is the mean of the BLs for each participant and period BL is the difference between the BL and the mean BL in each TP for each participant. Change from BL for each TP is the trough FEV1 at Day 15 minus the BL value for that TP.
Time Frame	Baseline and Day 14 of each treatment period (TP; up to Study Day 70)
Safety Issue?	No

Analysis Population Description

mITT Population. All participants with >=1 post-Baseline assessment and non-missing covariate data are included in the analysis. The number of participants represents participants who provided data at Day 14.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via dry powder inhaler (DPI) A and in the evening via DPI B for 14 days.
UMEC 62.5 µg QD	Participants received UMEC 62.5 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 125 µg QD	Participants received UMEC 125 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 250 µg QD	Participants received UMEC 250 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 500 µg QD	Participants received UMEC 500 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 1000 µg QD	Participants received UMEC 1000 µg in the morning via DPI A and

	Description
	placebo in the evening via DPI B for 14 days.
UMEC 62.5 µg BID	Participants received UMEC 62.5 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 125 µg BID	Participants received UMEC 125 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 250 µg BID	Participants received UMEC 250 µg in the morning via DPI A and in the evening via DPI B for 14 days.
Tio 18 µg QD	Participants received tiotropium bromide 18 µg in the morning via the HandiHaler and placebo in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
Number of Participants Analyzed	143	33	33	34	36	29
Change From Baseline (BL) in Weighted Mean FEV1 Over 0 to 24 Hours Obtained Post-dose on Day 14 of Each Treatment Period [units: Liters] Least Squares Mean (Standard Error)	-0.059 (0.014)	0.085 (0.025)	0.077 (0.025)	0.077 (0.025)	0.072 (0.024)	0.080 (0.027)

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tio 18 µg QD
Number of Participants Analyzed	30	32	31	33
Change From Baseline (BL) in Weighted Mean FEV1 Over 0 to 24 Hours Obtained	0.062 (0.026)	0.083 (0.025)	0.075 (0.026)	0.069 (0.025)

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tio 18 µg QD
Post-dose on Day 14 of Each Treatment Period [units: Liters] Least Squares Mean (Standard Error)				

3. Secondary Outcome Measure:

Measure Title	Change From Baseline (BL) in Serial FEV1 Over 0-28 Hours After the Morning Dose at Day 14 of Each Treatment Period
Measure Description	Serial FEV1 for OQ dosing is recorded at the pre-AM dose (time 0 h) and at 1, 3, 6, 9, 12,13, 15, 18, 21, 24 and 28 hs after the AM dose on D 14. For BID dosing, the 12 h AM dose corresponds to the pre-PM dose, 13 h AM dose corresponds to the 1 h PM dose, 15 h AM dose corresponds to the 3 h PM dose, 18 h AM corresponds to the 6 h PM dose, 21 h AM dose corresponds to 9 h PM dose, 24 h AM dose corresponds to the 12 h PM dose and 28 h AM dose corresponds to the 16 h PM dose in the table. Analysis performed using a mixed model with covariates of mean BL, period BL, trt, period, time, time by period BL interaction, time by mean BL interaction and time by trt interaction as fixed effects and par. as a random effect. BL is the FEV1 value recorded pre-dose on D 1 of each TP; mean BL is the mean of the BLs for each par. and period BL is the difference between the BL and the mean BL in each TP for each par. Change from BL for each TP is the trough FEV1 at Day 15 minus the BL value for that TP.
Time Frame	Baseline and Day (D) 14 of each treatment period (TP; up to Study Day 70)
Safety Issue?	No

Analysis Population Description

mITT Population. All par. with >=1 post-BL assessment and non-missing covariate data are included in the analysis. Different par. may have been analyzed at different time points (n=X, X, X, X in the category titles), so the overall number of par. analyzed reflects everyone in the mITT Population with data available at >=1 time point.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via dry powder inhaler (DPI) A and in the evening via DPI B for 14 days.
UMEC 62.5 µg QD	Participants received UMEC 62.5 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 125 µg QD	Participants received UMEC 125 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 250 µg QD	Participants received UMEC 250 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 500 µg QD	Participants received UMEC 500 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 1000 µg QD	Participants received UMEC 1000 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 62.5 µg BID	Participants received UMEC 62.5 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 125 µg BID	Participants received UMEC 125 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 250 µg BID	Participants received UMEC 250 µg in the morning via DPI A and in the evening via DPI B for 14 days.

	Description
Tio 18 µg QD	Participants received tiotropium bromide 18 µg in the morning via the HandiHaler and placebo in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
Number of Participants Analyzed	152	34	33	35	37	30
Change From Baseline (BL) in Serial FEV1 Over 0-28 Hours After the Morning Dose at Day 14 of Each Treatment Period [units: Liters] Mean (Standard Deviation)						
Pre-AM dose, n=152,34,33,35,37,30,32,33,32,34	-0.002 (0.016)	0.140 (0.031)	0.101 (0.032)	0.167 (0.031)	0.095 (0.030)	0.120 (0.033)
1 hour AM, n=151,34,31,35,37,29,32,33,32,34	0.022 (0.018)	0.246 (0.035)	0.164 (0.037)	0.140 (0.035)	0.056 (0.034)	0.072 (0.038)
3 hour AM, n=150,34,32,35,37,29,31,33,32,34	-0.003 (0.017)	0.157 (0.034)	0.158 (0.035)	0.222 (0.034)	0.142 (0.033)	0.148 (0.037)
6 hour AM, n=151,34,33,35,37,30,32,33,31,34	-0.019 (0.016)	0.137 (0.031)	0.114 (0.032)	0.149 (0.031)	0.120 (0.030)	0.105 (0.034)
9 hour AM, n=149,33,33,34,37,30,31,32,32,33	-0.033 (0.016)	0.121 (0.033)	0.077 (0.033)	0.123 (0.032)	0.118 (0.031)	0.076 (0.035)
12 hour AM, n=150,34,33,34,37,30,31,32,32,33	-0.068 (0.018)	0.087 (0.035)	0.083 (0.036)	0.084 (0.035)	0.096 (0.034)	0.074 (0.038)
13 hour AM, n=147,33,33,35,37,29,31,33,32,33	-0.082 (0.016)	0.071 (0.031)	0.077 (0.031)	0.071 (0.031)	0.103 (0.030)	0.096 (0.033)
15 hour AM,	-0.085 (0.016)	0.074 (0.031)	0.051 (0.032)	0.069 (0.031)	0.038 (0.030)	0.050 (0.033)

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
n=151,34,33,35,37,29,30,33,32,34						
18 hour AM, n=148,33,33,35,36,29,31,33,32,34	-0.145 (0.016)	-0.053 (0.033)	0.002 (0.033)	-0.018 (0.032)	-0.007 (0.031)	0.001 (0.035)
21 hour AM, n=150,34,33,35,37,29,29,33,32,34	-0.147 (0.017)	0.009 (0.034)	0.035 (0.034)	-0.036 (0.034)	0.004 (0.033)	0.006 (0.037)
24 hour AM, n=150,34,33,35,37,29,31,33,32,34	-0.051 (0.017)	0.067 (0.033)	0.093 (0.034)	0.045 (0.033)	0.088 (0.032)	0.142 (0.036)
28 hour AM, n=145,34,33,35,37,29,31,33,32,34	0.065 (0.018)	0.179 (0.035)	0.177 (0.036)	0.212 (0.035)	0.143 (0.034)	0.191 (0.038)

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tio 18 µg QD
Number of Participants Analyzed	32	33	32	34
Change From Baseline (BL) in Serial FEV1 Over 0-28 Hours After the Morning Dose at Day 14 of Each Treatment Period [units: Liters] Mean (Standard Deviation)				
Pre-AM dose, n=152,34,33,35,37,30,32,33,32,34	0.096 (0.032)	0.139 (0.032)	0.152 (0.032)	0.129 (0.031)
1 hour AM, n=151,34,31,35,37,29,32,33,32,34	0.159 (0.037)	0.132 (0.036)	0.142 (0.037)	0.229 (0.036)
3 hour AM, n=150,34,32,35,37,29,31,33,32,34	0.153 (0.036)	0.112 (0.035)	0.153 (0.036)	0.191 (0.035)
6 hour AM, n=151,34,33,35,37,30,32,33,31,34	0.090 (0.033)	0.100 (0.032)	0.141 (0.033)	0.152 (0.032)

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tio 18 µg QD
9 hour AM, n=149,33,33,34,37,30,31,32,32,33	0.105 (0.034)	0.104 (0.033)	0.099 (0.034)	0.105 (0.033)
12 hour AM, n=150,34,33,34,37,30,31,32,32,33	0.058 (0.037)	0.099 (0.036)	0.074 (0.036)	0.153 (0.036)
13 hour AM, n=147,33,33,35,37,29,31,33,32,33	0.066 (0.032)	0.018 (0.032)	0.048 (0.032)	0.065 (0.031)
15 hour AM, n=151,34,33,35,37,29,30,33,32,34	0.085 (0.033)	0.054 (0.032)	0.096 (0.032)	0.036 (0.031)
18 hour AM, n=148,33,33,35,36,29,31,33,32,34	-0.020 (0.034)	0.016 (0.033)	-0.048 (0.033)	-0.097 (0.032)
21 hour AM, n=150,34,33,35,37,29,29,33,32,34	-0.059 (0.036)	0.029 (0.035)	-0.005 (0.035)	-0.060 (0.034)
24 hour AM, n=150,34,33,35,37,29,31,33,32,34	0.021 (0.035)	0.091 (0.034)	0.139 (0.035)	0.047 (0.033)
28 hour AM, n=145,34,33,35,37,29,31,33,32,34	0.164 (0.037)	0.219 (0.036)	0.185 (0.037)	0.108 (0.035)

Reported Adverse Events

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via dry powder inhaler (DPI) A and in the evening via DPI B for 14 days.
UMEC 62.5 µg QD	Participants received UMEC 62.5 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.

	Description
UMEC 125 µg QD	Participants received UMEC 125 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 250 µg QD	Participants received UMEC 250 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 500 µg QD	Participants received UMEC 500 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 1000 µg QD	Participants received UMEC 1000 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 62.5 µg BID	Participants received UMEC 62.5 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 125 µg BID	Participants received UMEC 125 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 250 µg BID	Participants received UMEC 250 µg in the morning via DPI A and in the evening via DPI B for 14 days.
Tio 18 µg QD	Participants received tiotropium bromide 18 µg in the morning via the HandiHaler and placebo in the evening via DPI B for 14 days.

Time Frame

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of study medication up to 10 weeks.

Additional Description

On-treatment AEs and non-serious AEs are reported for members of the mITT Population, comprised of all participants who were randomized to treatment and who had received at least one dose of randomized study medication during treatment period.

Serious Adverse Events

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
Total # participants affected/at risk	0/158 (0%)	0/35 (0%)	0/34 (0%)	2/36 (5.56%)	0/38 (0%)	0/32 (0%)
Injury, poisoning and procedural complications						
Concussion † [A]						
# participants affected/at risk	0/158 (0%)	0/35 (0%)	0/34 (0%)	1/36 (2.78%)	0/38 (0%)	0/32 (0%)
# events						
Respiratory, thoracic and mediastinal disorders						
Chronic obstructive pulmonary disease † [A]						
# participants affected/at risk	0/158 (0%)	0/35 (0%)	0/34 (0%)	1/36 (2.78%)	0/38 (0%)	0/32 (0%)
# events						

† Indicates events were collected by systematic assessment.

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	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tio 18 µg QD
Total # participants affected/at risk	0/34 (0%)	1/37 (2.7%)	0/33 (0%)	0/35 (0%)
Injury, poisoning and procedural complications				

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tio 18 µg QD
Concussion † [A]				
# participants affected/at risk	0/34 (0%)	0/37 (0%)	0/33 (0%)	0/35 (0%)
# events				
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease † [A]				
# participants affected/at risk	0/34 (0%)	1/37 (2.7%)	0/33 (0%)	0/35 (0%)
# events				

† Indicates events were collected by systematic assessment.

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Other Adverse Events

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

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
Total # participants affected/at risk	11/158 (6.96%)	2/35 (5.71%)	3/34 (8.82%)	8/36 (22.22%)	9/38 (23.68%)	13/32 (40.62%)
Blood and lymphatic system disorders						
Thrombocytosis † [A]						
# participants affected/at risk	0/158 (0%)	0/35 (0%)	0/34 (0%)	0/36 (0%)	0/38 (0%)	1/32 (3.12%)

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
# events						
Gastrointestinal disorders						
Dry mouth † [A]						
# participants affected/at risk	1/158 (0.63%)	0/35 (0%)	0/34 (0%)	0/36 (0%)	1/38 (2.63%)	2/32 (6.25%)
# events						
Nausea † [A]						
# participants affected/at risk	0/158 (0%)	0/35 (0%)	0/34 (0%)	0/36 (0%)	0/38 (0%)	0/32 (0%)
# events						
Infections and infestations						
Cystitis † [A]						
# participants affected/at risk	0/158 (0%)	0/35 (0%)	0/34 (0%)	0/36 (0%)	0/38 (0%)	0/32 (0%)
# events						
Nasopharyngitis † [A]						
# participants affected/at risk	2/158 (1.27%)	0/35 (0%)	0/34 (0%)	2/36 (5.56%)	0/38 (0%)	4/32 (12.5%)
# events						
Upper respiratory tract infection † [A]						

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
# participants affected/at risk	1/158 (0.63%)	0/35 (0%)	0/34 (0%)	0/36 (0%)	0/38 (0%)	0/32 (0%)
# events						
Injury, poisoning and procedural complications						
Joint sprain † [A]						
# participants affected/at risk	0/158 (0%)	0/35 (0%)	0/34 (0%)	0/36 (0%)	0/38 (0%)	0/32 (0%)
# events						
Investigations						
Blood potassium increased † [A]						
# participants affected/at risk	0/158 (0%)	0/35 (0%)	0/34 (0%)	0/36 (0%)	0/38 (0%)	0/32 (0%)
# events						
Metabolism and nutrition disorders						
Hyperkalaemia † [A]						
# participants affected/at risk	0/158 (0%)	0/35 (0%)	0/34 (0%)	0/36 (0%)	0/38 (0%)	1/32 (3.12%)
# events						
Musculoskeletal and connective tissue						

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
disorders						
Arthralgia †[A]						
# participants affected/at risk	0/158 (0%)	0/35 (0%)	0/34 (0%)	0/36 (0%)	0/38 (0%)	1/32 (3.12%)
# events						
Pain in extremity †[A]						
# participants affected/at risk	0/158 (0%)	0/35 (0%)	0/34 (0%)	0/36 (0%)	0/38 (0%)	1/32 (3.12%)
# events						
Nervous system disorders						
Dysgeusia †[A]						
# participants affected/at risk	0/158 (0%)	0/35 (0%)	0/34 (0%)	2/36 (5.56%)	0/38 (0%)	2/32 (6.25%)
# events						
Headache †[A]						
# participants affected/at risk	4/158 (2.53%)	1/35 (2.86%)	1/34 (2.94%)	3/36 (8.33%)	1/38 (2.63%)	2/32 (6.25%)
# events						
Migraine †[A]						
# participants affected/at risk	0/158 (0%)	0/35 (0%)	0/34 (0%)	0/36 (0%)	0/38 (0%)	0/32 (0%)
# events						

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
Respiratory, thoracic and mediastinal disorders						
Chronic obstructive pulmonary disease † [A]						
# participants affected/at risk	0/158 (0%)	0/35 (0%)	0/34 (0%)	0/36 (0%)	0/38 (0%)	1/32 (3.12%)
# events						
Cough † [A]						
# participants affected/at risk	1/158 (0.63%)	1/35 (2.86%)	0/34 (0%)	1/36 (2.78%)	4/38 (10.53%)	2/32 (6.25%)
# events						
Dysphonia † [A]						
# participants affected/at risk	1/158 (0.63%)	0/35 (0%)	0/34 (0%)	0/36 (0%)	0/38 (0%)	0/32 (0%)
# events						
Dyspnoea † [A]						
# participants affected/at risk	1/158 (0.63%)	0/35 (0%)	0/34 (0%)	0/36 (0%)	1/38 (2.63%)	1/32 (3.12%)
# events						
Oropharyngeal pain † [A]						
# participants affected/at risk	2/158 (1.27%)	0/35 (0%)	0/34 (0%)	0/36 (0%)	1/38 (2.63%)	0/32 (0%)
# events						

	Placebo	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD	UMEC 500 µg QD	UMEC 1000 µg QD
Rhinitis allergic † [A]						
# participants affected/at risk	1/158 (0.63%)	0/35 (0%)	0/34 (0%)	0/36 (0%)	1/38 (2.63%)	1/32 (3.12%)
# events						
Vascular disorders						
Hypertension † [A]						
# participants affected/at risk	0/158 (0%)	0/35 (0%)	2/34 (5.88%)	1/36 (2.78%)	0/38 (0%)	0/32 (0%)
# events						

† Indicates events were collected by systematic assessment.

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	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tio 18 µg QD
Total # participants affected/at risk	4/34 (11.76%)	4/37 (10.81%)	10/33 (30.3%)	3/35 (8.57%)
Blood and lymphatic system disorders				
Thrombocytosis † [A]				
# participants affected/at risk	0/34 (0%)	0/37 (0%)	0/33 (0%)	0/35 (0%)
# events				
Gastrointestinal disorders				

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tio 18 µg QD
Dry mouth † [A]				
# participants affected/at risk	0/34 (0%)	1/37 (2.7%)	3/33 (9.09%)	1/35 (2.86%)
# events				
Nausea † [A]				
# participants affected/at risk	1/34 (2.94%)	0/37 (0%)	1/33 (3.03%)	0/35 (0%)
# events				
Infections and infestations				
Cystitis † [A]				
# participants affected/at risk	0/34 (0%)	1/37 (2.7%)	1/33 (3.03%)	0/35 (0%)
# events				
Nasopharyngitis † [A]				
# participants affected/at risk	2/34 (5.88%)	0/37 (0%)	0/33 (0%)	0/35 (0%)
# events				
Upper respiratory tract infection † [A]				
# participants affected/at risk	0/34 (0%)	0/37 (0%)	1/33 (3.03%)	0/35 (0%)
# events				

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tio 18 µg QD
Injury, poisoning and procedural complications				
Joint sprain † [A]				
# participants affected/at risk	0/34 (0%)	0/37 (0%)	1/33 (3.03%)	0/35 (0%)
# events				
Investigations				
Blood potassium increased † [A]				
# participants affected/at risk	0/34 (0%)	0/37 (0%)	1/33 (3.03%)	0/35 (0%)
# events				
Metabolism and nutrition disorders				
Hyperkalaemia † [A]				
# participants affected/at risk	0/34 (0%)	0/37 (0%)	0/33 (0%)	0/35 (0%)
# events				
Musculoskeletal and connective tissue disorders				
Arthralgia † [A]				
# participants affected/at	0/34 (0%)	0/37 (0%)	0/33 (0%)	0/35 (0%)

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tio 18 µg QD
risk				
# events				
Pain in extremity † [A]				
# participants affected/at risk	0/34 (0%)	0/37 (0%)	0/33 (0%)	0/35 (0%)
# events				
Nervous system disorders				
Dysgeusia † [A]				
# participants affected/at risk	1/34 (2.94%)	0/37 (0%)	2/33 (6.06%)	0/35 (0%)
# events				
Headache † [A]				
# participants affected/at risk	0/34 (0%)	1/37 (2.7%)	3/33 (9.09%)	2/35 (5.71%)
# events				
Migraine † [A]				
# participants affected/at risk	0/34 (0%)	0/37 (0%)	1/33 (3.03%)	0/35 (0%)
# events				
Respiratory, thoracic and mediastinal disorders				

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tio 18 µg QD
Chronic obstructive pulmonary disease †[A]				
# participants affected/at risk	0/34 (0%)	0/37 (0%)	0/33 (0%)	0/35 (0%)
# events				
Cough †[A]				
# participants affected/at risk	0/34 (0%)	0/37 (0%)	2/33 (6.06%)	0/35 (0%)
# events				
Dysphonia †[A]				
# participants affected/at risk	0/34 (0%)	2/37 (5.41%)	0/33 (0%)	0/35 (0%)
# events				
Dyspnoea †[A]				
# participants affected/at risk	0/34 (0%)	0/37 (0%)	0/33 (0%)	0/35 (0%)
# events				
Oropharyngeal pain †[A]				
# participants affected/at risk	0/34 (0%)	1/37 (2.7%)	2/33 (6.06%)	0/35 (0%)
# events				
Rhinitis allergic †[A]				
# participants affected/at	0/34 (0%)	0/37 (0%)	0/33 (0%)	0/35 (0%)

	UMEC 62.5 µg BID	UMEC 125 µg BID	UMEC 250 µg BID	Tio 18 µg QD
risk				
# events				
Vascular disorders				
Hypertension † [A]				
# participants affected/at risk	0/34 (0%)	0/37 (0%)	0/33 (0%)	0/35 (0%)
# 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: