Protocol Registration Receipt
08/18/2014

Grantor: CDER IND/IDE Number: 104479 Serial Number:

A 3-period Crossover Study With GSK573719 as Monotherapy in Adult Subjects With Asthma

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT01641692

Purpose

This is a multi-national, randomized, double-blind, 3-period crossover, incomplete block design to evaluate 5 once-daily and 2 twice-daily doses of GSK573719 in combination with placebo. The study will explore the dose range of GSK573719 in asthmatic subjects who are currently using non-ICS controller medications. Subjects will participate in the study for up to a maximum of 14 weeks. At randomization subjects will be stratified by age to ensure adequate exposure to GSK573719 throughout the expected age range. The primary endpoint will be trough FEV1 obtained 24 hours after the last morning dose on Day 14 of each treatment sequence.

A sub-group of subjects at selected sites (approximately 30% of the total population) will have additional serial assessments for spirometry, ECG and Holter, and pharmacokinetic sampling at the start and end of each treatment period. Safety assessments will include monitoring for adverse events, laboratory tests, asthma

symptom assessments and twice daily PEF evaluation. Consenting subjects will have a blood sample taken for pharmacogenetic analysis.

Condition	Intervention	Phase
Asthma	Drug: GSK573719 Active treatment or Placebo Procedure/Surgery: GSK573719 (Sub-group cohort) Drug: Salbutamol/Albuterol	Phase 2

Study Type: Interventional
Study Design: Treatment, Crossover Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study
Official Title: A Multi-national, Randomized, Double-blind, Placebo-controlled, 3-period Crossover Study With GSK 573719 as Monotherapy in Adult Subjects With Asthma

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Final Dose-response Model for Trough Forced Expiratory Volume in One Second (FEV1) [Time Frame: Day 15 of each treatment period (up to Study Day 71)] [Designated as safety issue: No]

  Dose-response was conducted for both QD and BID UMEC doses on trough FEV1 (measure of lung function, defined as the maximal amount of air that can be forcefully exhaled in 1 second) on D 15. Total daily dose of UMEC was used in the modeling. The null model was the final model. The null model is defined as: CFEV1,ij=(THETA1+ETA1j)*meanBL+(THETA2+ETA1j)*periodBL+EPSij, where CFEV1,ij represents the change from BL in trough FEV1 for participant j measured at period i. THETA1 and THETA2 were the slopes with respect to meanBL and periodBL, respectively. Omegas were the variance of the slopes on meanBL and periodBL (ETA1j, ETA2j) for each participant and Sigma was the variance of the residual errors (EPSij). MeanBL is the mean of the Baseline (BL) which is the FEV1 value recorded pre-dose on D 1 of each TP; periodBL is the difference between the BL and the meanBL in each TP for each participant.
- Change From Baseline in Trough FEV1 on Day 15 of Each Treatment Period [Time Frame: 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 was performed using a mixed model, including treatment, period, period Baseline FEV1 and mean Baseline FEV1 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.
- Number of Participants With Any Adverse Event (AE) or Serious Adverse Event (SAE) [Time Frame: From Baseline until the end of Treatment Period 3 (up

to Study Day 70)] [Designated as safety issue: No]

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is an event of possible drug-induced liver injury. Refer to the general Adverse AE/SAE module for a complete list of SAEs.

- Number of Participants With Asthma Exacerbations During the Treatment Period [Time Frame: From Baseline until the end of Treatment Period 3 (up to Study Day 70)] [Designated as safety issue: No]

  Worsening of asthma symptoms is monitored throughout the study. Severe exacerbation (deterioration of asthma requiring use of systemic corticosteroids for 3 days, inpatient hospitalization or emergency department visit due to asthma) is an exclusion criterion and requires withdrawal from the study. Asthma symptoms were assessed daily using an electronic diary throughout study.
- Change From Baseline in Systolic Blood Pressure on Day 14 of Each Treatment Period [Time Frame: Baseline and Day 14 of each treatment period (up to Study Day 70)] [Designated as safety issue: No]

  Blood pressure measurement included systolic blood pressure (SBP). Blood pressure was measured in a sitting position after the participant was kept at rest for at least 5 minutes. Analysis was performed using a mixed model, including treatment, period, period Baseline and mean Baseline for the measure as fixed effects and participant as a random effect. Baseline is the 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 was calculated as the assessment value at Day 14 minus the Baseline value.
- Change From Baseline in Diastolic Blood Pressure on Day 14 of Each Treatment Period [Time Frame: Baseline and Day 14 of each treatment period (up to Study Day 70)] [Designated as safety issue: No]

  Blood pressure measurement included diastolic blood pressure (DBP). Blood pressure was measured in a sitting position after the participant was kept at rest for at least 5 minutes. Analysis was performed using a mixed model, including treatment, period, period Baseline and mean Baseline for the measure as fixed effects and participant as a random effect. Baseline is the 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 was calculated as the assessment value at Day 14 minus the Baseline value.
- Change From Baseline in Pulse Rate on Day 14 of Each Treatment Period [Time Frame: Baseline and Day 14 of each treatment period (up to Study Day 70)] [Designated as safety issue: No]

  Pulse rate was measured in a sitting position after the participant was kept at rest for at least 5 minutes. Analysis was performed using a mixed model, including treatment, period, period Baseline and mean Baseline for the measure as fixed effects and participant as a random effect. Baseline is the 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 was calculated as the assessment value at Day 14 minus the Baseline value.
- Change From Baseline in Albumin, Total Protein, and Hemoglobin on Day 14 of Each Treatment Period [Time Frame: Baseline and Day 14 of each treatment period (up to Study Day 70))] [Designated as safety issue: No]

  Blood samples were collected for the measurement of albumin, total protein, and hemoglobin at Baseline and Day 14. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

- Change From Baseline in Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Creatine Kinase (CK), Gamma Glutamyl Transferase (GGT) and Lactate Dehydrogenase (LDH) on Day 14 of Each Treatment Period [Time Frame: Baseline and Day 14 of each treatment period (up to Study Day 70)] [Designated as safety issue: No]

  Blood samples were collected for the measurement of ALP, ALT, AST, CK, GGT, and LDH at Baseline and Day 14. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
- Change From Baseline in Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, and Creatinine on Day 14 of Each Treatment Period [Time Frame: Baseline and Day 14 of each treatment period (up to Study Day 70)] [Designated as safety issue: No]

  Blood samples were collected for the measurement of direct bilirubin, indirect (ind) bilirubin, total bilirubin, and creatinine at Baseline and Day 14. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
- Change From Baseline in Calcium, Chloride, Carbon Dioxide, Glucose, Potassium, Sodium, and Urea/Blood Urea Nitrogen (BUN) on Day 14 of Each Treatment Period [Time Frame: Baseline and Day 14 of each treatment period (up to Study Day 70)] [Designated as safety issue: No]

  Blood samples were collected for the measurement of chloride, caron dioxide, glucose, potassium, sodium, and urea/BUN at Baseline and Day 14. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
- Change From Baseline in Basophils, Eosinophils, Lymphocytes, Monocytes, Total Neutrophils (ANC - Absolute Neutrophil Count), Platelet, and Leukocytes Count on Day 14 of Each Treatment Period [Time Frame: Baseline and Day 14 of each treatment period (up to Study Day 70)] [Designated as safety issue: No]

  Blood samples were collected for the measurement of basophils, eosinophils, lymphocytes, monocytes, total neutrophils (ANC - Absolute neutrophil [neut] count), platelet, and leucocytes count at Day 14. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
- Change From Baseline in the Percentage of Basophils, Eosinophils, Lymphocytes, Monocytes, and Segmented Neutrophils in Blood on Day 14 of Each Treatment Period [Time Frame: Baseline and Day 14 of each treatment period (up to Study Day 70)] [Designated as safety issue: No]

  Blood samples were collected for the measurement of the percentage of basophils, eosinophils, lymphocytes, monocytes, and segmented neutrophils (neut) at Baseline and Day 14. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
- Change From Baseline in Hematocrit on Day 14 of Each Treatment Period [Time Frame: Baseline and Day 14 of each treatment period (up to Study Day 70)] [Designated as safety issue: No]

  Blood samples were collected for the measurement of hematocrit (proportion of red blood cells in blood) at Baseline and Day 14. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
- Number of Participants for the Indicated Urinalysis Parameters Tested by Dipstick on Day 14 of Each Treatment Period [Time Frame: Baseline and Day 14 of each treatment period (up to Study Day 70))] [Designated as safety issue: No]

  Urinalysis parameters included: Urine Bilirubin (UB), Urine Occult Blood (UOB), Urine Glucose (UG), Urine Ketones (UK), Urine Nitrite (UN), Urine Protein (UP), and Urine Leukocyte Esterase test for detecting White Blood Cell (UWBC). The dipstick was a strip used to detect the presence or absence of these parameters in the urine sample. The dipstick test gives results in a semi-quantitative manner, and results for urinalysis parameters can be read as negative (Neg), Trace (T), 1+, 2+, and 3+, and for UG the result can be read as Neg, T, T or 1/10 G/dL, 1+ or 1/4 G/dL, 3+ or 1 G/dL, indicating proportional concentrations in the urine sample. Data are reported as the number of participants who had neg, T, 1+, 2+ and 3+ levels at Day 14.
- Urine pH on Day 14 of Each Treatment Period [Time Frame: Day 14 of each treatment period (up to Study Day 70)] [Designated as safety issue: No]

  Urine samples were collected for the measurement of urine pH by dipstick method at Day 14. Urine pH is an acid-base measurement. pH is measured on

a numeric scale ranging from 0 to 14; values on the scale refer to the degree of alkalinity or acidity. A pH of 7 is neutral. A pH less than 7 is acidic, and a pH greater than 7 is basic. Normal urine has a slightly acid pH (5.0 - 6.0).

- Urine Specific Gravity on Day 14 of Each Treatment Period [Time Frame: Day 14 of each treatment period (up to Study Day 70)] [Designated as safety issue: No]

  Urine samples were collected for the measurement of urine specific gravity by dipstick method at Day 14. Urine specific gravity is a measure of the concentration of solutes in the urine and provides information on the kidney's ability to concentrate urine. The concentration of the excreted molecules determines the urine's specific gravity. A urinary specific gravity measurement is a routine part of urinalysis. The reference range is 1.002-1.030.
- Number of Participants With the Indicated Abnormal Electrocardiogram Findings [Time Frame: Day 14 of each treatment period (up to Study Day 70)] [Designated as safety issue: No]

  Electrocardiograph measurements performed at Screening (Visit 1) and at Day 1 and Day 14 (pre-dose, 10 minutes post-dose and 2 hours post-dose.of each treatment period). Any clinically significant findings were identified during participant monitoring.
- Number of Participants With the Indicated 24 Hour Holter Findings [Time Frame: Day 14 of each treatment period (up to Study Day 70)] [Designated as safety issue: No]

  Twenty-four hour Holter ECG measurements were obtained using a 12-lead Holter monitor. The Holter monitor is worn by the participant for 24 hours, and the monitor continuously records the heart's rhythm while the monitor is worn. Following the 24-hour period, the data from the monitor were downloaded and transmitted to the centralized vendor for analysis and interpretation by a licensed cardiologist. The 24-hour Holter ECG measurements were obtained at during the screening period and on Day 14 of each treatment period. The number of participants with clinically significant change (abnormal or normal) were reported.

Secondary Outcome Measures:

- Change From Baseline (BL) in the Weighted Mean (WM) 0-24 Hour FEV1 Obtained Post-AM Dose on Day 14 of Each Treatment Period [Time Frame: Baseline and Day 14 of each treatment period (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 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. Baseline is the 0h value obtained prior to the AM dose on Day 14 of the treatment period. Change from BL at a was calculated as WM at the evaluated time point minus BL. Analysis was performed using a mixed model, including treatment, period, period Baseline FEV1, and mean Baseline FEV1 as fixed effects and participant as a random effect.
- Change in Baseline in Serial FEV1 Over 0-24 Hours After the Morning Dose on Day 14 of Each Treatment Period [Time Frame: Baseline and Day 14 of each treatment period (up to Study Day 70)] [Designated as safety issue: No]

  Pulmonary function was measured by FEV1, defined as the maximal amount of air that can be forcefully exhaled in one second. Serial FEV1 measurements were taken electronically by spirometry. Serial FEV1 was measured at 5, 15, 30 minutes (min), 1, 3, 6, 9, 12, 16, 20, 23 and 24 hours (h) post-dose. Baseline is the 0h value obtained prior to the AM dose on Day 14 of the treatment period. Change from Baseline was calculated as FEV1 value at the evaluated time point minus Baseline. Analysis was preformed using a repeated measures model with terms for period, treatment, time, mean Baseline, period Baseline, and time by mean Baseline, time by period Baseline, and time by treatment interactions.
- Change From Baseline in Mean Morning (AM) and Evening (PM) Pre-treatment Peak Expiratory Flow (PEF) Over Day 7 to Day 14 of Each Treatment

Period [Time Frame: Baseline (Day 7 prior to each treatment period) and the last 7 days of each treatment period (up to Study Day 70)] [Designated as safety issue: No]

PEF is defined as the maximum airflow during a forced expiration beginning with the lungs fully inflated. PEF was measured by the participants daily in the morning and evening just prior to each dose, using an electronic peak flow meter, throughout the 14-day Treatment Period. Only the averaged daily AM and PM PEF over Days 7 to 14 was analyzed. The analysis was performed using a mixed effects analysis of covariance model with fixed effect terms for treatment and period; Baseline PEF AM and PM, gender and age fitted as covariates; and participant as a random effect.

- Change From Baseline in the Mean Number of Puffs Per Day of Rescue Albuterol/Salbutamol Over Day 7 to Day 14 of Each Treatment Period [Time Frame: Baseline (Day 7 prior to each treatment period) and the last 7 days of each treatment period (up to Study Day 70)] [Designated as safety issue: No]

  The mean number of puffs per day of rescue salbutamol at Baseline (i.e. run-in or washout data) and on-treatment were recorded. Total puffs was calculated as (Number of Puffs + (2 x number of Nebules)). Only the 7 days proceeding each treatment period were included in the Baseline calculations. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

Enrollment: 350
Study Start Date: May 2012
Study Completion Date: February 2013
Primary Completion Date: February 2013

Arms	Assigned Interventions
Experimental: GSK573719 15.6 mcg GSK573719 (Umeclinidium bromide) 15.6 mcg once-daily	Drug: GSK573719 Active treatment or Placebo Eligible subjects will be randomised to a sequence of three treatments from 8 possible arms: 7 active drug doses (15.6mcg, 31.25 mc, 62.5mcg 125mcg or 250mcg GSK573719 once daily; 15.6mcg or 31.25 mcg GSK573719 taken twice daily) or matched placebo. Procedure/Surgery: GSK573719 (Sub-group cohort) Subjects at selected Sub-group sites (approximately 30% of the total population) will have additional serial assessments and procedures (including blood and urine samples for pharmacokinetic analysis) at the start (Day 1) and at the end (Days 14 and 15) of each treatment period. On Day 14 of each treatment period subjects will remain overnight at the clinic for 24-hour assessments, including spirometry, ECGs, and

Arms	Assigned Interventions
	24-hour Holter monitoring. Drug: Salbutamol/Albuterol Salbutamol/Albuterol, short-activing beta agonist provided to all subjects to be taken as needed for the relief of asthma symptoms.throughout the study period, including washout periods
Experimental: GSK573719 31.25 mcg GSK573719 (Umeclinidium bromide) 31.25 mcg once-daily	Drug: GSK573719 Active treatment or Placebo Eligible subjects will be randomised to a sequence of three treatments from 8 possible arms: 7 active drug doses (15.6mcg, 31.25 mc, 62.5mcg 125mcg or 250mcg GSK573719 once daily; 15.6mcg or 31.25 mcg GSK573719 taken twice daily) or matched placebo. Procedure/Surgery: GSK573719 (Sub-group cohort) Subjects at selected Sub-group sites (approximately 30% of the total population) will have additional serial assessments and procedures (including blood and urine samples for pharmacokinetic analysis) at the start (Day 1) and at the end (Days 14 and 15) of each treatment period. On Day 14 of each treatment period subjects will remain overnight at the clinic for 24-hour assessments, including spirometry, ECGs, and 24-hour Holter monitoring. Drug: Salbutamol/Albuterol Salbutamol/Albuterol, short-activing beta agonist provided to all subjects to be taken as needed for the relief of asthma symptoms.throughout the study period, including washout periods
Experimental: GSK573719 62.5 mcg	Drug: GSK573719 Active treatment or Placebo

Arms	Assigned Interventions
GSK573719 (Umeclinidium bromide) 62.5 mcg once-daily	Eligible subjects will be randomised to a sequence of three treatments from 8 possible arms: 7 active drug doses (15.6mcg, 31.25 mc, 62.5mcg 125mcg or 250mcg GSK573719 once daily; 15.6mcg or 31.25 mcg GSK573719 taken twice daily) or matched placebo. Procedure/Surgery: GSK573719 (Sub-group cohort) Subjects at selected Sub-group sites (approximately 30% of the total population) will have additional serial assessments and procedures (including blood and urine samples for pharmacokinetic analysis) at the start (Day 1) and at the end (Days 14 and 15) of each treatment period. On Day 14 of each treatment period subjects will remain overnight at the clinic for 24-hour assessments, including spirometry, ECGs, and 24-hour Holter monitoring. Drug: Salbutamol/Albuterol Salbutamol/Albuterol, short-activing beta agonist provided to all subjects to be taken as needed for the relief of asthma symptoms.throughout the study period, including washout periods
Experimental: GSK573719 125 mcg GSK573719 (Umeclinidium bromide) 125 mcg once-daily	Drug: GSK573719 Active treatment or Placebo Eligible subjects will be randomised to a sequence of three treatments from 8 possible arms: 7 active drug doses (15.6mcg, 31.25 mc, 62.5mcg 125mcg or 250mcg GSK573719 once daily; 15.6mcg or 31.25 mcg GSK573719 taken twice daily) or matched placebo. Procedure/Surgery: GSK573719 (Sub-group cohort) Subjects at selected Sub-group sites (approximately 30% of the total population) will have additional serial

Arms	Assigned Interventions
	assessments and procedures (including blood and urine samples for pharmacokinetic analysis) at the start (Day 1) and at the end (Days 14 and 15) of each treatment period. On Day 14 of each treatment period subjects will remain overnight at the clinic for 24-hour assessments, including spirometry, ECGs, and 24-hour Holter monitoring. Drug: Salbutamol/Albuterol Salbutamol/Albuterol, short-activing beta agonist provided to all subjects to be taken as needed for the relief of asthma symptoms.throughout the study period, including washout periods
Experimental: GSK573719 250 mcg GSK573719 (Umeclinidium bromide) 250 mcg once-daily	Drug: GSK573719 Active treatment or Placebo Eligible subjects will be randomised to a sequence of three treatments from 8 possible arms: 7 active drug doses (15.6mcg, 31.25 mc, 62.5mcg 125mcg or 250mcg GSK573719 once daily; 15.6mcg or 31.25 mcg GSK573719 taken twice daily) or matched placebo. Procedure/Surgery: GSK573719 (Sub-group cohort) Subjects at selected Sub-group sites (approximately 30% of the total population) will have additional serial assessments and procedures (including blood and urine samples for pharmacokinetic analysis) at the start (Day 1) and at the end (Days 14 and 15) of each treatment period. On Day 14 of each treatment period subjects will remain overnight at the clinic for 24-hour assessments, including spirometry, ECGs, and 24-hour Holter monitoring. Drug: Salbutamol/Albuterol Salbutamol/Albuterol, short-activing beta agonist

Arms	Assigned Interventions
	provided to all subjects to be taken as needed for the relief of asthma symptoms.throughout the study period, including washout periods
Experimental: GSK573719 15.6 mcg twice-daily GSK573719 (Umeclinidium bromide) 15.6 mcg twice-daily	Drug: GSK573719 Active treatment or Placebo Eligible subjects will be randomised to a sequence of three treatments from 8 possible arms: 7 active drug doses (15.6mcg, 31.25 mc, 62.5mcg 125mcg or 250mcg GSK573719 once daily; 15.6mcg or 31.25 mcg GSK573719 taken twice daily) or matched placebo. Procedure/Surgery: GSK573719 (Sub-group cohort) Subjects at selected Sub-group sites (approximately 30% of the total population) will have additional serial assessments and procedures (including blood and urine samples for pharmacokinetic analysis) at the start (Day 1) and at the end (Days 14 and 15) of each treatment period. On Day 14 of each treatment period subjects will remain overnight at the clinic for 24-hour assessments, including spirometry, ECGs, and 24-hour Holter monitoring. Drug: Salbutamol/Albuterol Salbutamol/Albuterol, short-activing beta agonist provided to all subjects to be taken as needed for the relief of asthma symptoms.throughout the study period, including washout periods
Experimental: GSK573719 31.25 mcg twice daily Gsk573719 (Umeclinidium bromide) 31.25 mcg twice-daily	Drug: GSK573719 Active treatment or Placebo Eligible subjects will be randomised to a sequence of three treatments from 8 possible arms: 7 active drug doses (15.6mcg, 31.25 mc, 62.5mcg 125mcg or 250mcg GSK573719 once daily; 15.6mcg or 31.25

Arms	Assigned Interventions
	mcg GSK573719 taken twice daily) or matched placebo. Procedure/Surgery: GSK573719 (Sub-group cohort) Subjects at selected Sub-group sites (approximately 30% of the total population) will have additional serial assessments and procedures (including blood and urine samples for pharmacokinetic analysis) at the start (Day 1) and at the end (Days 14 and 15) of each treatment period. On Day 14 of each treatment period subjects will remain overnight at the clinic for 24-hour assessments, including spirometry, ECGs, and 24-hour Holter monitoring. Drug: Salbutamol/Albuterol Salbutamol/Albuterol, short-activing beta agonist provided to all subjects to be taken as needed for the relief of asthma symptoms.throughout the study period, including washout periods
Placebo Comparator: Matched Placebo Matched Placebo arm	Drug: GSK573719 Active treatment or Placebo Eligible subjects will be randomised to a sequence of three treatments from 8 possible arms: 7 active drug doses (15.6mcg, 31.25 mc, 62.5mcg 125mcg or 250mcg GSK573719 once daily; 15.6mcg or 31.25 mcg GSK573719 taken twice daily) or matched placebo. Procedure/Surgery: GSK573719 (Sub-group cohort) Subjects at selected Sub-group sites (approximately 30% of the total population) will have additional serial assessments and procedures (including blood and urine samples for pharmacokinetic analysis) at the start (Day 1) and at the end (Days 14 and 15) of each treatment period. On Day 14 of each treatment period

Arms	Assigned Interventions
	subjects will remain overnight at the clinic for 24-hour assessments, including spirometry, ECGs, and 24-hour Holter monitoring. Drug: Salbutamol/Albuterol Salbutamol/Albuterol, short-activing beta agonist provided to all subjects to be taken as needed for the relief of asthma symptoms.throughout the study period, including washout periods

Asthma, a reversible obstructive disease of the airways, is defined as a chronic inflammatory disorder of the airways in which many of the cells and cellular mediators play a role. The chronic inflammation is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or early in the morning. These episodes are usually associated with widespread, but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment (NIH 2007, GINA, 2010,). Guidelines recommend a stepwise approach to the management of asthma. For many patients with mild disease, asthma symptoms can be adequately relieved by ‘on demand’ use of a short acting beta-2 -agonist (SABA) alone. A long-acting, inhaled, muscarinic receptor antagonist (LAMA) exerts its effects via distinct and complementary bronchodilator mechanisms on large and small airways through antagonism of the endogenous agonist acetylcholine at the muscarinic receptors leading to smooth muscle relaxation and bronchodilation. However, most experience with older anti-cholinergics has been with acute use and little is known about their effect in chronic use or as maintenance in asthma.

Newer more selective muscarinic receptor antagonists are being developed for chronic use which appear to have a better adverse event profile compared with older anti-cholinergics in the treatment of asthma [Moulton 2011]. A once daily long-acting, inhaled, muscarinic receptor antagonist (LAMA) bronchodilator, GSK573719, may offer an alternative treatment option to patients with asthma.

The proposed study is a multi-national, randomized, double-blind, 3-period crossover, incomplete block study in outpatient subjects with mild asthma and who are not using inhaled corticosteroids (ICS) for symptom control. The primary objective of this study is to evaluate the dose response, efficacy and safety of five once-daily doses of GSK573719 compared with placebo, over a 14-day treatment period, in patients with asthma. A placebo arm will be included to determine an absolute treatment effect over placebo for each GSK573719 dose regimen.

Each eligible subject will be randomized to receive 3 out of 8 potential treatments in sequence over a total of three 14-day treatment periods. There will be 12 clinic visits including a safety follow-up visit at the end of the study. All subjects will be provided with albuterol (salbutamol) for use on an 'as-needed' basis throughout the run-in, treatment and washout periods. A sub-group (approximately 30%) of the study population will comprise subjects from selected sites. These subjects will have additional assessments at the start and end of each treatment period, including serial spirometry, serial ECGs, 24 hour Holter monitoring, and samples of blood and urine for pharmacokinetic analysis. Other safety parameters include the incidence of adverse events, vital signs, clinical laboratory

parameters, ECGs and spirometry, including twice daily peak expiratory flow, asthma exacerbation assessment. and use of salbutamol.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both

Inclusion Criteria:

- Written informed consent
- Outpatient (sub-group will have 3 overnight stays at clinic)
- Diagnosis of asthma (NIH 2007) for at least 6 months
- Male or Eligible female (females of child-bearing potential must use acceptable method of birth control)
- A best AM pre-bronchodilator FEV1 of 60% to 85% of predicted normal value at Screening
- Reversibility of disease demonstrated by at least 12% and 200mL increase in FEV1 .
- Subjects must have been prescribed a non-corticosteroid controller at least 3 months preceding Visit 1, and/or a short-acting beta 2 agonist, without the use of inhaled corticosteroids in the 4 weeks prior to Visit 1
- Subjects must be able to replace their current short-acting Beta-2-agonist with albuterol/salbutamol aerosol inhaler for the duration of the study
- Subjects must be judged capable of withholding albuterol/salbutamol for at least 4 hours prior to study visits

Exclusion Criteria:

- History of life threatening asthma
- Severe asthma exacerbation
- Respiratory infection within expected to affect subject's ability to participate
- Concurrent respiratory disease
- Current smoker or smoking history of 10 pack years or more
- Diseases preventing use of anticholinergics
- Other clinically significant, uncontrolled condition or disease which would pose a safety risk to the patient, or confound interpretation of study results
- Drug allergy to any Beta-2-agonist, sympathomimetic drug, intranasal, inhaled or systemic corticosteroid therapy
- Known or suspected sensitivity to the constituents of the Novel DPI (ie lactose)
- History of severe milk protein allergy
- Administration of prescription or over-the-counter medication that would significantly affect the course of asthma, or interact with the study drug
- Any infirmity, disability or disease of a child or family member likely to impair compliance
- Alcohol or substance abuse history
- Viral hepatitis B surface antigen or Hepatitis C antibody
- Known HIV-positive history.

- Affiliation with investigator or site staff

Contacts and Locations

Locations

United States, California

GSK Investigational Site

Newport Beach, California, United States, 92663

United States, Louisiana

GSK Investigational Site

Sunset, Louisiana, United States, 70584

United States, Maryland

GSK Investigational Site

Bethesda, Maryland, United States, 20814

United States, Missouri

GSK Investigational Site

Columbia, Missouri, United States, 65203

GSK Investigational Site

Rolla, Missouri, United States, 65401

GSK Investigational Site

St. Louis, Missouri, United States, 63141

United States, Nebraska

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United States, South Carolina

GSK Investigational Site

Orangeburg, South Carolina, United States, 29118

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Spartanburg, South Carolina, United States, 29303

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Bulgaria

GSK Investigational Site

Lovech, Bulgaria, 5500

GSK Investigational Site

Pleven, Bulgaria, 5800

GSK Investigational Site

Plovdiv, Bulgaria, 4003

GSK Investigational Site

Ruse, Bulgaria, 7000

GSK Investigational Site

Sofia, Bulgaria, 1431

GSK Investigational Site

Stara Zagora, Bulgaria, 6000

GSK Investigational Site

Varna, Bulgaria, 9000

Germany

GSK Investigational Site

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Berlin, Berlin, Germany, 12203

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Berlin, Berlin, Germany, 10787

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Berlin, Berlin, Germany, 10717

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Berlin, Berlin, Germany, 10789

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Hamburg, Hamburg, Germany, 22299

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Hamburg, Hamburg, Germany, 22767

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Frankfurt, Hessen, Germany, 60596

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Neu isenburg, Hessen, Germany, 63263

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Geesthacht, Schleswig-Holstein, Germany, 21502

Mexico

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Guadalajara, Jalisco, Mexico, 44100

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Zapopan, Jalisco, Mexico, 45040

Peru

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Lima, Lima, Peru, Lima 18

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Lima, Lima, Peru, Lima 1

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Lima 27, Lima, Peru, Lima 27

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San Borja, Lima, Peru, Lima 41

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San Miguel, Lima, Peru, Lima 32

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Santiago de Surco, Lima, Peru, Lima 33

Poland

GSK Investigational Site

Bialystok, Poland, 15-010

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Krakow, Poland, 31-024

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Krakow, Poland, 31-455

GSK Investigational Site
Ruda Slaska, Poland, 41-790
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Zawadzkie, Poland, 47-120
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Zgierz, Poland, 95-100

Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Responsible Party:	GlaxoSmithKline
Study ID Numbers:	116402
Health Authority:	Bulgaria: The Bulgarian Drug Agency Peru: Ministry of Health Poland: Urzad Rejestracji Produktow Leczniczych, Wyrobow Medycznych I Produktow Biobojczych Mexico: Comision Federal para la Proteccion contra Riesgos Sanitarios (COFEPRIS) Germany: Bundesinstitut für Arzneimittel und Medizinprodukte United States: Food and Drug Administration

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Study Results

Participant Flow

Pre-Assignment Details

Participants were randomized to receive a sequence of 3 of 8 possible treatments over 3 treatment periods. There are 56 combinations of 3 treatments from the 8 study treatments, each of which can be ordered in 6 ways (totaling 336 possible sequences; 246 were randomly assigned). 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 15.6 µg QD	Participants received umeclidinium bromide (UMEC) 15.6 micrograms (µg) in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Treatment Period 1

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Started	42	45	51	41	43	39
Completed	40	45	50	41	39	37

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Not Completed	2	0	1	0	4	2
Adverse Event	1	0	0	0	0	0
Lack of Efficacy	0	0	0	0	0	0
Protocol Violation	1	0	0	0	2	0
Protocol-defined Stopping Criteria	0	0	0	0	1	0
Lost to Follow-up	0	0	1	0	0	0
Physician Decision	0	0	0	0	1	0
Withdrawal by Subject	0	0	0	0	0	2

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Started	38	51
Completed	38	48
Not Completed	0	3
Adverse Event	0	0
Lack of Efficacy	0	1
Protocol Violation	0	0
Protocol-defined Stopping Criteria	0	1
Lost to Follow-up	0	0
Physician Decision	0	0

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Withdrawal by Subject	0	1

Washout Period 1 (12-14 Days)

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Started	40	45	50	41	39	37
Completed	36 [1]	44 [2]	47 [3]	39 [4]	35 [5]	37 [6]
Not Completed	4	1	3	2	4	0
Adverse Event	2	0	0	0	0	0
Protocol Violation	0	0	0	0	0	0
Protocol-defined Stopping Criteria	1	0	3	1	3	0
Withdrawal by Subject	1	1	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 15.6 µg BID	UMEC 31.25 µg BID
Started	38	48
Completed	36 [1]	47 [2]

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Not Completed	2	1
Adverse Event	0	0
Protocol Violation	1	0
Protocol-defined Stopping Criteria	0	1
Withdrawal by Subject	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.

Treatment Period 2

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Started	33 [1]	46 [2]	40 [3]	41 [4]	37 [5]	45 [6]
Completed	30	46	40	41	37	43
Not Completed	3	0	0	0	0	2
Lack of Efficacy	1	0	0	0	0	0
Protocol-defined Stopping Criteria	1	0	0	0	0	0
Lost to Follow-up	0	0	0	0	0	1
Withdrawal by Subject	1	0	0	0	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 15.6 µg BID	UMEC 31.25 µg BID
Started	43 [1]	36 [2]
Completed	43	35
Not Completed	0	1
Lack of Efficacy	0	0
Protocol-defined Stopping Criteria	0	0
Lost to Follow-up	0	0
Withdrawal by Subject	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.

Washout Period 2 (12-14 Days)

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Started	30	46	40	41	37	43
Completed	30 [1]	46 [2]	39 [3]	41 [4]	34 [5]	42 [6]
Not Completed	0	0	1	0	3	1
Protocol-defined Stopping Criteria	0	0	0	0	3	0

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Withdrawal by Subject	0	0	1	0	0	1

[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 15.6 µg BID	UMEC 31.25 µg BID
Started	43	35
Completed	42 [1]	34 [2]
Not Completed	1	1
Protocol-defined Stopping Criteria	1	0
Withdrawal by Subject	0	1

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

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

Treatment Period 3

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Started	43 [1]	33 [2]	38 [3]	42 [4]	40 [5]	39 [6]
Completed	43	32	37	42	40	39

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Not Completed	0	1	1	0	0	0
Adverse Event	0	0	0	0	0	0
Protocol Violation	0	0	1	0	0	0
Protocol-defined Stopping Criteria	0	0	0	0	0	0
Lost to Follow-up	0	1	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 15.6 µg BID	UMEC 31.25 µg BID
Started	35 [1]	38 [2]
Completed	33	38
Not Completed	2	0
Adverse Event	1	0
Protocol Violation	0	0
Protocol-defined Stopping Criteria	1	0
Lost to Follow-up	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.

Washout Period 3 or Follow-up

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Started	43	32	37	42	40	39
Completed	42 [1]	32 [2]	36 [3]	41 [4]	40 [5]	37 [6]
Not Completed	1	0	1	1	0	2
Protocol Violation	0	0	0	0	0	1
Protocol-defined Stopping Criteria	1	0	1	1	0	1

[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 15.6 µg BID	UMEC 31.25 µg BID
Started	33	38
Completed	32 [1]	38 [2]
Not Completed	1	0
Protocol Violation	0	0
Protocol-defined Stopping	1	0

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Criteria		

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

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

Baseline Characteristics

Reporting Groups

	Description
All Study Treatments	The treatment phase was comprised of three 14-day treatment periods. Treatment Period 1 and 2 were followed by a 12-14 day washout period. Treatment Period 3 was followed by a 5 to 9 day washout period before the Follow-up visit. Participants were randomly assigned to receive a sequence of 3 of the 8 active treatments : UMEC 15.6, 31.25, 62.5, 125, 250 µg QD and UMEC 15.6, 31.25 µg BID, placebo.

Baseline Measures

	All Study Treatments
Number of Participants	350
Age, Continuous [units: Years] Mean (Standard Deviation)	42.6 (14.84)
Gender, Male/Female [units: Participants]	
Female	232

	All Study Treatments
Male	118
Race/Ethnicity, Customized [units: Participants]	
African American/African Heritage (HER)	33
American Indian or Alaskan Native	85
Asian-Japanese/East Asian HER/South East Asian HER	4
White	197
American Indian or Alaskan Native & White	31

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Final Dose-response Model for Trough Forced Expiratory Volume in One Second (FEV1)
Measure Description	Dose-response was conducted for both QD and BID UMEC doses on trough FEV1 (measure of lung function, defined as the maximal amount of air that can be forcefully exhaled in 1 second) on D 15. Total daily dose of UMEC was used in the modeling. The null model was the final model. The null model is defined as: $CFEV1,ij=(THETA1+ETA1j)*meanBL+(THETA2+ETA1j)*periodBL+EPSij$, where CFEV1,ij represents the change from BL in trough FEV1 for participant j measured at period i. THETA1 and THETA2 were the

	slopes with respect to meanBL and periodBL, respectively. Omegas were the variance of the slopes on meanBL and periodBL (ETA1j, ETA2j) for each participant and Sigma was the variance of the residual errors (EPSij). MeanBL is the mean of the Baseline (BL) which is the FEV1 value recorded pre-dose on D 1 of each TP; periodBL is the difference between the BL and the meanBL in each TP for each participant.
Time Frame	Day 15 of each treatment period (up to Study Day 71)
Safety Issue?	No

Analysis Population Description

Intent-To-Treat (ITT) Population: : all participants randomized to treatment and 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
All Study Treatments	The treatment phase was comprised of three 14-day treatment periods. Treatment Period 1 and 2 were followed by a 12-14 day washout period. Treatment Period 3 was followed by a 5 to 9 day washout period before the Follow-up visit. Participants were randomly assigned to receive a sequence of 3 of the 8 active treatments : UMEC 15.6, 31.25, 62.5, 125, 250 µg QD and UMEC 15.6, 31.25 µg BID, placebo.

Measured Values

	All Study Treatments
Number of Participants Analyzed	332
Final Dose-response Model for Trough Forced Expiratory Volume in One Second	

	All Study Treatments
(FEV1) [units: unitless] Geometric Mean (95% Confidence Interval)	
Theta1 (mean Baseline)	0.0363 (0.0280 to 0.0450)
Theta2 (period Baseline)	-0.97 (-1.06 to -0.881)
Omega (mean Baseline)	0.00371 (0.002 to 0.005)
Omega (period Baseline)	0.149 (0 to 0.298)
Sigma (Variance of Residual error)	0.0393 (0.028 to 0.050)

2. Primary Outcome Measure:

Measure Title	Change From Baseline in Trough FEV1 on 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 was performed using a mixed model, including treatment, period, period Baseline FEV1 and mean Baseline FEV1 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	Day 15 of each treatment period (up to Study Day 71)
Safety Issue?	No

Analysis Population Description

ITT 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 15.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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.

	Description
UMEC 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	110	120	124	122	113	117
Change From Baseline in Trough FEV1 on Day 15 of Each Treatment Period [units: Liters] Least Squares Mean (Standard Error)	0.046 (0.0235)	0.112 (0.0226)	0.076 (0.0222)	0.080 (0.0224)	0.134 (0.0232)	0.057 (0.0228)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	113	118
Change From Baseline in Trough FEV1 on Day 15 of Each Treatment Period [units: Liters] Least Squares Mean (Standard Error)	0.103 (0.0232)	0.097 (0.0227)

Statistical Analysis 1 for Change From Baseline in Trough FEV1 on Day 15 of Each Treatment Period

Groups	Placebo, UMEC 15.6 µg QD
Method	Mixed Models Analysis
P-Value	0.036
Mean Difference (Final Values)	0.066

95% Confidence Interval	0.004 to 0.127

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 FEV1 on Day 15 of Each Treatment Period

Groups	Placebo, UMEC 31.25 µg QD
Method	Mixed Models Analysis
P-Value	0.331
Mean Difference (Final Values)	0.030
95% Confidence Interval	-0.030 to 0.090

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 FEV1 on Day 15 of Each Treatment Period

Groups	Placebo, UMEC 62.5 µg QD
Method	Mixed Models Analysis
P-Value	0.272

Mean Difference (Final Values)	0.034
95% Confidence Interval	-0.027 to 0.095

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 FEV1 on Day 15 of Each Treatment Period

Groups	Placebo, UMEC 125 µg QD
Method	Mixed Models Analysis
P-Value	0.005
Mean Difference (Final Values)	0.088
95% Confidence Interval	0.026 to 0.149

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 FEV1 on Day 15 of Each Treatment Period

Groups	Placebo, UMEC 250 µg QD
Method	Mixed Models Analysis

P-Value	0.722
Mean Difference (Final Values)	0.011
95% Confidence Interval	-0.050 to 0.073

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 FEV1 on Day 15 of Each Treatment Period

Groups	Placebo, UMEC 15.6 µg BID
Method	Mixed Models Analysis
P-Value	0.076
Mean Difference (Final Values)	0.057
95% Confidence Interval	-0.006 to 0.119

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 FEV1 on Day 15 of Each Treatment Period

Groups	Placebo, UMEC 31.25 µg BID

Method	Mixed Models Analysis
P-Value	0.101
Mean Difference (Final Values)	0.051
95% Confidence Interval	-0.010 to 0.113

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.]

3. Primary Outcome Measure:

Measure Title	Number of Participants With Any Adverse Event (AE) or Serious Adverse Event (SAE)
Measure Description	An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is an event of possible drug-induced liver injury. Refer to the general Adverse AE/SAE module for a complete list of SAEs.
Time Frame	From Baseline until the end of Treatment Period 3 (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	126	131	138	133	128	135
Number of Participants With Any Adverse Event (AE) or Serious Adverse Event (SAE) [units: Participants]						
Any AE	15	12	13	21	26	28
Any SAE	0	0	0	0	0	1

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	126	133
Number of Participants With Any Adverse Event (AE) or Serious Adverse Event (SAE) [units: Participants]		
Any AE	16	12
Any SAE	0	0

4. Primary Outcome Measure:

Measure Title	Number of Participants With Asthma Exacerbations During the Treatment Period
Measure Description	Worsening of asthma symptoms is monitored throughout the study. Severe exacerbation (deterioration of asthma requiring use of systemic corticosteroids for 3 days, inpatient hospitalization or emergency department visit due to asthma) is an exclusion criterion and requires withdrawal from the study. Asthma symptoms were assessed daily

	using an electronic diary throughout study.
Time Frame	From Baseline until the end of Treatment Period 3 (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants with data available at the specified time points were analyzed.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in

	Description
	the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	126	131	138	133	128	135
Number of Participants With Asthma Exacerbations During the Treatment Period [units: Participants]	2	0	0	0	0	0

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	126	133
Number of Participants With Asthma Exacerbations During the Treatment Period [units: Participants]	1	1

5. Primary Outcome Measure:

Measure Title	Change From Baseline in Systolic Blood Pressure on Day 14 of Each Treatment Period
Measure Description	Blood pressure measurement included systolic blood pressure (SBP). Blood pressure was measured in a sitting position after the participant was kept at rest for at least 5 minutes. Analysis was performed using a mixed model, including treatment, period, period Baseline and mean Baseline for the measure as fixed effects and participant as a random

	effect. Baseline is the 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 was calculated as the assessment value at Day 14 minus the Baseline value.
Time Frame	Baseline and Day 14 of each treatment period (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants with data available at the specified time points were analyzed.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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.

	Description
UMEC 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	112	122	127	123	114	119
Change From Baseline in Systolic Blood Pressure on Day 14 of Each Treatment Period [units: Millimeters of mercury (mmHg)] Least Squares Mean (Standard Error)	-0.4 (0.71)	-0.6 (0.68)	-1.0 (0.67)	1.1 (0.68)	-0.6 (0.71)	0.0 (0.69)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	114	122
Change From Baseline in Systolic Blood Pressure on Day 14 of Each Treatment Period [units: Millimeters of mercury (mmHg)] Least Squares Mean (Standard Error)	0.3 (0.71)	-1.2 (0.69)

Statistical Analysis 1 for Change From Baseline in Systolic Blood Pressure on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 15.6 µg QD
Method	Mixed Models Analysis
P-Value	0.840

Mean Difference (Final Values)	-0.2
95% Confidence Interval	-2.1 to 1.7

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 Systolic Blood Pressure on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 31.25 µg QD
Method	Mixed Models Analysis
P-Value	0.553
Mean Difference (Final Values)	-0.6
95% Confidence Interval	-2.4 to 1.3

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 Systolic Blood Pressure on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 62.5 µg QD
Method	Mixed Models Analysis

P-Value	0.121
Mean Difference (Final Values)	1.5
95% Confidence Interval	-0.4 to 3.3

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 Systolic Blood Pressure on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 125 µg QD
Method	Mixed Models Analysis
P-Value	0.814
Mean Difference (Final Values)	-0.2
95% Confidence Interval	-2.1 to 1.7

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 Systolic Blood Pressure on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 250 µg QD

Method	Mixed Models Analysis
P-Value	0.683
Mean Difference (Final Values)	0.4
95% Confidence Interval	-1.5 to 2.3

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 Systolic Blood Pressure on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 15.6 µg BID
Method	Mixed Models Analysis
P-Value	0.456
Mean Difference (Final Values)	0.7
95% Confidence Interval	-1.2 to 2.7

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 Systolic Blood Pressure on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 31.25 µg BID
Method	Mixed Models Analysis
P-Value	0.399
Mean Difference (Final Values)	-0.8
95% Confidence Interval	-2.7 to 1.1

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.]

6. Primary Outcome Measure:

Measure Title	Change From Baseline in Diastolic Blood Pressure on Day 14 of Each Treatment Period
Measure Description	Blood pressure measurement included diastolic blood pressure (DBP). Blood pressure was measured in a sitting position after the participant was kept at rest for at least 5 minutes. Analysis was performed using a mixed model, including treatment, period, period Baseline and mean Baseline for the measure as fixed effects and participant as a random effect. Baseline is the 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 was calculated as the assessment value at Day 14 minus the Baseline value.

Time Frame	Baseline and Day 14 of each treatment period (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants with data available at the specified time points were analyzed.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	112	122	127	123	114	119
Change From Baseline in Diastolic Blood Pressure on Day 14 of Each Treatment Period [units: Millimeters of mercury (mmHg)] Least Squares Mean (Standard Error)	-2.1 (0.57)	-0.5 (0.55)	-0.8 (0.53)	-0.2 (0.54)	0.3 (0.57)	0.0 (0.55)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	114	122
Change From Baseline in Diastolic Blood Pressure on Day 14 of Each Treatment Period [units: Millimeters of mercury (mmHg)] Least Squares Mean (Standard Error)	0.6 (0.56)	-0.7 (0.55)

Statistical Analysis 1 for Change From Baseline in Diastolic Blood Pressure on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 15.6 µg QD
Method	Mixed Models Analysis
P-Value	0.030
Mean Difference (Final Values)	1.7
95% Confidence Interval	0.2 to 3.2

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 Diastolic Blood Pressure on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 31.25 µg QD
Method	Mixed Models Analysis
P-Value	0.077
Mean Difference (Final Values)	1.3
95% Confidence Interval	-0.1 to 2.8

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 Diastolic Blood Pressure on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 62.5 µg QD
Method	Mixed Models Analysis
P-Value	0.010
Mean Difference (Final Values)	2.0
95% Confidence Interval	0.5 to 3.5

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 Diastolic Blood Pressure on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 125 µg QD
Method	Mixed Models Analysis
P-Value	0.002
Mean Difference (Final Values)	2.4
95% Confidence Interval	0.9 to 3.9

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 Diastolic Blood Pressure on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 250 µg QD
Method	Mixed Models Analysis
P-Value	0.005
Mean Difference (Final Values)	2.2
95% Confidence Interval	0.7 to 3.7

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 Diastolic Blood Pressure on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 15.6 µg BID
Method	Mixed Models Analysis
P-Value	<0.001
Mean Difference (Final Values)	2.7
95% Confidence Interval	1.2 to 4.3

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 Diastolic Blood Pressure on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 31.25 µg BID
Method	Mixed Models Analysis
P-Value	0.054
Mean Difference (Final Values)	1.5
95% Confidence Interval	0.0 to 3.0

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.]

7. Primary Outcome Measure:

Measure Title	Change From Baseline in Pulse Rate on Day 14 of Each Treatment Period
Measure Description	Pulse rate was measured in a sitting position after the participant was kept at rest for at least 5 minutes. Analysis was performed using a mixed model, including treatment, period, period Baseline and mean Baseline for the measure as fixed effects and participant as a random effect. Baseline is the 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 was calculated as the assessment value at Day 14 minus the Baseline value.
Time Frame	Baseline and Day 14 of each treatment period (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants with data available at the specified time points were analyzed.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	112	122	127	123	114	119
Change From Baseline in Pulse Rate on Day 14 of Each Treatment Period [units: Beats per minute]	-0.4 (0.64)	-0.1 (0.62)	1.2 (0.60)	0.2 (0.61)	0.2 (0.64)	1.1 (0.62)

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Least Squares Mean (Standard Error)						

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	114	122
Change From Baseline in Pulse Rate on Day 14 of Each Treatment Period [units: Beats per minute] Least Squares Mean (Standard Error)	-0.4 (0.64)	-1.1 (0.62)

Statistical Analysis 1 for Change From Baseline in Pulse Rate on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 15.6 µg QD
Method	Mixed Models Analysis
P-Value	0.752
Mean Difference (Final Values)	0.3
95% Confidence Interval	-1.4 to 2.0

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 Pulse Rate on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 31.25 µg QD

Method	Mixed Models Analysis
P-Value	0.072
Mean Difference (Final Values)	1.5
95% Confidence Interval	-0.1 to 3.2

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 Pulse Rate on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 62.5 µg QD
Method	Mixed Models Analysis
P-Value	0.503
Mean Difference (Final Values)	0.6
95% Confidence Interval	-1.1 to 2.2

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 Pulse Rate on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 125 µg QD
Method	Mixed Models Analysis
P-Value	0.476
Mean Difference (Final Values)	0.6
95% Confidence Interval	-1.1 to 2.3

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 Pulse Rate on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 250 µg QD
Method	Mixed Models Analysis
P-Value	0.084
Mean Difference (Final Values)	1.5
95% Confidence Interval	-0.2 to 3.2

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 Pulse Rate on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 15.6 µg BID
Method	Mixed Models Analysis
P-Value	0.970
Mean Difference (Final Values)	0.0
95% Confidence Interval	-1.8 to 1.7

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 Pulse Rate on Day 14 of Each Treatment Period

Groups	Placebo, UMEC 31.25 µg BID
Method	Mixed Models Analysis
P-Value	0.423
Mean Difference (Final Values)	-0.7
95% Confidence Interval	-2.4 to 1.0

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.]

8. Primary Outcome Measure:

Measure Title	Change From Baseline in Albumin, Total Protein, and Hemoglobin on Day 14 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of albumin, total protein, and hemoglobin at Baseline and Day 14. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
Time Frame	Baseline and Day 14 of each treatment period (up to Study Day 70))
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants remaining in the study and contributing evaluable data for the indicated parameter were indicated by "n=X, X" in the category title and the overall number of participants analyzed reflects everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	126	131	138	133	128	135
Change From Baseline in Albumin, Total Protein, and Hemoglobin on Day 14 of Each Treatment Period [units: Grams per liter (G/L)] Mean (Standard Deviation)						
Albumin, n=111, 118, 120, 121, 112, 112, 112, 117	-1.1 (2.46)	-1.0 (2.63)	-0.8 (2.47)	-0.9 (2.59)	-1.1 (2.65)	-1.0 (2.47)
Total protein, n=111,118,120,121,112,112,112,117	-1.9 (3.63)	-1.9 (3.83)	-1.4 (3.82)	-1.7 (3.48)	-1.9 (4.02)	-1.8 (3.58)
Hemogloin, n=109,121,124,120,110,113,112,121	-2.2 (7.24)	-2.8 (6.55)	-1.6 (6.66)	-2.3 (7.13)	-1.8 (7.44)	-1.4 (6.76)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	126	133
Change From Baseline in Albumin, Total Protein, and Hemoglobin on Day 14 of Each Treatment Period [units: Grams per liter (G/L)] Mean (Standard Deviation)		
Albumin, n=111, 118, 120, 121, 112, 112, 112, 117	-0.6 (2.41)	-0.7 (2.14)
Total protein, n=111,118,120,121,112,112,112,117	-1.1 (3.58)	-1.2 (3.09)
Hemogloin, n=109,121,124,120,110,113,112,121	-1.3 (6.59)	-2.0 (7.06)

9. Primary Outcome Measure:

Measure Title	Change From Baseline in Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Creatine Kinase (CK), Gamma Glutamyl Transferase (GGT) and Lactate Dehydrogenase (LDH) on Day 14 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of ALP, ALT, AST, CK, GGT, and LDH at Baseline and Day 14. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
Time Frame	Baseline and Day 14 of each treatment period (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants remaining in the study and contributing evaluable data for the indicated parameter were indicated by "n=X, X" in the category title and the overall number of participants analyzed reflects everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	126	131	138	133	128	135
Change From Baseline in Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Creatine Kinase (CK), Gamma Glutamyl Transferase (GGT) and Lactate Dehydrogenase (LDH) on Day 14 of Each Treatment Period [units: International Units/Liter (IU/L)] Mean (Standard Deviation)						
ALP, n=111, 118, 120, 121, 112, 112, 112, 117	-0.7 (16.13)	-1.1 (14.35)	-1.8 (13.55)	-2.0 (10.73)	-2.8 (14.16)	-0.6 (10.90)
ALT, n=111, 117, 120, 121, 112, 112, 112, 117	0.7 (12.15)	0.6 (11.56)	0.4 (11.24)	-0.1 (7.18)	-1.7 (8.44)	1.4 (9.80)
AST, n=110, 118, 120, 120, 112, 112, 112, 117	0.6 (7.53)	-0.3 (6.26)	1.9 (18.69)	-0.4 (6.31)	-0.6 (7.51)	0.7 (8.39)
CK, n=111, 118, 120, 121, 112, 112, 112, 117	5.2 (69.94)	6.3 (70.20)	143.0 (1486.66)	-10.0 (73.53)	-2.5 (147.85)	7.7 (105.96)
GGT, n=111, 118, 120, 121, 112, 112, 112, 117	1.2 (15.06)	0.7 (9.63)	0.4 (10.63)	0.0 (9.74)	-0.6 (8.31)	0.2 (12.15)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	126	133
Change From Baseline in Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Creatine Kinase		

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
(CK), Gamma Glutamyl Transferase (GGT) and Lactate Dehydrogenase (LDH) on Day 14 of Each Treatment Period [units: International Units/Liter (IU/L)] Mean (Standard Deviation)		
ALP, n=111, 118, 120, 121, 112, 112, 112, 117	-0.6 (14.05)	-1.5 (9.88)
ALT, n=111, 117, 120, 121, 112, 112, 112, 117	1.7 (16.17)	-1.3 (8.73)
AST, n=110, 118, 120, 120, 112, 112, 112, 117	0.6 (7.24)	-0.3 (9.59)
CK, n=111, 118, 120, 121, 112, 112, 112, 117	6.9 (100.44)	19.8 (284.94)
GGT, n=111, 118, 120, 121, 112, 112, 112, 117	2.0 (10.18)	0.9 (10.61)

10. Primary Outcome Measure:

Measure Title	Change From Baseline in Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, and Creatinine on Day 14 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of direct bilirubin, indirect (ind) bilirubin, total bilirubin, and creatinine at Baseline and Day 14. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
Time Frame	Baseline and Day 14 of each treatment period (up to Study Day 70)

Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants remaining in the study and contributing evaluable data for the indicated parameter were indicated by "n=X, X" in the category title and the overall number of participants analyzed reflects everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	126	131	138	133	128	135
Change From Baseline in Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, and Creatinine on Day 14 of Each Treatment Period [units: Micromoles/Liter (µM/L)] Mean (Standard Deviation)						
Direct bilirubin,n=111,118,120,121,112,112,112,117	-0.2 (1.10)	-0.1 (1.10)	-0.1 (0.99)	-0.1 (0.95)	-0.1 (1.15)	-0.1 (1.15)
Bilirubin, n=111,118,120,121,112,112,112,117	-1.0 (3.94)	-0.9 (3.69)	-0.7 (3.36)	-0.9 (3.85)	-1.1 (5.15)	-0.9 (4.17)
Ind Bilirubin, n=111,118,120,121,112,112,112,117	-0.8 (3.42)	-0.8 (3.03)	-0.6 (2.93)	-0.8 (3.37)	-1.1 (4.42)	-0.8 (3.60)
Creatinine, n=111,118,120,121,112,112,112,117	0.27 (9.218)	-0.67 (8.037)	-0.76 (6.242)	0.94 (6.811)	-0.24 (7.450)	0.15 (6.826)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	126	133
Change From Baseline in Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, and Creatinine on Day 14 of Each Treatment Period [units: Micromoles/Liter (µM/L)] Mean (Standard Deviation)		
Direct bilirubin,n=111,118,120,121,112,112,112,117	-0.1 (1.08)	-0.1 (1.10)
Bilirubin,	-0.8 (4.19)	-0.9 (3.68)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
n=111,118,120,121,112,112,112,117		
Ind Bilirubin, n=111,118,120,121,112,112,112,117	-0.7 (3.63)	-0.8 (3.16)
Creatinine, n=111,118,120,121,112,112,112,117	0.30 (7.297)	0.22 (7.671)

11. Primary Outcome Measure:

Measure Title	Change From Baseline in Calcium, Chloride, Carbon Dioxide, Glucose, Potassium, Sodium, and Urea/Blood Urea Nitrogen (BUN) on Day 14 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of chloride, caron dioxide, glucose, potassium, sodium, and urea/BUN at Baseline and Day 14. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
Time Frame	Baseline and Day 14 of each treatment period (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants remaining in the study and contributing evaluable data for the indicated parameter were indicated by "n=X, X" in the category title and the overall number of participants analyzed reflects everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.

	Description
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	126	131	138	133	128	135
Change From Baseline in Calcium, Chloride, Carbon Dioxide, Glucose, Potassium, Sodium, and Urea/Blood Urea Nitrogen (BUN) on Day 14 of Each Treatment Period [units: Micromoles/Liter (µM/L)]						

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Mean (Standard Deviation)						
Chloride, n=111, 118, 120, 121, 112, 112, 112, 117	0.1 (2.11)	0.4 (2.29)	0.4 (2.29)	0.3 (2.21)	0.6 (2.18)	0.3 (1.84)
Carbon dioxide, n=110,118,120,120,112,112,112,117	-0.6 (2.16)	-0.4 (2.73)	-0.6 (2.54)	-0.2 (2.88)	-0.4 (2.11)	-0.0 (2.55)
Glucose, n=111, 118, 120, 121, 112, 112, 112, 117	0.01 (1.134)	0.04 (0.975)	-0.15 (0.950)	0.01 (1.012)	-0.29 (0.848)	-0.08 (1.048)
Potassium, n=110, 118, 120, 120, 112, 112, 112,117	0.02 (0.400)	0.05 (0.338)	0.05 (0.416)	0.03 (0.420)	0.05 (0.353)	0.02 (0.412)
Sodium, n=111, 118, 120, 121, 112, 112, 112, 117	-0.2 (1.78)	0.2 (2.06)	-0.0 (2.14)	-0.2 (2.33)	-0.1 (1.99)	-0.3 (1.88)
Urea/BUN, n=111, 118, 120, 121, 112, 112, 112, 117	0.11 (1.382)	0.34 (1.149)	0.02 (1.197)	0.11 (1.283)	-0.04 (1.322)	0.20 (1.303)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	126	133
Change From Baseline in Calcium, Chloride, Carbon Dioxide, Glucose, Potassium, Sodium, and Urea/Blood Urea Nitrogen (BUN) on Day 14 of Each Treatment Period [units: Micromoles/Liter (µM/L)] Mean (Standard Deviation)		
Chloride, n=111, 118, 120, 121, 112, 112, 112, 117	0.3 (2.22)	0.3 (2.00)
Carbon dioxide,	-0.5 (2.69)	-0.6 (2.38)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
n=110,118,120,120,112,112,112,117		
Glucose, n=111, 118, 120, 121, 112, 112, 112, 117	-0.09 (1.022)	-0.14 (0.778)
Potassium, n=110, 118, 120, 120, 112, 112, 112,117	0.08 (0.387)	0.09 (0.398)
Sodium, n=111, 118, 120, 121, 112, 112, 112, 117	-0.2 (2.23)	-0.4 (1.82)
Urea/BUN, n=111, 118, 120, 121, 112, 112, 112, 117	0.02 (1.184)	0.13 (1.265)

12. Primary Outcome Measure:

Measure Title	Change From Baseline in Basophils, Eosinophils, Lymphocytes, Monocytes, Total Neutrophils (ANC - Absolute Neutrophil Count), Platelet, and Leukocytes Count on Day 14 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of basophils, eosinophils, lymphocytes, monocytes, total neutrophils (ANC - Absolute neutrophil [neut] count), platelet, and leucocytes count at Day 14. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
Time Frame	Baseline and Day 14 of each treatment period (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants remaining in the study and contributing evaluable data for the indicated parameter were indicated by "n=X, X" in

the category title and the overall number of participants analyzed reflects everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	126	131	138	133	128	135

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Change From Baseline in Basophils, Eosinophils, Lymphocytes, Monocytes, Total Neutrophils (ANC - Absolute Neutrophil Count), Platelet, and Leukocytes Count on Day 14 of Each Treatment Period [units: 10^9 cells/Liter (GI/L)] Mean (Standard Deviation)						
Basophil, n=109, 121, 124, 117, 110, 112, 111, 121	0.003 (0.0212)	-0.001 (0.0173)	-0.000 (0.0184)	0.001 (0.0178)	0.006 (0.0230)	-0.001 (0.0162)
Eosinophils, n= 109, 121, 124, 117,110,112,111,121	0.097 (0.2400)	0.023 (0.1988)	0.029 (0.1928)	0.036 (0.2056)	0.036 (0.1944)	0.039 (0.2583)
Lymphocytes, n=109, 121, 124, 117,110,112,111,121	-0.038 (0.5767)	-0.064 (0.5882)	-0.050 (0.5850)	-0.033 (0.4986)	-0.043 (0.5366)	-0.152 (0.5203)
Monocytes, n=109, 121, 124, 117, 110, 112, 111,121	0.017 (0.1278)	0.029 (0.1366)	0.005 (0.1173)	0.017 (0.1185)	0.029 (0.1348)	0.030 (0.1289)
Total Neut, n= 109, 121, 124, 117, 110,112,111,121	-0.204 (1.4615)	0.032 (1.2279)	0.119 (1.8710)	-0.175 (1.5228)	-0.161 (1.1780)	0.107 (1.8329)
Segmented Neut, n=109,121,124,117,110,112,111,121	-0.204 (1.4615)	0.032 (1.2279)	0.119 (1.8710)	-0.175 (1.5228)	-0.161 (1.1780)	0.107 (1.8329)
Platelets,n=109, 121, 124, 119, 110, 112, 111, 119	-1.4 (40.21)	-0.7 (30.35)	-1.0 (36.65)	-2.3 (36.32)	-2.1 (34.17)	-8.4 (40.89)
Leukocytes,n=109,121,124, 117, 110, 112, 111, 121	-0.12 (1.740)	0.01 (1.385)	0.10 (1.867)	-0.15 (1.664)	-0.14 (1.400)	0.02 (1.913)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	126	133
Change From Baseline in Basophils, Eosinophils, Lymphocytes, Monocytes, Total Neutrophils (ANC - Absolute Neutrophil Count), Platelet, and Leukocytes Count on Day 14 of Each Treatment Period [units: 10^9 cells/Liter (GI/L)] Mean (Standard Deviation)		
Basophil, n=109, 121, 124, 117, 110, 112, 111, 121	-0.002 (0.0161)	0.000 (0.0184)
Eosinophils, n= 109, 121, 124, 117,110,112,111,121	0.040 (0.1799)	0.039 (0.1862)
Lymphocytes, n=109, 121, 124, 117,110,112,111,121	-0.156 (0.5552)	-0.069 (0.6148)
Monocytes, n=109, 121, 124, 117, 110, 112, 111,121	0.010 (0.1168)	-0.000 (0.1060)
Total Neut, n= 109, 121, 124, 117, 110,112,111,121	-0.133 (1.2785)	-0.080 (1.1597)
Segmented Neut, n=109,121,124,117,110,112,111,121	-0.133 (1.2785)	-0.080 (1.1597)
Platelets,n=109, 121, 124, 119, 110, 112, 111, 119	-2.2 (33.07)	-1.0 (39.34)
Leukocytes,n=109,121,124, 117, 110, 112, 111, 121	-0.24 (1.423)	-0.11 (1.402)

13. Primary Outcome Measure:

Measure Title	Change From Baseline in the Percentage of Basophils, Eosinophils, Lymphocytes, Monocytes, and Segmented Neutrophils in Blood on Day 14 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of the percentage of basophils, eosinophils, lymphocytes, monocytes, and segmented neutrophils (neut) at Baseline and Day 14. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
Time Frame	Baseline and Day 14 of each treatment period (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants remaining in the study and contributing evaluable data for the indicated parameter were indicated by "n=X, X" in the category title and the overall number of participants analyzed reflects everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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

	Description
	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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	126	131	138	133	128	135
Change From Baseline in the Percentage of Basophils, Eosinophils, Lymphocytes, Monocytes, and Segmented Neutrophils in Blood on Day 14 of Each Treatment Period [units: Percentage of cells in blood] Mean (Standard Deviation)						
Basophils, n=109,121,124,117,111,112,111,121	0.05 (0.302)	-0.01 (0.240)	-0.02 (0.273)	0.03 (0.286)	0.08 (0.318)	0.00 (0.212)
Eosinophils, n= 109,121,124,117,110,112,111,121	1.45 (3.380)	0.30 (2.782)	0.32 (2.896)	0.68 (3.100)	0.56 (2.403)	0.55 (3.142)
Lymphocytes, n=109,121,124,117,110,112,111,121	-0.00 (6.861)	-0.64 (7.590)	-0.29 (7.485)	0.62 (8.069)	-0.06 (6.996)	-1.97 (8.203)
Monocytes,	0.30 (1.735)	0.45 (1.941)	0.04 (1.798)	0.41 (1.787)	0.52 (1.719)	0.45 (1.622)

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
n=109,121,124,117,110,112,111,121						
Neutrophils, n=109,121,124,117,110,112,111,121	-1.80 (8.264)	-0.11 (8.872)	-0.04 (8.739)	-1.73 (9.048)	-1.11 (8.107)	0.96 (9.319)
Segmented Neut, n=109,121,124,117,110,112,111,121	-1.80 (8.264)	-0.11 (8.872)	-0.04 (8.739)	-1.73 (9.048)	-1.11 (8.107)	0.96 (9.319)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	126	133
Change From Baseline in the Percentage of Basophils, Eosinophils, Lymphocytes, Monocytes, and Segmented Neutrophils in Blood on Day 14 of Each Treatment Period [units: Percentage of cells in blood] Mean (Standard Deviation)		
Basophils, n=109,121,124,117,111,112,111,121	-0.02 (0.248)	0.00 (0.268)
Eosinophils, n= 109,121,124,117,110,112,111,121	0.65 (2.537)	0.56 (2.481)
Lymphocytes, n=109,121,124,117,110,112,111,121	-0.76 (8.001)	-0.46 (7.650)
Monocytes, n=109,121,124,117,110,112,111,121	0.43 (2.626)	0.07 (1.585)
Neutrophils, n=109,121,124,117,110,112,111,121	-0.30 (9.252)	-0.17 (8.676)
Segmented Neut,	-0.30 (9.252)	-0.17 (8.676)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
n=109,121,124,117,110,112,111,121		

14. Primary Outcome Measure:

Measure Title	Change From Baseline in Hematocrit on Day 14 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of hematocrit (proportion of red blood cells in blood) at Baseline and Day 14. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
Time Frame	Baseline and Day 14 of each treatment period (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants with data available at the specified time points were analyzed.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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

	Description
	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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	109	121	124	120	110	113
Change From Baseline in Hematocrit on Day 14 of Each Treatment Period [units: Proportion of red blood cells in blood] Mean (Standard Deviation)	-0.0093 (0.02298)	-0.0118 (0.02180)	-0.0075 (0.02271)	-0.0092 (0.02198)	-0.0082 (0.02452)	-0.0079 (0.02053)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	112	121
Change From Baseline in Hematocrit on Day 14 of Each Treatment Period [units: Proportion of red blood cells in blood] Mean (Standard Deviation)	-0.0084 (0.02259)	-0.0087 (0.02279)

15. Primary Outcome Measure:

Measure Title	Number of Participants for the Indicated Urinalysis Parameters Tested by Dipstick on Day 14 of Each Treatment Period
Measure Description	Urinalysis parameters included: Urine Bilirubin (UB), Urine Occult Blood (UOB), Urine Glucose (UG), Urine Ketones (UK), Urine Nitrite (UN), Urine Protein (UP), and Urine Leukocyte Esterase test for detecting White Blood Cell (UWBC). The dipstick was a strip used to detect the presence or absence of these parameters in the urine sample. The dipstick test gives results in a semi-quantitative manner, and results for urinalysis parameters can be read as negative (Neg), Trace (T), 1+, 2+, and 3+, and for UG the result can be read as Neg, T, T or 1/10 G/dL, 1+ or 1/4 G/dL, 3+ or 1 G/dL, indicating proportional concentrations in the urine sample. Data are reported as the number of participants who had neg, T, 1+, 2+ and 3+ levels at Day 14.
Time Frame	Baseline and Day 14 of each treatment period (up to Study Day 70))
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants remaining in the study and contributing evaluable data for the indicated parameter were indicated by "n=X, X" in the category title and the overall number of participants analyzed reflects everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.

	Description
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	126	131	138	133	128	135
Number of Participants for the Indicated Urinalysis Parameters Tested by Dipstick on Day 14 of Each Treatment Period [units: Participants]						
UB, Neg, n=109,121,125,120,112, 113,112,119	109	121	125	120	112	112
UOB, T, n=109,121,125,120,112,113,112,119	8	8	14	12	13	11

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
UOB, 1+, n=109,121,125,120,112,113,112,119	5	8	4	5	5	7
UOB, 2+, n=109,121,125,120,112,113,112,119	5	1	3	2	0	1
UOB, 3+, n=109,121,125,120,112,113,112,119	6	3	1	1	4	3
UOB, Neg, n=109,121,125,120,112,113,112,119	85	101	103	100	90	91
UG, T, n=109,121,125,120,112,113,112,119	0	1	1	0	0	1
UG, T or 1/10, n=109,121,125,120,112,113,112,119	0	1	0	0	0	0
UG, 1+ or 1/4, n=109,121,125,120,112,113,112,119	1	1	0	0	0	0
UG, 3+ or 1, n=109,121,125,120,112,113,112,119	1	0	0	1	0	0
UG, Neg, n=109,121,125,120,112,113,112,119	107	118	124	119	112	112
UK, T, n=109,121,125,120,112,113,112,119	4	3	5	2	8	0
UK, Neg, n=109,121,125,120,112,113,112,119	103	118	119	116	104	112
UK, 1+, n=109,121,125,120,112,113,112,119	1	0	0	0	0	1
UK, 2+,	0	0	1	1	0	0

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
n=109,121,125,120,112,113,112,119						
UK, 3+, n=109,121,125,120,112,113,112,119	1	0	0	1	0	0
UN, Neg, n=109,121,125,120,112,113,112,119	97	113	116	108	108	109
UN, Pos, n=109,121,125,120,112,113,112,119	12	8	9	12	4	4
UP, Neg, n=109,121,125,120,112,113,112,119	99	112	110	116	102	108
UP, T, n=109,121,125,120,112,113,112,119	4	6	8	2	6	3
UP, 1+, n=109,121,125,120,112,113,112,119	4	2	6	1	4	2
UP, 2+, n=109,121,125,120,112,113,112,119	2	1	1	1	0	0
UWBC, Neg, n=109,121,125,120,112,113,112,119	88	96	100	90	82	88
UWBC, T, n=109,121,125,120,112,113,112,119	6	5	6	11	8	5
UWBC, 1+, n=109,121,125,120,112,113,112,119	6	9	12	12	12	12
UWBC, 2+, n=109,121,125,120,112,113,112,119	4	8	5	3	5	8
UWBC, 3+, n=109,121,125,120,112,113,112,119	5	3	2	3	5	0

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	126	133
Number of Participants for the Indicated Urinalysis Parameters Tested by Dipstick on Day 14 of Each Treatment Period [units: Participants]		
UB, Neg, n=109,121,125,120,112, 113,112,119	112	119
UOB, T, n=109,121,125,120,112,113,112,119	8	13
UOB, 1+, n=109,121,125,120,112,113,112,119	5	2
UOB, 2+, n=109,121,125,120,112,113,112,119	3	2
UOB, 3+, n=109,121,125,120,112,113,112,119	2	3
UOB, Neg, n=109,121,125,120,112,113,112,119	94	99
UG, T, n=109,121,125,120,112,113,112,119	0	0
UG, T or 1/10, n=109,121,125,120,112,113,112,119	0	0
UG, 1+ or 1/4, n=109,121,125,120,112,113,112,119	0	0
UG, 3+ or 1, n=109,121,125,120,112,113,112,119	1	0
UG, Neg,	111	119

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
n=109,121,125,120,112,113,112,119		
UK, T, n=109,121,125,120,112,113,112,119	2	3
UK, Neg, n=109,121,125,120,112,113,112,119	110	113
UK, 1+, n=109,121,125,120,112,113,112,119	0	1
UK, 2+, n=109,121,125,120,112,113,112,119	0	2
UK, 3+, n=109,121,125,120,112,113,112,119	0	0
UN, Neg, n=109,121,125,120,112,113,112,119	103	105
UN, Pos, n=109,121,125,120,112,113,112,119	9	14
UP, Neg, n=109,121,125,120,112,113,112,119	107	111
UP, T, n=109,121,125,120,112,113,112,119	4	4
UP, 1+, n=109,121,125,120,112,113,112,119	1	4
UP, 2+, n=109,121,125,120,112,113,112,119	0	0
UWBC, Neg, n=109,121,125,120,112,113,112,119	89	85

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
UWBC, T, n=109,121,125,120,112,113,112,119	5	11
UWBC, 1+, n=109,121,125,120,112,113,112,119	4	10
UWBC, 2+, n=109,121,125,120,112,113,112,119	11	12
UWBC, 3+, n=109,121,125,120,112,113,112,119	3	1

16. Primary Outcome Measure:

Measure Title	Urine pH on Day 14 of Each Treatment Period
Measure Description	Urine samples were collected for the measurement of urine pH by dipstick method at Day 14. Urine pH is an acid-base measurement. pH is measured on a numeric scale ranging from 0 to 14; values on the scale refer to the degree of alkalinity or acidity. A pH of 7 is neutral. A pH less than 7 is acidic, and a pH greater than 7 is basic. Normal urine has a slightly acid pH (5.0 - 6.0).
Time Frame	Day 14 of each treatment period (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants with data available at the specified time points were analyzed.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	109	121	125	120	112	113
Urine pH on Day 14 of Each Treatment Period [units: Scores on a scale]	5.89 (0.635)	5.97 (0.709)	6.05 (0.718)	6.07 (0.743)	5.90 (0.678)	5.99 (0.720)

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Mean (Standard Deviation)						

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	112	119
Urine pH on Day 14 of Each Treatment Period [units: Scores on a scale] Mean (Standard Deviation)	5.89 (0.690)	5.90 (0.684)

17. Primary Outcome Measure:

Measure Title	Urine Specific Gravity on Day 14 of Each Treatment Period
Measure Description	Urine samples were collected for the measurement of urine specific gravity by dipstick method at Day 14. Urine specific gravity is a measure of the concentration of solutes in the urine and provides information on the kidney's ability to concentrate urine. The concentration of the excreted molecules determines the urine's specific gravity. A urinary specific gravity measurement is a routine part of urinalysis. The reference range is 1.002-1.030.
Time Frame	Day 14 of each treatment period (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants with data available at the specified time points were analyzed.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	109	121	125	120	112	113
Urine Specific Gravity on Day 14 of Each Treatment Period [units: Ratio]	1.0194 (0.00703)	1.0198 (0.00628)	1.0194 (0.00732)	1.0185 (0.00653)	1.0201 (0.00780)	1.0192 (0.00707)

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Mean (Standard Deviation)						

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	112	118
Urine Specific Gravity on Day 14 of Each Treatment Period [units: Ratio] Mean (Standard Deviation)	1.0189 (0.00734)	1.0193 (0.00671)

18. Primary Outcome Measure:

Measure Title	Number of Participants With the Indicated Abnormal Electrocardiogram Findings
Measure Description	Electrocardiograph measurements performed at Screening (Visit 1) and at Day 1 and Day 14 (pre-dose, 10 minutes post-dose and 2 hours post-dose.of each treatment period). Any clinically significant findings were identified during participant monitoring.
Time Frame	Day 14 of each treatment period (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants remaining in the study and contributing evaluable data at the indicated time points were analyzed.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in

	Description
	the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	126	131	138	133	128	135
Number of Participants With the Indicated Abnormal Electrocardiogram Findings [units: Participants]						

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Conduction	14	17	10	12	10	11
Depolarisation/Repolarisation(QRS-T)	21	20	26	20	32	25
Myocardial Infarction	2	3	1	2	1	0
P-Wave and QRS Morphology	0	0	0	0	1	0
Rhythm	12	13	15	12	13	15

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	126	133
Number of Participants With the Indicated Abnormal Electrocardiogram Findings [units: Participants]		
Conduction	7	12
Depolarisation/Repolarisation(QRS-T)	22	28
Myocardial Infarction	1	2
P-Wave and QRS Morphology	2	0
Rhythm	17	21

19. Primary Outcome Measure:

Measure Title	Number of Participants With the Indicated 24 Hour Holter Findings
Measure Description	Twenty-four hour Holter ECG measurements were obtained using a 12-lead Holter monitor. The Holter monitor is worn by the participant for

	24 hours, and the monitor continuously records the heart's rhythm while the monitor is worn. Following the 24-hour period, the data from the monitor were downloaded and transmitted to the centralized vendor for analysis and interpretation by a licensed cardiologist. The 24-hour Holter ECG measurements were obtained at during the screening period and on Day 14 of each treatment period. The number of participants with clinically significant change (abnormal or normal) were reported.
Time Frame	Day 14 of each treatment period (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only participants with sufficient data (at least 16 hours of recorded data) at the specified time points were analyzed.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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

	Description
	placebo in the evening via DPI B for 14 days.
UMEC 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	41	41	51	46	46	42
Number of Participants With the Indicated 24 Hour Holter Findings [units: Participants]						
Abnormal	6	3	7	7	8	8
Normal	35	38	44	39	38	34

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	39	49
Number of Participants With the Indicated 24 Hour Holter Findings [units: Participants]		
Abnormal	7	7
Normal	32	42

20. Secondary Outcome Measure:

Measure Title	Change From Baseline (BL) in the Weighted Mean (WM) 0-24 Hour FEV1 Obtained Post-AM 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 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. Baseline is the 0h value obtained prior to the AM dose on Day 14 of the treatment period. Change from BL at a was calculated as WM at the evaluated time point minus BL. Analysis was performed using a mixed model, including treatment, period, period Baseline FEV1, and mean Baseline FEV1 as fixed effects and participant as a random effect.
Time Frame	Baseline and Day 14 of each treatment period (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants with data available at the specified time points were analyzed.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.

	Description
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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	33	35	49	42	45	38
Change From Baseline (BL) in the Weighted Mean (WM) 0-24 Hour FEV1 Obtained Post-AM Dose on Day 14 of Each Treatment Period [units: Liters] Least Squares Mean (Standard Error)	-0.025 (0.0255)	0.060 (0.0249)	0.077 (0.0222)	0.092 (0.0232)	0.094 (0.0229)	0.048 (0.0243)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	35	43
Change From Baseline (BL) in the	0.097	0.043

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Weighted Mean (WM) 0-24 Hour FEV1 Obtained Post-AM Dose on Day 14 of Each Treatment Period [units: Liters] Least Squares Mean (Standard Error)	(0.0252)	(0.0231)

21. Secondary Outcome Measure:

Measure Title	Change in Baseline in Serial FEV1 Over 0-24 Hours After the Morning Dose on Day 14 of Each Treatment Period
Measure Description	Pulmonary function was measured by FEV1, defined as the maximal amount of air that can be forcefully exhaled in one second. Serial FEV1 measurements were taken electronically by spirometry. Serial FEV1 was measured at 5, 15, 30 minutes (min), 1, 3, 6, 9, 12, 16, 20, 23 and 24 hours (h) post-dose. Baseline is the 0h value obtained prior to the AM dose on Day 14 of the treatment period. Change from Baseline was calculated as FEV1 value at the evaluated time point minus Baseline. Analysis was preformed using a repeated measures model with terms for period, treatment, time, mean Baseline, period Baseline, and time by mean Baseline, time by period Baseline, and time by treatment interactions.
Time Frame	Baseline and Day 14 of each treatment period (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants remaining in the study and contributing evaluable data for the indicated parameter were indicated by "n=X, X" in the category title and the overall number of participants analyzed reflects everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	126	131	138	133	128	135
Change in Baseline in Serial FEV1 Over 0-24 Hours After the Morning Dose on Day 14 of Each Treatment Period						

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
[units: Liters] Least Squares Mean (Standard Error)						
5 min, n=41, 39, 49, 46, 44, 42, 38, 48	0.024 (0.0329)	0.095 (0.0330)	0.110 (0.0296)	0.077 (0.0309)	0.123 (0.0312)	0.042 (0.0326)
15 min, n=41, 41, 51, 46, 46, 42, 39, 49	0.002 (0.0322)	0.082 (0.0322)	0.124 (0.0290)	0.090 (0.0303)	0.115 (0.0305)	0.038 (0.0320)
30 min, n=45, 42, 39, 49, 45, 42, 39, 49	0.012 (0.0318)	0.109 (0.0317)	0.115 (0.0285)	0.092 (0.0299)	0.149 (0.0301)	0.040 (0.0315)
1 h, n=41, 41, 51, 46, 46, 42, 39, 49	0.025 (0.0319)	0.127 (0.0318)	0.161 (0.0286)	0.143 (0.0300)	0.165 (0.0302)	0.113 (0.0316)
3 h, n=41, 41, 51, 46, 46, 42, 39, 49	0.000 (0.0353)	0.141 (0.0353)	0.175 (0.0317)	0.156 (0.0332)	0.143 (0.0335)	0.143 (0.0350)
6 h, n=41, 40, 51, 46, 46, 42, 39, 48	0.007 (0.0368)	0.099 (0.0369)	0.089 (0.0330)	0.108 (0.0346)	0.134 (0.0349)	0.076 (0.0365)
9 h, n=41, 40, 51, 46, 46, 42, 39, 49	-0.049 (0.0354)	0.043 (0.0356)	0.061 (0.0318)	0.118 (0.0333)	0.117 (0.0335)	0.081 (0.0351)
12 h, n=41, 41, 51, 46, 46, 41, 39, 49	-0.044 (0.0395)	0.015 (0.0394)	0.021 (0.0354)	0.060 (0.0372)	0.056 (0.0374)	0.016 (0.0393)
16 h, n=40, 40, 51, 46, 46, 42, 38, 49	-0.074 (0.0408)	0.006 (0.0407)	0.022 (0.0364)	0.052 (0.0382)	0.035 (0.0384)	0.008 (0.0402)
20 h, n=40, 41, 51, 45, 46, 41, 39, 49	-0.149 (0.0441)	-0.046 (0.0438)	-0.003 (0.0393)	0.057 (0.0415)	0.029 (0.0416)	-0.050 (0.0437)
23 h, n=40, 40, 51, 46, 46, 42, 39, 48	0.013 (0.0391)	0.033 (0.0390)	0.056 (0.0349)	0.107 (0.0366)	0.087 (0.0369)	0.058 (0.0386)
24 h, n=41, 41, 51, 45, 46, 42, 39, 49	0.039 (0.0387)	0.105 (0.0386)	0.110 (0.0347)	0.143 (0.0366)	0.139 (0.0366)	0.088 (0.0384)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	126	133
Change in Baseline in Serial FEV1 Over 0-24 Hours After the Morning Dose on Day 14 of Each Treatment Period [units: Liters] Least Squares Mean (Standard Error)		
5 min, n=41, 39, 49, 46, 44, 42, 38, 48	0.141 (0.0338)	0.118 (0.0301)
15 min, n=41, 41, 51, 46, 46, 42, 39, 49	0.160 (0.0331)	0.108 (0.0294)
30 min, n=45, 42, 39, 49, 45, 42, 39, 49	0.158 (0.0326)	0.110 (0.0290)
1 h, n=41, 41, 51, 46, 46, 42, 39, 49	0.164 (0.0327)	0.168 (0.0291)
3 h, n=41, 41, 51, 46, 46, 42, 39, 49	0.182 (0.0362)	0.165 (0.0322)
6 h, n=41, 40, 51, 46, 46, 42, 39, 48	0.157 (0.0378)	0.100 (0.0337)
9 h, n=41, 40, 51, 46, 46, 42, 39, 49	0.072 (0.0363)	0.075 (0.0323)
12 h, n=41, 41, 51, 46, 46, 41, 39, 49	0.050 (0.0405)	0.056 (0.0360)
16 h, n=40, 40, 51, 46, 46, 42, 38, 49	0.053 (0.0419)	0.009 (0.0370)
20 h, n=40, 41, 51, 45, 46, 41, 39, 49	-0.005 (0.0450)	-0.012 (0.0400)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
23 h, n=40, 40, 51, 46, 46, 42, 39, 48	0.081 (0.0399)	0.037 (0.0356)
24 h, n=41, 41, 51, 45, 46, 42, 39, 49	0.187 (0.0397)	0.124 (0.0353)

22. Secondary Outcome Measure:

Measure Title	Change From Baseline in Mean Morning (AM) and Evening (PM) Pre-treatment Peak Expiratory Flow (PEF) Over Day 7 to Day 14 of Each Treatment Period
Measure Description	PEF is defined as the maximum airflow during a forced expiration beginning with the lungs fully inflated. PEF was measured by the participants daily in the morning and evening just prior to each dose, using an electronic peak flow meter, throughout the 14-day Treatment Period. Only the averaged daily AM and PM PEF over Days 7 to 14 was analyzed. The analysis was performed using a mixed effects analysis of covariance model with fixed effect terms for treatment and period; Baseline PEF AM and PM, gender and age fitted as covariates; and participant as a random effect.
Time Frame	Baseline (Day 7 prior to each treatment period) and the last 7 days of each treatment period (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants remaining in the study and contributing evaluable data for the indicated parameter were indicated by "n=X, X" in the category title and the overall number of participants analyzed reflects everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	126	131	138	133	128	135
Change From Baseline in Mean Morning (AM) and Evening (PM) Pre-treatment Peak Expiratory Flow (PEF) Over Day 7 to						

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Day 14 of Each Treatment Period [units: Liters per minute] Mean (Standard Deviation)						
AM, n=112, 120, 125, 122, 113, 116, 110, 122	0.8 (31.98)	5.2 (42.17)	1.7 (37.95)	1.1 (31.23)	6.4 (32.31)	6.4 (43.24)
PM, n=116, 123, 123, 119, 115, 118, 108, 121	-5.1 (34.43)	10.0 (43.47)	1.5 (37.95)	-0.9 (31.32)	9.8 (31.25)	9.3 (40.03)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	126	133
Change From Baseline in Mean Morning (AM) and Evening (PM) Pre-treatment Peak Expiratory Flow (PEF) Over Day 7 to Day 14 of Each Treatment Period [units: Liters per minute] Mean (Standard Deviation)		
AM, n=112, 120, 125, 122, 113, 116, 110, 122	5.0 (35.82)	5.8 (33.00)
PM, n=116, 123, 123, 119, 115, 118, 108, 121	2.5 (35.89)	8.7 (30.55)

23. Secondary Outcome Measure:

Measure Title	Change From Baseline in the Mean Number of Puffs Per Day of Rescue Albuterol/Salbutamol Over Day 7 to Day 14 of Each Treatment Period

Measure Description	The mean number of puffs per day of rescue salbutamol at Baseline (i.e. run-in or washout data) and on-treatment were recorded. Total puffs was calculated as (Number of Puffs + (2 x number of Nebules)). Only the 7 days proceeding each treatment period were included in the Baseline calculations. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.
Time Frame	Baseline (Day 7 prior to each treatment period) and the last 7 days of each treatment period (up to Study Day 70)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants with data available at the specified time points were analyzed.

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.25 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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.

	Description
UMEC 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and in the evening via DPI B for 14 days.

Measured Values

	Placebo	UMEC 15.6 µg QD	UMEC 31.25 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Number of Participants Analyzed	109	117	119	114	108	111
Change From Baseline in the Mean Number of Puffs Per Day of Rescue Albuterol/Salbutamol Over Day 7 to Day 14 of Each Treatment Period [units: Number of puffs] Mean (Standard Deviation)	-0.3 (1.25)	-0.4 (1.42)	-0.2 (1.06)	-0.3 (1.14)	-0.4 (1.19)	-0.3 (1.31)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Number of Participants Analyzed	105	118
Change From Baseline in the Mean Number of Puffs Per Day of Rescue Albuterol/Salbutamol Over Day 7 to Day 14 of Each Treatment Period [units: Number of puffs] Mean (Standard Deviation)	-0.6 (1.49)	-0.3 (1.04)

Reported Adverse Events

Reporting Groups

	Description
Placebo	Participants received matching placebo in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 15.6 µg QD	Participants received UMEC 15.6 µg in the morning via DPI A and placebo in the evening via DPI B for 14 days.
UMEC 31.5 µg QD	Participants received UMEC 31.25 µg in the morning via DPI A and placebo 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 15.6 µg BID	Participants received UMEC 15.6 µg in the morning via DPI A and in the evening via DPI B for 14 days.
UMEC 31.25 µg BID	Participants received UMEC 31.25 µg in the morning via DPI A and 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 until the end of treatment (up to Study Day 70).

Additional Description

On-treatment 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. Provision was made for the collection of any SAEs during the 9 – 14 days screening (pre-treatment) period. None was reported.

Serious Adverse Events

	Placebo	UMEC 15.6 µg QD	UMEC 31.5 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Total # participants affected/at risk	0/126 (0%)	0/131 (0%)	0/138 (0%)	0/133 (0%)	0/128 (0%)	1/135 (0.74%)
Pregnancy, puerperium and perinatal conditions						
Spontaneous abortion † [A]						
# participants affected/at risk	0/126 (0%)	0/131 (0%)	0/138 (0%)	0/133 (0%)	0/128 (0%)	1/135 (0.74%)
# events						

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Total # participants affected/at risk	0/126 (0%)	0/133 (0%)
Pregnancy, puerperium and perinatal conditions		
Spontaneous abortion † [A]		
# participants affected/at risk	0/126 (0%)	0/133 (0%)
# events		

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

Other Adverse Events

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

	Placebo	UMEC 15.6 µg QD	UMEC 31.5 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Total # participants affected/at risk	4/126 (3.17%)	7/131 (5.34%)	7/138 (5.07%)	12/133 (9.02%)	11/128 (8.59%)	12/135 (8.89%)
General disorders						
Product taste abnormal † [A]						
# participants affected/at risk	0/126 (0%)	0/131 (0%)	2/138 (1.45%)	1/133 (0.75%)	4/128 (3.12%)	5/135 (3.7%)
# events						
Infections and infestations						
Nasopharyngitis † [A]						
# participants affected/at risk	1/126 (0.79%)	3/131 (2.29%)	0/138 (0%)	1/133 (0.75%)	3/128 (2.34%)	1/135 (0.74%)
# events						
Pharyngitis † [A]						
# participants affected/at risk	1/126 (0.79%)	0/131 (0%)	1/138 (0.72%)	5/133 (3.76%)	0/128 (0%)	1/135 (0.74%)
# events						
Nervous system disorders						

	Placebo	UMEC 15.6 µg QD	UMEC 31.5 µg QD	UMEC 62.5 µg QD	UMEC 125 µg QD	UMEC 250 µg QD
Headache † [A]						
# participants affected/at risk	2/126 (1.59%)	5/131 (3.82%)	4/138 (2.9%)	5/133 (3.76%)	4/128 (3.12%)	6/135 (4.44%)
# events						

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
Total # participants affected/at risk	7/126 (5.56%)	7/133 (5.26%)
General disorders		
Product taste abnormal † [A]		
# participants affected/at risk	1/126 (0.79%)	0/133 (0%)
# events		
Infections and infestations		
Nasopharyngitis † [A]		
# participants affected/at risk	4/126 (3.17%)	2/133 (1.5%)
# events		
Pharyngitis † [A]		
# participants affected/at	1/126 (0.79%)	0/133 (0%)

	UMEC 15.6 µg BID	UMEC 31.25 µg BID
risk		
# events		
Nervous system disorders		
Headache † [A]		
# participants affected/at risk	2/126 (1.59%)	6/133 (4.51%)
# 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: