Protocol Registration Receipt
03/27/2014

A Study to Assess the Safety and Tolerability of Once Daily Inhaled Doses of GSK573719 Made With Magnesium Stearate in Subjects With Chronic Obstructive Pulmonary Disease(COPD)for 7 Days

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT00732472

Purpose

The study drug which is an inhaled bronchodilator (lung airway relaxant)has been given to both healthy volunteers and to COPD patients before. This study will assess a new formulation of GSK573719. Many drugs are known to deteriorate over time. To make the study medicine less likely to deteriorate in its container, it is mixed with an inactive substance that helps to to maintain the quality of the study medicine. Previous studies have looked at GSK573719 with another inactive substance called Cellobiose Octaacetate (COA). This study will be looking at a new formulation of GSK573719 using Magnesium Stearate (MgSt) as the inactive substance. MgSt itself is not a medicine but is approved as a food ingredient and has also has been approved to be used in a number of marketed medical inhalers. The purpose of this study is to assess the safety and tolerability of compound GSK573719 with Magnesium Stearate for once-daily treatment of COPD(Chronic Obstructive Pulmonary Disease). This drug will be given to 2 groups of 12 people for 7 days. Group 1 will receive 250mcg or placebo and group 2

will receive 1000mcg or placebo. Group 2 will not be dosed until at least 6 people have completed dosing in group 1 without any significant safety concerns. The following safety measures will be assessed including: ECGs, heart rate, blood pressure, blood samples for safety labs, lung function and 24 hour monitoring of the heart. We will also take blood and urine samples to measure medication levels in the body.

GlaxoSmithKline will be funding the research and it will be recruiting at Synexus in 7 of their centres in the UK.

Condition	Intervention	Phase
Pulmonary Disease, Chronic Obstructive	Drug: GSK573719	Phase 2

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety Study
Official Title: A Randomised, Double-blind, Placebo-controlled, Dose Ascending, 2-cohort, Parallel Group Study to Examine the Safety, Tolerability and Pharmacokinetics of Once-daily Inhaled Doses of GSK573719 Formulated With the Excipient Magnesium Stearatein COPD Subjects for 7 Days

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Number of Participants With Any On-treatment Adverse Event (AE) or Any On-treatment Serious Adverse Event (SAE) [Time Frame: From start of treatment to study day 12] [Designated as safety issue: No]

  An AE is defined as any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An on-treatment adverse event is defined as an event that occurred between the start of investigational product and follow-up contact. Refer to the general SAE/non-serious AE module for a complete list of AEs reported in the study. 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, or is a congenital anomaly/birth defect.
- Mean Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) on Days 1 and 7 [Time Frame: Day 1 (pre-dose and 15 minutes [min], 45 min, 1.5 hours [hr], 4 hr, and 8 hr post-dose) and Day 7 (pre-dose and 15 min, 45 min, 1.5 hr, 4 hr, 8 hr, and 24 hr post-dose)] [Designated as safety issue: No]

  Blood pressure was measured in a semi-recumbent position at approximately 45 degrees after the participant was kept at rest for at least 5 minutes. SBP and DBP were obtained at pre-dose and 15 min, 45 min, 1.5 hr, 4 hr, and 8 hr post-dose (PD) on Day 1 and at pre-dose and 15 min, 45 min, 1.5 hr, 4 hr, 8 hr, and 24 hr PD on Day 7.
- Mean Heart Rate (HR) on Days 1 and 7 [Time Frame: Day 1 (pre-dose and 15 minutes [min], 45 min, 1.5 hours [hr], 4 hr, and 8 hr post-dose) and Day 7 (pre-dose and 15 min, 45 min, 1.5 hr, 4 hr, 8 hr, and 24 hr post-dose)] [Designated as safety issue: No]

  HR was measured in a semi-recumbent position at approximately 45 degrees after the participant was kept at rest for at least 5 minutes. HR was obtained at pre-dose and 15 min, 45 min, 1.5 hr, 4 hr, and 8 hr post-dose (PD) on Day 1 and at pre-dose and 15 min, 45 min, 1.5 hr, 4 hr, 8 hr, and 24 hr PD on Day 7.
- Maximum and Weighted Mean (0-4 Hour) Heart Rate at Days 1 and 7 [Time Frame: Day 1 and Day 7] [Designated as safety issue: No]

Maximum heart rate (Max HR) and weighted mean (WM) from 0-4 hour on Days 1 and 7 were derived. Max HR (0-4 h) is defined as the maximum heart rate attained within 0-4 h. The weighted mean HR (0-4 h) was derived by calculating the area under the curve, and then dividing the value by the relevant time interval. Each of the maximum and weighted mean (0-4h) endpoints for heart rate, was statistically analyzed using a mixed effects model. The terms treatment, baseline, day and any relevant interactions were considered in the model. Least squares means are adjusted for treatment, Baseline, day, treatment by Baseline and Baseline by day interaction, where Baseline is defined as the mean of the three pre-dose assessments.

- Number of Participants With the Indicated 12-lead Electrocardiogram (ECG) Values on Days 1 and 7 [Time Frame: Day 1 (pre-dose and 15 min, 45 min, 1.5 hr, 4 hr, and 8 hr post-dose) and Day 7 (pre-dose and 15 min, 45 min, 1.5 hr, 4 hr, 8 hr, and 24 hr)] [Designated as safety issue: No]

  The number of participants with normal (NL), abnormal not clinically significant (Abn NCS), and abnormal clinically significant (Abn CS) ECG findings, as well as those with unavailable results (NA) at pre-dose (PD1, PD2, PD3), and 15 min, 45 min, 1.5 hr, 4 hr, and 8 hr post-dose (PD) on Day 1 and at pre-dose (PD1, PD2, PD3), and 15 min, 45 min, 1.5 hr, 4 hr, 8 hr, and 24 hr post-dose on Day 7 are reported. The following are of potential clinical importance: absolute QTc interval >450 milliseconds (msec); increase from Baseline QTc >60 msec; PR interval <110 and >220 msec; QRS interval <75 and >110 msec. Clinical significance was based on the medical and scientific judgement of the investigator or qualified designee.

- Number of Participants With Abnormal 24-hour Holter Findings at Screening and Day 7 [Time Frame: Screening and Day 7] [Designated as safety issue: No]

  Twenty-four hour Holter ECG values were obtained at Screening and on Day 7. During the Screening procedure and study, standard Holter monitors were used (in order to exclude participants with underlying cardiac arrhythmogenicity). During the treatment periods, Holter monitors were only switched on immediately prior to dosing (up to 15 minutes pre-dose) so as to capture Holter ECG data from the 24 hour period following dosing. The following summary data were transcribed into the Case Report Form: Maximum and mean (0 to24 hour) heart rate; normal and aberrant beats and arrhythmias. Analysis of the Holter tapes was arranged by GlaxoSmithKline.The number of participants with normal (NL), abnormal not clinically significant (Abn NCS), and abnormal clinically significant (Abn CS) ECG findings, as well as those with unavailable results (NA) at Screening and Day 7, are reported. Clinical significance was based on the medical and scientific judgement of the investigator or qualified designee.

- Maximum and Mean (0-24 Hour) Heart Rate From Holter Monitoring on Day 7 [Time Frame: Day 7] [Designated as safety issue: No]

  Maximum heart rate (Max HR) and mean HR from 0-24 hour Holter monitoring on treatment Day 7 were derived. The analysis was adjusted for treatment and Baseline, where Baseline is defined as the corresponding summary measure (i.e., mean heart rate [0-24 hours] or maximum heart rate [0-24 hours]) from screening records.

- Mean Forced Expiratory Volume in One Second (FEV1) at Screening and on Days 1 and 7 [Time Frame: Screening, Day 1, and Day 7] [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. FEV1 was measured at Screening, pre-dose, and 4 hours (hr) post-dose on Day 1 and Day 7. FEV1 tests were repeated until three technically acceptable measurements were made.

- Total Number of Salbutamol Doses Taken Over the 7 -Day Study Period [Time Frame: Day 1 to Day 7] [Designated as safety issue: No]

  The total number of salbutamol doses taken per day was recorded by the participants in their dairy card over the entire 7-day treatment period. Diaries were reviewed by the Investigator when participants were admitted to the unit on Day 1, Day 7, and Day 8. Salbutamol was given as rescue medication, defined as a quick-relief or fast-acting medication that is given in addition to the investigational drug or placebo that can alleviate symptoms due to disease or lack of efficacy of the study treatment.

- Albumin, Total Protein, Hemoglobin, and Mean Corpuscle Hemoglobin Concentration (MCHC) Values on Day 1 and Day 7 [Time Frame: Day 1 and Day 7] [Designated as safety issue: No]

  Blood samples were collected for the measurement of albumin, total protein, hemoglobin, and MCHC values pre-dose on Day 1 and Day 7.
- Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and Gamma Glutamyl Transferase (GGT) Values on Day1 and Day 7 [Time Frame: Day 1 and Day 7] [Designated as safety issue: No]

  Blood samples were collected for the measurement of ALP, ALT, AST, and GGT Pre-dose on Day 1 and Day 7.
- Direct Bilirubin, Total Bilirubin, and Creatinine Values on Day 1 and Day 7 [Time Frame: Day 1 and Day 7] [Designated as safety issue: No]

  Blood samples were collected for the measurement of direct bilirubin, total bilirubin, and creatinine at pre-dose on Day 1 and Day 7.
- Calcium, Glucose, Potassium, Sodium, and Urea/Blood Urea Nitrogen (BUN) Values on Day 1 and Day 7 [Time Frame: Day 1 and Day 7] [Designated as safety issue: No]

  Blood samples were collected for the measurement of calcium, glucose, potassium, sodium, and urea/BUN pre-dose on Day 1 and Day 7.
- Basophil, Eosinophil, Lymphocyte, Monocyte, Total Neutrophil (ANC: Absolute Neutrophil Count), Platelet, and White Blood Cell (WBC) Count Values on Day 1 and Day 7 [Time Frame: Day 1 and Day 7] [Designated as safety issue: No]

  Blood samples were collected for the measurement of basophils, eosinophils, lymphocytes, monocytes, total neutrophils (ANC), platelets, and white blood cell (WBC) count pre-dose on Day 1 and Day 7.
- Mean Corpuscle Hemoglobin (MCH) Values on Day 1 and Day 7 [Time Frame: Day 1 and Day 7] [Designated as safety issue: No]

  Blood samples were collected for the measurement of MCH pre-dose on Day 1 and Day 7.
- Mean Corpuscle Volume (MCV) Values on Day 1 and Day 7 [Time Frame: Day 1 and Day 7] [Designated as safety issue: No]

  Blood samples were collected for the measurement of MCV pre-dose on Day 1 and Day 7.

Secondary Outcome Measures:

- Mean AUC(0-2), AUC(0-8), and AUC(0-t) of UMEC on Day 1 and Day 7 [Time Frame: Day 1 and Day 7: pre-dose, and 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, and 8 hr post-dose; 24 hr post-dose on Day 7] [Designated as safety issue: No]

  Area under the concentration-time (AUC) curve from time zero (pre-dose) to 2 hours (AUC[0-2]), from time zero to 8 hours (AUC[0-8]), from time zero to the last time of a quantifiable concentration of UMEC (AUC[0-t]) on Day 1 and Day 7 were measured. AUC is a measure of systemic exposure. Blood samples were collected pre-dose and 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, and 8 hr post-dose on Day 1 and Day 7. Also, a 24 hr blood sample was collected on Day 7.
- Cmax of UMEC on Day 1 and Day 7 [Time Frame: Day 1 and Day 7: pre-dose, and 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, and 8 hr post-dose; 24 hr post-dose on Day 7] [Designated as safety issue: No]

  Cmax is defined as the maximum observed concentration of UMEC and was measured on Day 1 and Day 7. Blood samples were collected pre-dose and 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, and 8 hr post-dose on Day 1 and Day 7. Also, a 24 hr blood sample was collected on Day 7.
- Tmax and Tlastof UMEC on Day 1 and Day 7 [Time Frame: Day 1 and Day 7: pre-dose, and 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, and 8 hr post-dose; 24 hr post-dose on Day 7] [Designated as safety issue: No]

  Tmax is defined as the time to reach the observed maximum concentration, and tlast is defined as the time of the last quantifiable concentration of UMEC; both were measured on Day 1 and Day 7. Blood samples were collected pre-dose, and 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, and 8 hr post-dose

on Day 1 and Day 7. Also, a 24 hr blood sample was collected on Day 7.

- Ae(0-4), Ae(0-8), Ae(0-12), and Ae(0-24) of UMEC on Day 1 and Day 7 [Time Frame: From 0-8 hours (hr), 8-12 hr, and 12-24 hr on Day 1; from 0-4 hr, 4-8 hr, 8-12 hr, and 12-24 hr on Day 7] [Designated as safety issue: No]
  Urinary recovery of unchanged drug (UMEC) within the first 8, 12, and 24 hours (Ae[0-8], Ae[0-12], and Ae[0-24], respectively) on Day 1 and within the first 4, 8, 12, and 24 hours (Ae[0-4], Ae[0-8], Ae[0-12], and Ae[0-24], respectively) on Day 7 was estimated. Urine samples were collected from 0-8 hours (hr), 8-12 hr, and 12-24 hr on Day 1 and from 0-4 hr, 4-8 hr, 8-12 hr, and 12-24 hr on Day 7.
- Fe(0-4), Fe(0-8), Fe(0-12), and Fe(0-24) of UMEC on Day 1 and Day 7 [Time Frame: From 0-8 hours (hr), 8-12 hr, and 12-24 hr on Day 1; from 0-4 hr, 4-8 hr, 8-12 hr, and 12-24 hr on Day 7] [Designated as safety issue: No]
  The fraction of the total dose excreted (Fe) in each interval was estimated as the urinary recovery of unchanged drug (Ae) per dose. Urine samples were collected from 0-8 hours (hr), 8-12 hr, and 12-24 hr on Day 1 and from 0-4 hr, 4-8 hr, 8-12 hr, and 12-24 hr on Day 7.
- Renal Clearance of UMEC on Day 1 and Day 7 [Time Frame: From 0-8 hours (hr), 8-12 hr, and 12-24 hr on Day 1; from 0-4 hr, 4-8 hr, 8-12 hr, and 12-24 hr on Day 7] [Designated as safety issue: No]
  Renal clearance was calculated as the urinary recovery of unchanged drug from time zero to time x (Ae[0-x])/area under concentration from time zero to time x (AUC[0-x]) for the longest period of time after dosing when both could be accurately determined (where x is either 8, 12, or 24). Urine samples were collected from 0-8 hours (hr), 8-12 hr, and 12-24 hr on Day 1 and from 0-4 hr, 4-8 hr, 8-12 hr, and 12-24 hr on Day 7.
- Urine Half Life (t1/2) of UMEC on Day 7 [Time Frame: From 0-4 hours (hr), 4-8 hr, 8-12 hr, and 12-24 hr on Day 7] [Designated as safety issue: No]
  Urine half life (t1/2) of UMEC on Day 7 was estimated. Urine samples were collected from 0-4 hours (hr), 4-8 hr, 8-12 hr, and 12-24 hr on Day 7.

Enrollment: 37
Study Start Date: October 2008
Study Completion Date: August 2009
Primary Completion Date: August 2009

Arms	Assigned Interventions
Experimental: 7 day repeat dose 7 day repeat dose	Drug: GSK573719 7 day repeat dose Other Names: GSK573719

Eligibility

Ages Eligible for Study: 40 Years to 75 Years
Genders Eligible for Study: Both

Inclusion Criteria:

- Male or female between 40 and 75 years of age
- A female subject is eligible to participate if she is of:
    - Non childbearing potential including pre-menopausal females with documented (medical report verification) hysterectomy, bilateral salpingectomy or bilateral oophorectomy or postmenopausal defined as 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL and estradiol < 40 pg/ml (<140 pmol/L) or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.
- Male subjects must agree to use one of the listed contraception methods. This criterion must be followed from the time of the first dose of study medication until 90 days post-last dose.
- Subject diagnosed with COPD, as defined by the GOLD guidelines.
- BMI within the range 18 - 34 kg/m2 (inclusive).
- Subject is a smoker or an ex-smoker with a smoking history of at least 10 pack years (Pack years = (cigarettes per day smoked/20) x number of years smoked)).
- Average QTcB or QTcF ≤ 450 msec taken from triplicate assessments at screening; or QTc ≤ 480 msec in subjects with Bundle Branch Block.
- Subject has a post-bronchodilator (400 µg salbutamol) FEV1 of ≥ 35% to ≤ 80% of predicted normal.
- Subject has FEV1/FVC < 0.7 post-bronchodilator (400 µg salbutamol).
- Subjects have a 24hour holter recording that is within normal limits for the individual and does not demonstrate any clinically important abnormality that, in the opinion of the investigator, would make the subject unsuitable for participation in the study.
- Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
- Subject is available to complete all study measurements and procedures.

Exclusion Criteria:

- Subjects who have a past or present disease, which as judged by the Investigator, may affect subject safety or influence the outcome of the study.
- The subject has a positive pre-study drug/alcohol screen. A minimum list of drugs that will be screened for include amphetamines, barbiturates, cocaine and opiates.

The detection of drugs taken for a legitimate medical purpose would not necessarily be an exclusion to study participation. The detection of alcohol would not be an exclusion at screening but would need to be negative pre-dose and during the study.

- Female subject has a positive pregnancy test.
- A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months of screening.
- A positive test for HIV antibody (if tested, according to local SOP's).
- History of high alcohol consumption within 1 month of the study defined as:
    - an average weekly intake of greater than 21 units or an average daily intake of greater than 3 units (males), or defined as an average weekly intake of greater than 14 units or an average daily intake of greater than 2 units (females). One unit is equivalent to a half-pint (220mL) of beer or 1 (25ml)

measure of spirits or 1 glass (125ml) of wine.

- The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
- Exposure to more than four new chemical entities within 12 months prior to the first dosing day.
- History of sensitivity to any of the study medications, or components thereof (including allergy to milk protein/lactose) or a history of drug or other allergy that, in the opinion of the Investigator or GSK Medical Monitor, contraindicates their participation.
- Subject has donated a unit (400 mL) of blood within 60 days of screening or, intends to donate during the study.
- Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56 day period.
- Unwillingness or inability to follow the procedures outlined in the protocol.
- The subject is unable to use the novel dry powder inhaler correctly.
- The subject requires treatment for prostate hypertrophy.
- The subject has a history of narrow angle glaucoma.

Respiratory criteria

- Subject has a diagnosis of active tuberculosis, lung cancer, clinically overt bronchiectasis, pulmonary fibrosis, asthma or any other respiratory condition that might, in the opinion of the Investigator, compromise the safety of the subject or affect the interpretation of the results.
- Subject has poorly controlled COPD, defined as the occurrence of any of the following:
    - Either: acute worsening of COPD that is managed by the subject at home requiring treatment with corticosteroids in the 2 weeks prior to the screening visit.
    - Or: more than two exacerbations in the previous 4 months prior to the screening visit that required a course of oral corticosteroids or, for which the subject was hospitalised.
- Subject has had a respiratory tract infection in the 2 weeks prior to first dose.

Cardiovascular criteria

- Current congestive heart failure (greater than NYHA II) and myocardial infarction (within 9 months of the screening date).
- A history of clinically significant arrhythmia or clinically important 24 h Holter findings that, in the opinion of the Investigator, would cause a safety concern for entry into the study.
- A mean QTc(B) value at screening >450msec, or an ECG that is not suitable for QT measurements (e.g. LBBB or poorly defined termination of the T wave).
- Third degree heart block or pacemaker.
- Risk factors for torsades des pointes (heart failure NYHA II-IV, familial long QT syndrome).
- Elevated resting blood pressure or a mean blood pressure equal to or higher than 150/90 mmHg at screening. A history of and treatment for hypertension is acceptable provided control has been achieved for > 2 months prior to screening.
- A mean heart rate outside the range 50-100 bpm at screening.

Concurrent medication criteria

- Subject requires treatment with nebulised beta-2 agonist or nebulised anticholinergics.
- Subject has received oral or parenteral corticosteroids within 2 weeks of screening.
- Subject is unable to abstain from long-acting bronchodilators from 48 hours prior to the screening and treatment periods (i.e. the last assessment in the dosing period).

(Note, subjects may resume use of their usual medication in between screening and the treatment period if the restrictions in Section 9 Concomitant Medications and Non-Drug Therapies are followed and provided the long acting bronchodilator component is stopped again 48h or more prior to dosing).

- Subject is receiving co-medication with drugs which are commonly recognised to prolong the QTc interval (e.g. quinolones, amiodorane, disopyramide, quinidine, sotalol, chlorpromazine, haloperidol, ketoconazole, terfenadine, cisapride and terodiline).
- Subject requires regular treatment with oral corticosteroids (prednisolone or equivalent).
- Subject is receiving treatment with beta-blockers, except eye drops.
- Subject is receiving treatment with long-term or short-term oxygen therapy, NIPPV or requires nocturnal positive pressure for sleep apnea.

Contacts and Locations

Locations

United Kingdom

GSK Investigational Site
Clydebank, Glasgow, United Kingdom, G81 2DR

GSK Investigational Site
Edgbaston, Birmingham, United Kingdom, B15 2SQ

GSK Investigational Site
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GSK Investigational Site
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GSK Investigational Site
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GSK Investigational Site
Buckshaw Village, Chorley, Lancashire, United Kingdom, PR7 7NA

GSK Investigational Site
Waterloo, Liverpool, Merseyside, United Kingdom, L22 0LG

Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Publications:

Tal-Singer R, Cahn T, Mehta R, Preece A, Crater G, Kelleher D, Pouliquen IJ. Initial assessment of single and repeat doses of inhaled umeclidinium in patients with chronic obstructive pulmonary disease: Two randomised studies. Eur J Pharmacol. 2013;701:40-48.

Responsible Party:	GlaxoSmithKline
Study ID Numbers:	105211
Health Authority:	United Kingdom: Medicines and Healthcare Products Regulatory Agency

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Study Results

Participant Flow

Recruitment Details

Participants=par.; umeclidinium=UMEC. A total of 37 unique par. were enrolled in the study; however, 1 par. was randomized and dosed on two separate occasions and is counted as two separate par. on all outputs (thus, 38 par. started study treatment).

Pre-Assignment Details

Participants were assigned to one of two cohorts: UMEC 250 micrograms (µg) once daily (QD) or placebo (Cohort 1) and UMEC 1000 µg QD or placebo (Cohort 2) for 7 days. After reporting of Cohorts 1 and 2, it was found that par. in Cohort 2 received UMEC 250 µg in error. Cohort 3 was then recruited, in which par. received UMEC 1000 µg QD or placebo.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).

	Description
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Overall Study

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Started	9	10 [1]	10	9
Completed	9	7	9	6
Not Completed	0	3	1	3
Adverse Event	0	1	1	1
Protocol Violation	0	0	0	1
Withdrawal by Subject	0	2	0	1

[1] One par. (counted as 2 on outputs) was randomized/dosed with UMEC 250 µg on 2 separate occasions.

Baseline Characteristics

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Baseline Measures

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg	Total
Number of Participants	9	10	10	9	38
Age, Continuous [units: Years] Mean (Standard Deviation)	66.2 (4.47)	63.3 (8.21)	64.7 (6.31)	64.2 (7.97)	64.6 (6.72)
Gender, Male/Female [units: Participants]					
Female	4	4	2	4	14
Male	5	6	8	5	24

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg	Total
Race/Ethnicity, Customized White - White/Caucasian/European Heritage [units: participants]	9	10	10	9	38

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants With Any On-treatment Adverse Event (AE) or Any On-treatment Serious Adverse Event (SAE)
Measure Description	An AE is defined as any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An on-treatment adverse event is defined as an event that occurred between the start of investigational product and follow-up contact. Refer to the general SAE/non-serious AE module for a complete list of AEs reported in the study. 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, or is a congenital anomaly/birth defect.
Time Frame	From start of treatment to study day 12
Safety Issue?	No

Analysis Population Description

All Subjects Population: all participants who received at least one dose of study medication

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	9	10	10	9
Number of Participants With Any On-treatment Adverse Event (AE) or Any On-treatment Serious Adverse Event (SAE) [units: participants]				
Any on-treatment AE	6	2	8	5
Any on-treatment SAE	0	0	0	0

2. Primary Outcome Measure:

Measure Title	Mean Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) on Days 1 and 7
Measure Description	Blood pressure was measured in a semi-recumbent position at approximately 45 degrees after the participant was kept at rest for at least 5 minutes. SBP and DBP were obtained at pre-dose and 15 min, 45 min, 1.5 hr, 4 hr, and 8 hr post-dose (PD) on Day 1 and at pre-dose and 15 min, 45 min, 1.5 hr, 4 hr, 8 hr, and 24 hr PD on Day 7.
Time Frame	Day 1 (pre-dose and 15 minutes [min], 45 min, 1.5 hours [hr], 4 hr, and 8 hr post-dose) and Day 7 (pre-dose and 15 min, 45 min, 1.5 hr, 4 hr, 8 hr, and 24 hr post-dose)
Safety Issue?	No

Analysis Population Description

All Subjects Population (ASP). Only participants with data available at the indicated time points were summarized. Different participants may have been summarized for different parameters/at different time points (reflected by n=X, X, X, X in the category titles), so the overall number of participants summarized reflects everyone in the ASP.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were

	Description
	to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	9	10	10	9
Mean Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) on Days 1 and 7 [units: Millimeters of mercury (mmHg)] Mean (Standard Deviation)				
SBP, Day 1, pre-dose, n=9, 10, 10, 9	138.9 (11.43)	132.8 (11.97)	137.4 (10.71)	138.6 (19.13)
SBP, Day 1, 15 min PD, n=9, 9, 10, 8	135.1 (12.96)	134.9 (15.05)	137.7 (9.94)	135.0 (14.72)
SBP, Day 1, 45 min PD, n=9, 9, 10, 9	133.3 (9.35)	135.8 (14.63)	133.9 (11.28)	140.1 (17.64)
SBP, Day 1, 1.5 hr PD, n=9, 9, 10, 9	140.0 (19.42)	138.2 (15.79)	142.1 (12.91)	145.0 (21.27)
SBP, Day 1, 4 hr PD, n=9, 9, 10, 9	141.0 (15.41)	139.4 (21.43)	141.6 (8.86)	138.9 (11.79)
SBP, Day 1, 8 hr PD, n=9, 9, 10, 9	134.8 (12.22)	135.7 (15.28)	140.8 (13.14)	146.2 (14.19)
SBP, Day 7, pre-dose, n=9, 7, 9, 6	134.3 (9.16)	131.8 (14.47)	139.3 (10.59)	120.2 (10.97)
SBP, Day 7, 15 min PD, n=9, 7, 9, 6	141.3 (13.95)	134.4 (15.54)	138.8 (12.67)	127.5 (14.29)
SBP, Day 7, 45 min PD, n=9, 7, 9, 6	139.7 (13.93)	135.4 (19.08)	135.8 (9.28)	126.3 (14.28)
SBP, Day 7, 1.5 hr PD, n=9, 7, 9, 6	137.8 (15.34)	141.6 (18.35)	141.3 (10.9)	130.2 (10.76)

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
SBP, Day 7, 4 hr PD, n=9, 7, 9, 6	139.4 (12.91)	139.6 (15.18)	141.6 (8.56)	135.0 (14.6)
SBP, Day 7, 8 hr PD, n=9, 7, 9, 6	136.1 (13.17)	129.4 (14.32)	136.1 (13.7)	125.7 (8.29)
SBP, Day 7, 24 hr PD, n=9, 7, 9, 6	132.1 (9.49)	135.7 (9.39)	136.0 (9.82)	127.5 (7.71)
DBP, Day 1, pre-dose, n=9, 10, 10, 9	81.6 (8.52)	79.0 (6.69)	82.1 (7.63)	82.4 (5.25)
DBP, Day 1, 15 min PD, n=9, 9, 10, 8	79.6 (9.76)	83.6 (7.47)	81.4 (7.71)	85.8 (10.46)
DBP, Day 1, 45 min PD, n=9, 9, 10, 9	78.9 (8.85)	79.6 (9.58)	82.8 (9.96)	83.8 (7.90)
DBP, Day 1, 1.5 hr PD, n=9, 9, 10, 9	79.3 (8.54)	82.3 (9.26)	84.0 (6.55)	85.4 (6.88)
DBP, Day 1, 4 hr PD, n=9, 9, 10, 9	83.4 (11.14)	81.0 (10.91)	83.1 (11.13)	83.7 (6.06)
DBP, Day 1, 8 hr PD, n=9, 9, 10, 9	77.8 (8.67)	79.9 (8.85)	80.5 (7.84)	85.3 (6.08)
DBP, Day 7, pre-dose, n=9, 7, 9, 6	78.7 (8.64)	82.6 (8.85)	85.8 (7.79)	76.5 (4.35)
DBP, Day 7, 15 min PD, n=9, 7, 9, 6	82.8 (11.78)	82.7 (9.11)	82.9 (9.29)	81.8 (5.46)
DBP, Day 7, 45 min PD, n=9, 7, 9, 6	80.6 (10.36)	81.4 (9.45)	82.4 (7.04)	81.8 (6.49)
DBP, Day 7, 1.5 hr PD, n=9, 7, 9, 6	82.2 (9.91)	82.6 (8.90)	83.1 (9.97)	81.7 (3.50)
DBP, Day 7, 4 hr PD, n=9, 7, 9, 6	79.0 (8.97)	84.0 (7.68)	83.0 (8.09)	81.0 (4.00)
DBP, Day 7, 8 hr PD, n=9, 7, 9, 6	76.2 (8.70)	77.1 (11.51)	80.7 (7.45)	77.8 (3.54)
DBP, Day 7, 24 hr PD, n=9, 7, 9, 6	78.2 (8.87)	81.6 (9.05)	81.7 (9.70)	79.8 (4.79)

3. Primary Outcome Measure:

Measure Title	Mean Heart Rate (HR) on Days 1 and 7
Measure Description	HR was measured in a semi-recumbent position at approximately 45

	degrees after the participant was kept at rest for at least 5 minutes. HR was obtained at pre-dose and 15 min, 45 min, 1.5 hr, 4 hr, and 8 hr post-dose (PD) on Day 1 and at pre-dose and 15 min, 45 min, 1.5 hr, 4 hr, 8 hr, and 24 hr PD on Day 7.
Time Frame	Day 1 (pre-dose and 15 minutes [min], 45 min, 1.5 hours [hr], 4 hr, and 8 hr post-dose) and Day 7 (pre-dose and 15 min, 45 min, 1.5 hr, 4 hr, 8 hr, and 24 hr post-dose)
Safety Issue?	No

Analysis Population Description

All Subjects Population. Only participants with data available at the indicated time points were summarized. Different participants may have been summarized for different parameters/at different time points (reflected by n=X, X, X, X in the category titles), so the overall number of participants summarized reflects everyone in the ASP.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	9	10	10	9
Mean Heart Rate (HR) on Days 1 and 7 [units: Beats per minute] Mean (Standard Deviation)				
Day 1, pre-dose, n=9, 10, 10, 9	70.9 (11.09)	68.3 (10.42)	72.8 (11.69)	64.7 (10.34)
Day 1, 15 min PD, n=9, 9, 10, 8	68.2 (10.28)	67.4 (11.28)	71.4 (9.86)	72.3 (13.56)
Day 1, 45 min PD, n=9, 9, 10, 9	66.0 (9.33)	62.3 (10.90)	70.2 (11.95)	66.4 (14.78)
Day 1, 1.5 hr PD, n=9, 9, 10, 9	63.3 (9.42)	60.7 (12.06)	65.8 (10.30)	64.2 (11.05)
Day 1, 4 hr PD, n=9, 9, 10, 9	64.0 (10.37)	62.0 (10.31)	70.2 (10.74)	65.7 (10.20)
Day 1, 8 hr PD, n=9, 9, 10, 9	72.6 (9.93)	67.4 (9.62)	77.2 (11.73)	74.4 (7.35)
Day 7, pre-dose, n=9, 7, 9, 6	70.1 (7.90)	71.3 (12.64)	71.4 (14.01)	69.7 (10.51)
Day 7, 15 min PD, n=9, 7, 9, 6	67.0 (6.61)	69.4 (12.16)	68.9 (12.19)	74.8 (9.39)
Day 7, 45 min PD, n=9, 6, 9, 6	66.8 (9.16)	66.3 (11.88)	66.6 (10.98)	70.0 (10.00)
Day 7, 1.5 hr PD, n=9, 7, 9, 6	65.3 (7.86)	64.0 (10.92)	63.8 (8.96)	67.7 (11.13)
Day 7, 4 hr PD, n=9, 7, 9, 6	64.1 (7.61)	62.7 (7.74)	62.6 (9.79)	67.5 (7.50)
Day 7, 8 hr PD, n=9, 7, 9, 6	74.8 (6.83)	71.0 (8.60)	74.8 (8.91)	73.8 (7.41)
Day 7, 24 hr PD, n=9, 7, 9, 6	73.8 (7.00)	75.6 (11.50)	72.6 (8.97)	70.8 (9.89)

4. Primary Outcome Measure:

Measure Title	Maximum and Weighted Mean (0-4 Hour) Heart Rate at

	Days 1 and 7
Measure Description	Maximum heart rate (Max HR) and weighted mean (WM) from 0-4 hour on Days 1 and 7 were derived. Max HR (0-4 h) is defined as the maximum heart rate attained within 0-4 h. The weighted mean HR (0-4 h) was derived by calculating the area under the curve, and then dividing the value by the relevant time interval. Each of the maximum and weighted mean (0-4h) endpoints for heart rate, was statistically analyzed using a mixed effects model. The terms treatment, baseline, day and any relevant interactions were considered in the model. Least squares means are adjusted for treatment, Baseline, day, treatment by Baseline and Baseline by day interaction, where Baseline is defined as the mean of the three pre-dose assessments.
Time Frame	Day 1 and Day 7
Safety Issue?	No

Analysis Population Description

All Subjects Population (ASP). The number of participants presented represent those with data available at the time point being presented; however, all participants in the ASP without missing covariate information are included in the analysis.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they

	Description
	received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	9	10	10	9
Maximum and Weighted Mean (0-4 Hour) Heart Rate at Days 1 and 7 [units: Beats per minute] Least Squares Mean (Standard Error)				
Day 1, Max HR, n=9, 10, 10, 9	68.30 (2.009)	70.56 (1.910)	71.57 (1.924)	75.79 (2.066)
Day 7, Max HR, n=9, 7, 9, 6	68.99 (1.917)	70.24 (2.203)	66.74 (1.964)	77.69 (2.398)
Day 1, WM, n=9, 9, 10, 9	63.84 (1.582)	63.62 (1.584)	66.17 (1.514)	70.00 (1.627)
Day 7, WM, n=9, 7, 9, 6	64.83 (1.682)	64.98 (1.874)	62.32 (1.698)	71.89 (2.026)

Statistical Analysis 1 for Maximum and Weighted Mean (0-4 Hour) Heart Rate at Days 1 and 7

Groups	Placebo, Cohort 1 UMEC 250 µg
Method	
Mean Difference (Final Values)	2.26
Standard Error of the mean	± 2.777
95% Confidence Interval	-3.39 to 7.91

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

[Not specified.]

Other relevant estimation information:

Day 1, Max HR

Statistical Analysis 2 for Maximum and Weighted Mean (0-4 Hour) Heart Rate at Days 1 and 7

Groups	Placebo, Cohort 1 UMEC 250 µg
Method	
Mean Difference (Final Values)	1.25
Standard Error of the mean	± 2.922
95% Confidence Interval	-4.78 to 7.28

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

[Not specified.]

Other relevant estimation information:

Day 7, Max HR

Statistical Analysis 3 for Maximum and Weighted Mean (0-4 Hour) Heart Rate at Days 1 and 7

Groups	Placebo, Cohort 2 UMEC 250 µg in Error
Method	
Mean Difference (Final Values)	3.27
Standard Error of the mean	± 2.772
95% Confidence Interval	-2.37 to 8.91

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

[Not specified.]

Other relevant estimation information:

Day 1, Max HR

Statistical Analysis 4 for Maximum and Weighted Mean (0-4 Hour) Heart Rate at Days 1 and 7

Groups	Placebo, Cohort 2 UMEC 250 µg in Error
Method	
Mean Difference (Final Values)	-2.25
Standard Error of the mean	± 2.729
95% Confidence Interval	-7.89 to 3.39

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

[Not specified.]

Other relevant estimation information:

Day 7, Max HR

Statistical Analysis 5 for Maximum and Weighted Mean (0-4 Hour) Heart Rate at Days 1 and 7

Groups	Placebo, Cohort 3 UMEC 1000 µg
Method	
Mean Difference (Final Values)	7.49
Standard Error of the mean	± 2.899
95% Confidence Interval	1.59 to 13.39

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

[Not specified.]

Other relevant estimation information:

Day 1, Max HR

Statistical Analysis 6 for Maximum and Weighted Mean (0-4 Hour) Heart Rate at Days 1 and 7

Groups	Placebo, Cohort 3 UMEC 1000 µg
Method	
Mean Difference (Final Values)	8.70

Standard Error of the mean	± 3.079
95% Confidence Interval	2.34 to 15.05

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

[Not specified.]

Other relevant estimation information:

Day 7, Max HR

Statistical Analysis 7 for Maximum and Weighted Mean (0-4 Hour) Heart Rate at Days 1 and 7

Groups	Placebo, Cohort 1 UMEC 250 µg
Method	
Mean Difference (Final Values)	-0.23
Standard Error of the mean	± 2.243
95% Confidence Interval	-4.80 to 4.34

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

[Not specified.]

Other relevant estimation information:

Day 1, WM

Statistical Analysis 8 for Maximum and Weighted Mean (0-4 Hour) Heart Rate at Days 1 and 7

Groups	Placebo, Cohort 1 UMEC 250 µg
Method	
Mean Difference (Final Values)	0.15
Standard Error of the mean	± 2.520
95% Confidence Interval	-5.09 to 5.40

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

[Not specified.]

Other relevant estimation information:

Day 7, WM

Statistical Analysis 9 for Maximum and Weighted Mean (0-4 Hour) Heart Rate at Days 1 and 7

Groups	Placebo, Cohort 2 UMEC 250 µg in Error
Method	
Mean Difference (Final Values)	2.33
Standard Error of the mean	± 2.182
95% Confidence Interval	-2.12 to 6.77

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

[Not specified.]

Other relevant estimation information:

Day 1, WM

Statistical Analysis 10 for Maximum and Weighted Mean (0-4 Hour) Heart Rate at Days 1 and 7

Groups	Placebo, Cohort 2 UMEC 250 µg in Error
Method	
Mean Difference (Final Values)	-2.51
Standard Error of the mean	± 2.378
95% Confidence Interval	-7.48 to 2.45

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

[Not specified.]

Other relevant estimation information:

Day 7, WM

Statistical Analysis 11 for Maximum and Weighted Mean (0-4 Hour) Heart Rate at Days 1 and 7

Groups	Placebo, Cohort 3 UMEC 1000 µg
Method	
Mean Difference (Final Values)	6.16
Standard Error of the mean	± 2.282
95% Confidence Interval	1.51 to 10.81

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

[Not specified.]

Other relevant estimation information:

Day 1, WM

Statistical Analysis 12 for Maximum and Weighted Mean (0-4 Hour) Heart Rate at Days 1 and 7

Groups	Placebo, Cohort 3 UMEC 1000 µg
Method	
Mean Difference (Final Values)	7.06
Standard Error of the mean	± 2.642
95% Confidence Interval	1.57 to 12.54

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

[Not specified.]

Other relevant estimation information:

Day 7, WM

5. Primary Outcome Measure:

Measure Title	Number of Participants With the Indicated 12-lead Electrocardiogram (ECG) Values on Days 1 and 7

Measure Description	The number of participants with normal (NL), abnormal not clinically significant (Abn NCS), and abnormal clinically significant (Abn CS) ECG findings, as well as those with unavailable results (NA) at pre-dose (PD1, PD2, PD3), and 15 min, 45 min, 1.5 hr, 4 hr, and 8 hr post-dose (PD) on Day 1 and at pre-dose (PD1, PD2, PD3), and 15 min, 45 min, 1.5 hr, 4 hr, 8 hr, and 24 hr post-dose on Day 7 are reported. The following are of potential clinical importance: absolute QTc interval >450 milliseconds (msec); increase from Baseline QTc >60 msec; PR interval <110 and >220 msec; QRS interval <75 and >110 msec. Clinical significance was based on the medical and scientific judgement of the investigator or qualified designee.
Time Frame	Day 1 (pre-dose and 15 min, 45 min, 1.5 hr, 4 hr, and 8 hr post-dose) and Day 7 (pre-dose and 15 min, 45 min, 1.5 hr, 4 hr, 8 hr, and 24 hr)
Safety Issue?	No

Analysis Population Description

All Subjects Population. Only participants with data available at the indicated time points were summarized.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.

	Description
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	9	10	10	9
Number of Participants With the Indicated 12-lead Electrocardiogram (ECG) Values on Days 1 and 7 [units: Participants]				
Day 1, PD1, NL, n=9, 10, 10, 9	5	3	6	6
Day 1, PD1, Abn NCS, n=9, 10, 10, 9	4	7	4	3
Day 1, PD1, Abn CS, n=9, 10, 10, 9	0	0	0	0
Day 1, PD1, NA, n=9, 10, 10, 9	0	0	0	0
Day 1, PD2, NL, n=9, 10, 10, 9	5	3	5	5
Day 1, PD2, Abn NCS, n=9, 10, 10, 9	4	7	5	3
Day 1, PD2, Abn CS, n=9, 10, 10, 9	0	0	0	0
Day 1, PD2, NA, n=9, 10, 10, 9	0	0	0	1
Day 1, PD3, NL, n=9, 10, 10, 9	4	4	5	5
Day 1, PD3, Abn NCS, n=9, 10, 10, 9	5	6	5	3
Day 1, PD3, Abn CS, 9, 10, 10, 9	0	0	0	0
Day 1, PD3, NA, n=9, 10, 10, 9	0	0	0	1

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Day 1, 15 min PD, NL, n=9, 9, 10, 9	4	3	7	6
Day 1, 15 min PD, Abn NCS, n=9, 9, 10, 9	5	6	3	3
Day 1, 15 min PD, Abn CS, n=9, 9, 10, 9	0	0	0	0
Day 1, 15 min PD, NA, n=9, 9, 10, 9	0	0	0	0
Day 1, 45 min PD, NL, n=9, 9, 10, 9	5	3	7	6
Day 1, 45 min PD, Abn NCS, n=9, 9, 10, 9	4	6	3	3
Day 1, 45 min PD, Abn CS, n=9, 9, 10, 9	0	0	0	0
Day 1, 45 min PD, NA, n=9, 9, 10, 9	0	0	0	0
Day 1, 1.5 hr PD, NL, n=9, 9, 10, 9	5	6	6	5
Day 1, 1.5 hr PD, Abn NCS, n=9, 9, 10, 9	4	3	4	4
Day 1, 1.5 hr PD, Abn CS, n=9, 9, 10, 9	0	0	0	0
Day 1, 1.5 hr PD, NA, n=9, 9, 10, 9	0	0	0	0
Day 1, 4 hr PD, NL, n=9, 9, 10, 9	4	4	6	5
Day 1, 4 hr PD, Abn NCS, n=9, 9, 10, 9	5	5	4	4
Day 1, 4 hr PD, Abn CS, n=9, 9, 10, 9	0	0	0	0
Day 1, 4 hr PD, NA, n=9, 9, 10, 9	0	0	0	0
Day 1, 8 hr PD, NL, n=9, 9, 10, 9	5	6	7	6

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Day 1, 8 hr PD, Abn NCS, n=9, 9, 10, 9	4	3	3	3
Day 1, 8 hr PD, Abn CS, n=9, 9, 10, 9	0	0	0	0
Day 1, 8 hr PD, NA, n=9, 9, 10, 9	0	0	0	0
Day 7, PD1, NL, n=9, 7, 9, 6	4	4	7	3
Day 7, PD1, Abn NCS, n=9, 7, 9, 6	5	3	2	3
Day 7, PD1, Abn CS, n=9, 7, 9, 6	0	0	0	0
Day 7, PD1, NA, n=9, 7, 9, 6	0	0	0	0
Day 7, PD2, NL, n=9, 7, 8, 6	4	4	6	3
Day 7, PD2, Abn NCS, n=9, 7, 8, 6	5	3	2	3
Day 7, PD2, Abn CS, n=9, 7, 8, 6	0	0	0	0
Day 7, PD2, NA, n=9, 7, 8, 6	0	0	0	0
Day 7, PD3, NL, n=9, 7, 8, 6	4	3	6	3
Day 7, PD3, Abn NCS, n=9, 7, 8, 6	5	4	2	3
Day 7, PD3, Abn CS, 9, 7, 8, 6	0	0	0	0
Day 7, PD3, NA, n=9, 7, 8, 6	0	0	0	0
Day 7, 15 min PD, NL, n=9, 7, 9, 6	4	4	7	3
Day 7, 15 min PD, Abn NCS, n=9, 7, 9, 6	5	3	2	3
Day 7, 15 min PD, Abn CS, n=9, 7, 9, 6	0	0	0	0
Day 7, 15 min PD, NA, n=9, 7, 9, 6	0	0	0	0

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Day 7, 45 min PD, NL, n=9, 7, 9, 6	4	4	6	3
Day 7, 45 min PD, Abn NCS, n=9, 7, 9, 6	5	3	3	3
Day 7, 45 min PD, Abn CS, n=9, 7, 9, 6	0	0	0	0
Day 7, 45 min PD, NA, n=9, 7, 9, 6	0	0	0	0
Day 7, 1.5 hr PD, NL, n=9, 7, 9, 6	4	4	7	3
Day 7, 1.5 hr PD, Abn NCS, n=9, 7, 9, 6	5	3	2	3
Day 7, 1.5 hr PD, Abn CS, n=9, 7, 9, 6	0	0	0	0
Day 7, 1.5 hr PD, NA, n=9, 7, 9, 6	0	0	0	0
Day 7, 4 hr PD, NL, n=9, 7, 9, 6	5	5	7	3
Day 7, 4 hr PD, Abn NCS, n=9, 7, 9, 6	4	2	2	3
Day 7, 4 hr PD, Abn CS, n=9, 7, 9, 6	0	0	0	0
Day 7, 4 hr PD, NA, n=9, 7, 9, 6	0	0	0	0
Day 7, 8 hr PD, NL, n=9, 7, 9, 6	4	4	7	3
Day 7, 8 hr PD, Abn NCS, n=9, 7, 9, 6	5	3	2	3
Day 7, 8 hr PD, Abn CS, n=9, 7, 9, 6	0	0	0	0
Day 7, 8 hr PD, NA, n=9, 7, 9, 6	0	0	0	0
Day 7, 24 hr PD, NL, n=9, 7, 9, 6	4	2	6	3
Day 7, 24 hr PD, Abn NCS, n=9, 7, 9, 6	5	5	3	3
Day 7, 24 hr PD, Abn CS, n=9, 7, 9, 6	0	0	0	0

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Day 7, 24 hr PD, NA, n=9, 7, 9, 6	0	0	0	0

6. Primary Outcome Measure:

Measure Title	Number of Participants With Abnormal 24-hour Holter Findings at Screening and Day 7
Measure Description	Twenty-four hour Holter ECG values were obtained at Screening and on Day 7. During the Screening procedure and study, standard Holter monitors were used (in order to exclude participants with underlying cardiac arrhythmogenicity). During the treatment periods, Holter monitors were only switched on immediately prior to dosing (up to 15 minutes pre-dose) so as to capture Holter ECG data from the 24 hour period following dosing. The following summary data were transcribed into the Case Report Form: Maximum and mean (0 to24 hour) heart rate; normal and aberrant beats and arrhythmias. Analysis of the Holter tapes was arranged by GlaxoSmithKline.The number of participants with normal (NL), abnormal not clinically significant (Abn NCS), and abnormal clinically significant (Abn CS) ECG findings, as well as those with unavailable results (NA) at Screening and Day 7, are reported. Clinical significance was based on the medical and scientific judgement of the investigator or qualified designee.
Time Frame	Screening and Day 7
Safety Issue?	No

Analysis Population Description

All Subjects Population. Only participants with data available at the indicated time points were summarized.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	9	10	10	9
Number of Participants With Abnormal 24-hour Holter Findings at Screening and Day 7 [units: Participants]				
Screening, NL, n=9 ,10, 10, 9	2	6	5	3
Screening, Abn NCS, n=9 ,10, 10, 9	7	4	4	5
Screening, Abn CS, n=9 ,10, 10, 9	0	0	1	1
Day7, NL, n=9, 7, 9, 6	3	3	2	1

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Day7, Abn NCS, n=9, 7, 9, 6	6	3	6	5
Day7, Abn CS, n=9, 7, 9, 6	0	0	1	0
Day7, NA, n=9, 7, 9, 6	0	1	0	0

7. Primary Outcome Measure:

Measure Title	Maximum and Mean (0-24 Hour) Heart Rate From Holter Monitoring on Day 7
Measure Description	Maximum heart rate (Max HR) and mean HR from 0-24 hour Holter monitoring on treatment Day 7 were derived. The analysis was adjusted for treatment and Baseline, where Baseline is defined as the corresponding summary measure (i.e., mean heart rate [0-24 hours] or maximum heart rate [0-24 hours]) from screening records.
Time Frame	Day 7
Safety Issue?	No

Analysis Population Description

All Subjects Population. The number of participants presented represent those with data available at the time point being presented; however, all participants in the ASP without missing covariate information are included in the analysis.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).

	Description
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	9	6	9	6
Maximum and Mean (0-24 Hour) Heart Rate From Holter Monitoring on Day 7 [units: Beats per minute] Least Squares Mean (Standard Error)				
Max HR	125.19 (4.744)	134.08 (5.810)	127.48 (4.724)	126.91 (5.785)
Mean HR	77.47 (1.896)	75.94 (2.306)	75.96 (1.888)	76.75 (2.312)

8. Primary Outcome Measure:

Measure Title	Mean Forced Expiratory Volume in One Second (FEV1) at Screening and on Days 1 and 7

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. FEV1 was measured at Screening, pre-dose, and 4 hours (hr) post-dose on Day 1 and Day 7. FEV1 tests were repeated until three technically acceptable measurements were made.
Time Frame	Screening, Day 1, and Day 7
Safety Issue?	No

Analysis Population Description

All Subjects Population. Only participants with data available at the indicated time points were summarized.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	9	10	10	9
Mean Forced Expiratory Volume in One Second (FEV1) at Screening and on Days 1 and 7 [units: Liters] Mean (Standard Deviation)				
Screening, n=9, 10, 10, 9	1.556 (0.6315)	1.253 (0.4338)	1.562 (0.5066)	1.364 (0.3504)
Day 1, pre-dose, n=9, 10, 10, 9	1.294 (0.4642)	1.059 (0.3509)	1.443 (0.4840)	1.289 (0.2968)
Day 1, 4 hr post-dose, n=9, 9, 10, 9	1.309 (0.4333)	1.250 (0.3934)	1.565 (0.5858)	1.534 (0.3389)
Day 7, pre-dose, n=9, 7, 9, 6	1.263 (0.4695)	1.153 (0.4066)	1.593 (0.5425)	1.483 (0.3055)
Day 7, 4 hr post-dose, n=9, 7, 9, 6	1.250 (0.5143)	1.181 (0.3875)	1.564 (0.5476)	1.517 (0.2685)

9. Primary Outcome Measure:

Measure Title	Total Number of Salbutamol Doses Taken Over the 7 -Day Study Period
Measure Description	The total number of salbutamol doses taken per day was recorded by the participants in their dairy card over the entire 7-day treatment period. Diaries were reviewed by the Investigator when participants were admitted to the unit on Day 1, Day 7, and Day 8. Salbutamol was given as rescue medication, defined as a quick-relief or fast-acting

	medication that is given in addition to the investigational drug or placebo that can alleviate symptoms due to disease or lack of efficacy of the study treatment.
Time Frame	Day 1 to Day 7
Safety Issue?	No

Analysis Population Description

All Subjects Population. Only those participants who took at least one dose of salbutamol were summarized.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	6	3	5	5
Total Number of Salbutamol Doses Taken Over the 7 -Day Study Period [units: salbutamol doses]	18	33	33	29

10. Primary Outcome Measure:

Measure Title	Albumin, Total Protein, Hemoglobin, and Mean Corpuscle Hemoglobin Concentration (MCHC) Values on Day 1 and Day 7
Measure Description	Blood samples were collected for the measurement of albumin, total protein, hemoglobin, and MCHC values pre-dose on Day 1 and Day 7.
Time Frame	Day 1 and Day 7
Safety Issue?	No

Analysis Population Description

All Subjects Population. Only participants with data available at the indicated time points were summarized. Different participants may have been summarized for different parameters/at different time points (reflected by n=X, X, X, X in the category titles), so the overall number of participants summarized reflects everyone in the ASP.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).

	Description
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	9	10	10	9
Albumin, Total Protein, Hemoglobin, and Mean Corpuscle Hemoglobin Concentration (MCHC) Values on Day 1 and Day 7 [units: Grams per liter (G/L)] Mean (Standard Deviation)				
Albumin, Day 1, n=9, 9, 10, 9	42.3 (3.43)	43.9 (2.09)	43.7 (2.16)	44.1 (3.10)
Albumin, Day 7, n=8, 7, 9, 6	43.1 (1.81)	44.0 (1.15)	43.8 (2.64)	44.0 (2.61)
Total protein, Day 1, n=9, 9, 10, 9	69.4 (5.48)	70.0 (3.24)	69.9 (3.70)	69.8 (3.46)
Total protein, Day 7, n=8, 7, 9, 6	68.6 (3.16)	70.0 (2.16)	71.0 (4.53)	69.7 (3.83)
Hemoglobin, Day 1, n=9, 9, 10, 9	152.2 (8.60)	148.0 (14.19)	147.4 (11.84)	145.4 (16.18)

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Hemoglobin, Day 7, n=9, 6, 9, 6	151.4 (7.80)	145.8 (14.77)	147.4 (13.71)	143.5 (16.61)
MCHC, Day 1, n=9, 9, 10, 9	340.0 (6.10)	338.7 (5.39)	339.9 (5.49)	337.2 (3.63)
MCHC, Day 7, n=9, 6, 9, 6	337.6 (7.84)	340.7 (5.20)	337.4 (5.59)	337.3 (5.20)

11. Primary Outcome Measure:

Measure Title	Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and Gamma Glutamyl Transferase (GGT) Values on Day1 and Day 7
Measure Description	Blood samples were collected for the measurement of ALP, ALT, AST, and GGT Pre-dose on Day 1 and Day 7.
Time Frame	Day 1 and Day 7
Safety Issue?	No

Analysis Population Description

All Subjects Population. Only participants with data available at the indicated time points were summarized. Different participants may have been summarized for different parameters/at different time points (reflected by n=X, X, X, X in the category titles), so the overall number of participants summarized reflects everyone in the ASP.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC)

	Description
	250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	9	10	10	9
Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and Gamma Glutamyl Transferase (GGT) Values on Day1 and Day 7 [units: International units per liter (IU/L)] Mean (Standard Deviation)				
ALP, Day 1, n=9, 9, 10, 9	74.0 (20.20)	76.8 (15.11)	69.0 (18.43)	63.8 (20.00)
ALP, Day 7, n=8, 7, 9, 6	71.6 (20.18)	73.1 (16.16)	71.1 (16.47)	67.7 (18.15)
ALT, Day 1, n=9, 9, 10, 9	15.6 (10.36)	15.6 (6.06)	24.2 (9.66)	18.6 (9.49)
ALT, Day 7, n=8, 7, 9, 6	15.9 (6.85)	15.6 (7.11)	29.8 (12.81)	20.7 (9.85)
AST, Day 1, n=9, 9, 10, 9	20.9 (5.90)	18.9 (3.48)	26.5 (10.28)	22.6 (8.65)

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
AST, Day 7, n=8, 7, 9, 6	19.3 (6.16)	19.4 (4.31)	30.7 (12.16)	25.2 (8.18)
GGT, Day 1, n=9, 9, 10, 9	31.3 (20.62)	28.0 (13.19)	61.0 (56.20)	37.7 (31.25)
GGT, Day 7, n=8, 7, 9, 6	29.9 (18.88)	24.7 (6.78)	66.0 (68.81)	39.8 (32.73)

12. Primary Outcome Measure:

Measure Title	Direct Bilirubin, Total Bilirubin, and Creatinine Values on Day 1 and Day 7
Measure Description	Blood samples were collected for the measurement of direct bilirubin, total bilirubin, and creatinine at pre-dose on Day 1 and Day 7.
Time Frame	Day 1 and Day 7
Safety Issue?	No

Analysis Population Description

All Subjects Population. Only participants with data available at the indicated time points were summarized. Different participants may have been summarized for different parameters/at different time points (reflected by n=X, X, X, X in the category titles), so the overall number of participants summarized reflects everyone in the ASP.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD

	Description
	for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC19 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	9	10	10	9
Direct Bilirubin, Total Bilirubin, and Creatinine Values on Day 1 and Day 7 [units: Micromoles per liter (µmol/L)] Mean (Standard Deviation)				
Direct bilirubin, Day 1, n=6, 9, 10	2.3 (1.97)	1.7 (0.50)	2.0 (1.15)	NA (NA) [1]
Direct bilirubin, Day 7, n=5, 7, 9	2.0 (1.41)	2.0 (0.58)	2.2 (0.67)	NA (NA) [2]
Total bilirubin, Day 1, n=9, 9, 10, 9	10.8 (4.44)	8.2 (1.20)	10.9 (4.01)	10.2 (3.03)
Total bilirubin, Day 7, n=8, 7, 9, 6	9.3 (4.03)	9.9 (2.27)	10.8 (3.11)	11.0 (3.16)
Creatinine, Day 1, n=9, 9, 10, 9	76.2 (12.15)	84.3 (15.64)	80.1 (14.26)	87.0 (33.59)
Creatinine, Day 7, n=8, 7, 9, 6	78.8 (10.53)	80.1 (14.37)	82.6 (12.83)	93.0 (39.80)

[1] Per protocol, data were collected for participants in all 3 cohorts; however, Cohort 3 data were not fully reported to GSK by the

vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.
[2] Per protocol, data were collected for participants in all 3 cohorts; however, Cohort 3 data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.

13. Primary Outcome Measure:

Measure Title	Calcium, Glucose, Potassium, Sodium, and Urea/Blood Urea Nitrogen (BUN) Values on Day 1 and Day 7
Measure Description	Blood samples were collected for the measurement of calcium, glucose, potassium, sodium, and urea/BUN pre-dose on Day 1 and Day 7.
Time Frame	Day 1 and Day 7
Safety Issue?	No

Analysis Population Description

All Subjects Population. Only participants with data available at the indicated time points were summarized. Different participants may have been summarized for different parameters/at different time points (reflected by n=X, X, X, X in the category titles), so the overall number of participants summarized reflects everyone in the ASP.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in	Participants received a single inhaled dose of UMEC 250 µg

	Description
Error	formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	9	10	10	9
Calcium, Glucose, Potassium, Sodium, and Urea/Blood Urea Nitrogen (BUN) Values on Day 1 and Day 7 [units: Millimoles per liter (mmol/L)] Mean (Standard Deviation)				
Calcium, Day 1, n=9, 9, 10, 9	2.317 (0.0622)	2.329 (0.0697)	2.342 (0.1215)	2.311 (0.0807)
Calcium, Day 7, n=8, 7, 9, 6	2.320 (0.0454)	2.321 (0.0308)	2.370 (0.1411)	2.343 (0.0631)
Glucose, Day 1, n=9, 9, 10, 9	5.16 (0.937)	5.13 (0.524)	5.38 (0.751)	5.26 (0.921)
Glucose, Day 7, n=8, 7, 9, 6	5.25 (0.746)	5.10 (0.792)	5.84 (0.948)	5.42 (0.717)
Potassium, Day 1, n=9, 9, 10, 9	4.67 (0.472)	4.70 (0.485)	4.50 (0.579)	4.36 (0.364)
Potassium, Day 7, n=8, 7, 9, 6	4.58 (0.276)	4.74 (0.431)	4.48 (0.519)	4.45 (0.428)
Sodium, Day 1, n=9, 9, 10, 9	138.8 (2.59)	140.6 (1.51)	140.6 (2.27)	139.6 (1.59)
Sodium, Day 7, n=8, 7, 9, 6	140.4 (2.88)	140.0 (1.15)	140.2 (2.44)	139.2 (2.40)

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Urea/BUN, Day 1, n=9, 9, 10, 9	4.92 (1.730)	5.29 (0.842)	5.77 (1.854)	5.72 (2.440)
Urea/BUN, Day 7, n=8, 7, 9, 6	5.15 (1.032)	5.51 (0.691)	5.70 (1.562)	5.88 (3.020)

14. Primary Outcome Measure:

Measure Title	Basophil, Eosinophil, Lymphocyte, Monocyte, Total Neutrophil (ANC: Absolute Neutrophil Count), Platelet, and White Blood Cell (WBC) Count Values on Day 1 and Day 7
Measure Description	Blood samples were collected for the measurement of basophils, eosinophils, lymphocytes, monocytes, total neutrophils (ANC), platelets, and white blood cell (WBC) count pre-dose on Day 1 and Day 7.
Time Frame	Day 1 and Day 7
Safety Issue?	No

Analysis Population Description

All Subjects Population. Only participants with data available at the indicated time points were summarized. Different participants may have been summarized for different parameters/at different time points (reflected by n=X, X, X, X in the category titles), so the overall number of participants summarized reflects everyone in the ASP.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).

	Description
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	9	10	10	9
Basophil, Eosinophil, Lymphocyte, Monocyte, Total Neutrophil (ANC: Absolute Neutrophil Count), Platelet, and White Blood Cell (WBC) Count Values on Day 1 and Day 7 [units: 10^9 cells per liter (GI/L)] Mean (Standard Deviation)				
Basophils, Day 1, n=9, 9, 10, 9	NA (NA) [1]	NA (NA) [2]	NA (NA) [3]	NA (NA) [4]
Basophils, Day 7, n=9, 6, 9, 6	NA (NA) [5]	NA (NA) [6]	NA (NA) [7]	NA (NA) [8]
Eosinophils, Day 1, n=9, 9, 10, 9	0.248 (0.1052)	0.319 (0.1968)	0.352 (0.2951)	0.144 (0.0910)
Eosinophils, Day 7, n=9, 6, 9, 6	0.232	0.280	0.312	0.153

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
	(0.0793)	(0.1754)	(0.2672)	(0.0911)
Lymphocytes, Day 1, n=9, 9, 10, 9	NA (NA) [9]	NA (NA) [10]	NA (NA) [11]	NA (NA) [12]
Lymphocytes, Day 7, n=9, 6, 9, 6	NA (NA) [13]	NA (NA) [14]	NA (NA) [15]	NA (NA) [16]
Monocytes, Day 1, n=9, 9, 10, 9	0.510 (0.1348)	0.614 (0.3648)	0.607 (0.1594)	0.506 (0.2010)
Monocytes, Day 7, n=9, 6, 9, 6	0.448 (0.1313)	0.562 (0.2791)	0.657 (0.1993)	0.503 (0.2430)
ANC, Day 1, n=9, 9, 10, 9	5.233 (2.0968)	5.306 (1.3061)	4.244 (1.3332)	4.946 (2.3879)
ANC, Day 7, n=9, 6, 9, 6	4.706 (1.8634)	5.023 (1.4969)	4.067 (1.0184)	5.323 (1.8539)
Platelets, Day 1, n=9, 9, 10, 9	278.1 (66.25)	238.2 (39.71)	254.7 (51.04)	222.4 (43.16)
Platelets, Day 7, n=9, 6, 9, 6	271.8 (53.73)	256.8 (36.71)	255.1 (61.42)	250.3 (59.37)
WBC count, Day 1, n=9, 9, 10, 9	8.06 (2.220)	8.52 (2.153)	7.11 (1.692)	7.56 (2.572)
WBC count, Day 7, n=9, 6, 9, 6	7.49 (2.211)	8.15 (2.519)	7.13 (1.564)	7.87 (2.067)

[1] Per protocol, data were collected for participants in all 3 cohorts; however, data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.

[2] Per protocol, data were collected for participants in all 3 cohorts; however, data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.

[3] Per protocol, data were collected for participants in all 3 cohorts; however, data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.

[4] Per protocol, data were collected for participants in all 3 cohorts; however, data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.

[5] Per protocol, data were collected for participants in all 3 cohorts; however, data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.
[6] Per protocol, data were collected for participants in all 3 cohorts; however, data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.
[7] Per protocol, data were collected for participants in all 3 cohorts; however, data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.
[8] Per protocol, data were collected for participants in all 3 cohorts; however, data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.
[9] Per protocol, data were collected for participants in all 3 cohorts; however, data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.
[10] Per protocol, data were collected for participants in all 3 cohorts; however, data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.
[11] Per protocol, data were collected for participants in all 3 cohorts; however, data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.
[12] Per protocol, data were collected for participants in all 3 cohorts; however, data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.
[13] Per protocol, data were collected for participants in all 3 cohorts; however, data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.
[14] Per protocol, data were collected for participants in all 3 cohorts; however, data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.
[15] Per protocol, data were collected for participants in all 3 cohorts; however, data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.
[16] Per protocol, data were collected for participants in all 3 cohorts; however, data were not fully reported to GSK by the vendor. This oversight was recently detected, and this summary will be amended once remedial work has been completed.

15. Primary Outcome Measure:

Measure Title	Mean Corpuscle Hemoglobin (MCH) Values on Day 1 and Day 7

Measure Description	Blood samples were collected for the measurement of MCH pre-dose on Day 1 and Day 7.
Time Frame	Day 1 and Day 7
Safety Issue?	No

Analysis Population Description

All Subjects Population. Only participants with data available at the indicated time points were summarized. Different participants may have been summarized for different parameters/at different time points (reflected by n=X, X, X, X in the category titles), so the overall number of participants summarized reflects everyone in the ASP.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	9	10	10	9
Mean Corpuscle Hemoglobin (MCH) Values on Day 1 and Day 7 [units: picograms/cell (pg)] Mean (Standard Deviation)				
Day 1, n=9, 9, 10, 9	31.92 (1.711)	32.44 (2.371)	31.25 (1.978)	31.70 (1.859)
Day 7, n=9, 6, 9, 6	31.71 (1.661)	32.20 (2.871)	31.22 (1.999)	31.95 (2.146)

16. Primary Outcome Measure:

Measure Title	Mean Corpuscle Volume (MCV) Values on Day 1 and Day 7
Measure Description	Blood samples were collected for the measurement of MCV pre-dose on Day 1 and Day 7.
Time Frame	Day 1 and Day 7
Safety Issue?	No

Analysis Population Description

All Subjects Population. Only participants with data available at the indicated time points were summarized. Different participants may have been summarized for different parameters/at different time points (reflected by n=X, X, X, X in the category titles), so the overall number of participants summarized reflects everyone in the ASP.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder

	Description
	inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	9	10	10	9
Mean Corpuscle Volume (MCV) Values on Day 1 and Day 7 [units: 10^-15 liters (femtoliters)] Mean (Standard Deviation)				
Day 1, n=9, 9, 10, 9	93.9 (3.66)	95.9 (7.06)	91.9 (4.93)	94.0 (5.32)
Day 7, n=9, 6, 9, 6	94.0 (3.50)	94.5 (7.12)	92.6 (5.34)	94.8 (5.49)

17. Secondary Outcome Measure:

Measure Title	Mean AUC(0-2), AUC(0-8), and AUC(0-t) of UMEC on Day

	1 and Day 7
Measure Description	Area under the concentration-time (AUC) curve from time zero (pre-dose) to 2 hours (AUC[0-2]), from time zero to 8 hours (AUC[0-8]), from time zero to the last time of a quantifiable concentration of UMEC (AUC[0-t]) on Day 1 and Day 7 were measured. AUC is a measure of systemic exposure. Blood samples were collected pre-dose and 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, and 8 hr post-dose on Day 1 and Day 7. Also, a 24 hr blood sample was collected on Day 7.
Time Frame	Day 1 and Day 7: pre-dose, and 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, and 8 hr post-dose; 24 hr post-dose on Day 7
Safety Issue?	No

Analysis Population Description

Pharmacokinetic (PK) Population: participants (par.) in the ASP for whom a PK sample was obtained and analyzed. Different par. may have been summarized for different parameters/at different time points (reflected by n=X, X, X, X in the category titles), so the overall number of par. summarized reflects everyone in the PK Population.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.

	Description
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	0	8	9	9
Mean AUC(0-2), AUC(0-8), and AUC(0-t) of UMEC on Day 1 and Day 7 [units: hr * nanograms per milliliter (ng/mL)] Geometric Mean (Geometric Coefficient of Variation)				
AUC(0-2), Day 1, n=0, 8, 9, 9		0.19675 (19.7%)	0.08134 (108.0%)	0.95719 (233.2%)
AUC(0-2), Day 7, n=0, 6, 8, 6		0.31951 (51.6%)	0.15527 (66.5%)	1.92508 (31.1%)
AUC(0-8), Day 1, n=0, 0, 0, 9		NA (NA%) [1]	NA (NA%) [2]	2.029 (69.8%)
AUC(0-8), Day 7, n=0, 0, 0, 6		NA (NA%) [3]	NA (NA%) [4]	3.320 (33.3%)
AUC(0-t), Day 1, n=0, 8, 9, 9		0.26071 (39.1%)	0.03614 (1707.8%)	0.93299 (5820.5%)
AUC(0-t), Day 7, n=0, 6, 8, 6		0.55514 (113.2%)	0.30526 (134.3%)	4.86204 (42.8%)

[1] Due to non-quantifiable data at the lower dose (250 µg) at later time points, data for this parameter could not be calculated.
[2] Due to non-quantifiable data at the lower dose (250 µg) at later time points, data for this parameter could not be calculated.
[3] Due to non-quantifiable data at the lower dose (250 µg) at later time points, data for this parameter could not be calculated.
[4] Due to non-quantifiable data at the lower dose (250 µg) at later time points, data for this parameter could not be calculated.

18. Secondary Outcome Measure:

Measure Title	Cmax of UMEC on Day 1 and Day 7
Measure Description	Cmax is defined as the maximum observed concentration of UMEC and was measured on Day 1 and Day 7. Blood samples were collected pre-dose and 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, and 8 hr post-dose on Day 1 and Day 7. Also, a 24 hr blood sample was collected on Day 7.
Time Frame	Day 1 and Day 7: pre-dose, and 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, and 8 hr post-dose; 24 hr post-dose on Day 7
Safety Issue?	No

Analysis Population Description

PK Population. Only participants with data available at the indicated time points were summarized.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.

	Description
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	0	8	9	9
Cmax of UMEC on Day 1 and Day 7 [units: nanograms per milliliter (ng/mL)] Geometric Mean (Geometric Coefficient of Variation)				
Day 1, n=0, 8, 9, 9		0.21654 (32.0%)	0.07915 (147.6%)	1.52835 (53.6%)
Day 7, n=0, 6, 8, 6		0.33206 (58.3%)	0.16448 (74.2%)	2.75864 (60.5%)

19. Secondary Outcome Measure:

Measure Title	Tmax and Tlastof UMEC on Day 1 and Day 7
Measure Description	Tmax is defined as the time to reach the observed maximum concentration, and tlast is defined as the time of the last quantifiable concentration of UMEC; both were measured on Day 1 and Day 7. Blood samples were collected pre-dose, and 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, and 8 hr post-dose on Day 1 and Day 7. Also, a 24 hr blood sample was collected on Day 7.
Time Frame	Day 1 and Day 7: pre-dose, and 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, and 8 hr post-dose; 24 hr post-dose on Day 7

Safety Issue?	No

Analysis Population Description

PK Population. Only participants with data available at the indicated time points were summarized. Different participants may have been summarized for different parameters/at different time points (reflected by n=X, X, X, X in the category titles), so the overall number of participants summarized reflects everyone in the PK Population.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	0	8	9	9
Tmax and Tlastof UMEC on Day 1 and Day 7				

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
[units: hours] Median (Full Range)				
tmax, Day 1, n=0, 8, 8, 9		0.080 (0.08 to 0.50)	0.250 (0.08 to 0.28)	0.250 (0.08 to 0.28)
tmax, Day 7, n=0, 6, 8, 6		0.080 (0.02 to 0.25)	0.165 (0.08 to 0.32)	0.240 (0.07 to 0.25)
tlast, Day 1, n=0, 8, 8, 9		4.000 (2.00 to 8.12)	2.000 (0.08 to 4.00)	8.000 (0.08 to 8.00)
tlast, Day 7, n=0, 6, 8, 6		6.000 (2.00 to 27.05)	6.015 (2.00 to 24.00)	24.010 (24.00 to 24.48)

20. Secondary Outcome Measure:

Measure Title	Ae(0-4), Ae(0-8), Ae(0-12), and Ae(0-24) of UMEC on Day 1 and Day 7
Measure Description	Urinary recovery of unchanged drug (UMEC) within the first 8, 12, and 24 hours (Ae[0-8], Ae[0-12], and Ae[0-24], respectively) on Day 1 and within the first 4, 8, 12, and 24 hours (Ae[0-4], Ae[0-8], Ae[0-12], and Ae[0-24], respectively) on Day 7 was estimated. Urine samples were collected from 0-8 hours (hr), 8-12 hr, and 12-24 hr on Day 1 and from 0-4 hr, 4-8 hr, 8-12 hr, and 12-24 hr on Day 7.
Time Frame	From 0-8 hours (hr), 8-12 hr, and 12-24 hr on Day 1; from 0-4 hr, 4-8 hr, 8-12 hr, and 12-24 hr on Day 7
Safety Issue?	No

Analysis Population Description

PK Population. Only participants with data available at the indicated time points were summarized. Different participants may have been summarized for different parameters/at different time points (reflected by n=X, X, X, X in the category titles), so the overall number of participants summarized reflects everyone in the PK Population.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	0	8	9	9
Ae(0-4), Ae(0-8), Ae(0-12), and Ae(0-24) of UMEC on Day 1 and Day 7 [units: nanograms (ng)] Geometric Mean (Geometric Coefficient of Variation)				
Ae(0-4), Day 7, n=0, 5, 8, 6		1223.6	669.5	11854.5

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
		(77.8%)	(129.8%)	(65.8%)
Ae(0-8), Day 1, n=0, 6, 7, 8		1756.0 (46.6%)	755.9 (101.5%)	13435.9 (53.8%)
Ae(0-8), Day 7, n=0, 5, 8, 6		3115.8 (27.2%)	1430.8 (49.6%)	19319.3 (50.5%)
Ae(0-12), Day 1, n=0, 6, 7, 8		2022.3 (41.2%)	921.7 (97.6%)	16069.2 (56.0%)
Ae(0-12), Day 7, n=0, 5, 8, 6		4165.6 (15.3%)	1960.5 (53.6%)	23496.1 (44.7%)
Ae(0-24), Day 1, n=0, 6, 7, 8		2503.5 (38.0%)	1420.3 (130.9%)	19552.7 (47.4%)
Ae(0-24), Day 7, n=0, 5, 8, 6		5606.2 (15.3%)	2984.5 (52.9%)	32140.0 (36.2%)

21. Secondary Outcome Measure:

Measure Title	Fe(0-4), Fe(0-8), Fe(0-12), and Fe(0-24) of UMEC on Day 1 and Day 7
Measure Description	The fraction of the total dose excreted (Fe) in each interval was estimated as the urinary recovery of unchanged drug (Ae) per dose. Urine samples were collected from 0-8 hours (hr), 8-12 hr, and 12-24 hr on Day 1 and from 0-4 hr, 4-8 hr, 8-12 hr, and 12-24 hr on Day 7.
Time Frame	From 0-8 hours (hr), 8-12 hr, and 12-24 hr on Day 1; from 0-4 hr, 4-8 hr, 8-12 hr, and 12-24 hr on Day 7

Safety Issue?	No

Analysis Population Description

PK Population: Only participants with data available at the indicated time points were summarized. Different participants may have been summarized for different parameters/at different time points (reflected by n=X, X, X, X in the category titles), so the overall number of participants summarized reflects everyone in the PK Population.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	0	8	9	9
Fe(0-4), Fe(0-8), Fe(0-12), and Fe(0-24) of UMEC on Day 1 and Day 7				

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
[units: Percentage of dose administered] Mean (Standard Deviation)				
Fe(0-4), Day 7, n=0, 5, 8, 6		0.58 (0.35)	0.37 (0.30)	1.35 (0.70)
Fe(0-8), Day 1, n=0, 6, 8, 8		0.76 (0.35)	0.34 (0.28)	1.49 (0.68)
Fe(0-8), Day 7, n=0, 5, 8, 6		1.28 (0.30)	0.62 (0.26)	2.10 (0.84)
Fe(0-12), Day 1, n=0, 6, 8, 8		0.87 (0.38)	0.41 (0.32)	1.78 (0.77)
Fe(0-12), Day 7, n=0, 5, 8, 6		1.68 (0.25)	0.86 (0.36)	2.52 (0.99)
Fe(0-24), Day 1, n=0, 6, 8, 8		1.06 (0.41)	0.70 (0.61)	2.12 (0.82)
Fe(0-24), Day 7, n=0, 5, 8, 6		2.26 (0.33)	1.31 (0.54)	3.38 (1.15)

22. Secondary Outcome Measure:

Measure Title	Renal Clearance of UMEC on Day 1 and Day 7
Measure Description	Renal clearance was calculated as the urinary recovery of unchanged drug from time zero to time x (Ae[0-x])/area under concentration from time zero to time x (AUC[0-x]) for the longest period of time after dosing when both could be accurately determined (where x is either 8, 12, or 24). Urine samples were collected from 0-8 hours (hr), 8-12 hr, and 12-24 hr on Day 1 and from 0-4 hr, 4-8 hr, 8-12 hr, and 12-24 hr on Day 7.
Time Frame	From 0-8 hours (hr), 8-12 hr, and 12-24 hr on Day 1; from 0-4 hr, 4-8 hr, 8-12 hr, and 12-24 hr on Day 7
Safety Issue?	No

Analysis Population Description

PK Population. Only participants with data available at the indicated time points were summarized. Different participants may have been summarized for different parameters/at different time points (reflected by n=X, X, X, X in the category titles), so the overall number of participants summarized reflects everyone in the PK Population.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	0	8	9	9
Renal Clearance of UMEC on Day 1 and Day 7 [units: Liters/hour (L/hr)] Geometric Mean (Geometric Coefficient of Variation)				

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Day 1, n=0, 1, 0, 8		6.5229 (NA%) [1]	NA (NA%) [2]	5.6173 (39.5%)
Day 7, n=0, 4, 6, 6		2.5923 (103.6%)	4.0826 (19.3%)	6.6104 (33.1%)

[1] A dispersion cannot be calculated for a single participant.

[2] Due to non-quantifiable data at the lower dose (250 µg) at later time points, data for this parameter could not be calculated.

23. Secondary Outcome Measure:

Measure Title	Urine Half Life (t1/2) of UMEC on Day 7
Measure Description	Urine half life (t1/2) of UMEC on Day 7 was estimated. Urine samples were collected from 0-4 hours (hr), 4-8 hr, 8-12 hr, and 12-24 hr on Day 7.
Time Frame	From 0-4 hours (hr), 4-8 hr, 8-12 hr, and 12-24 hr on Day 7
Safety Issue?	No

Analysis Population Description

PK Population. Only participants with data available at the indicated time points were summarized.

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).

	Description
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Measured Values

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Number of Participants Analyzed	0	2	4	4
Urine Half Life (t1/2) of UMEC on Day 7 [units: hours] Geometric Mean (Geometric Coefficient of Variation)		5.785 (39.4%)	8.299 (37.3%)	7.643 (33.4%)

Reported Adverse Events

Reporting Groups

	Description
Placebo	Participants received either a single inhaled dose or four inhaled doses of matching placebo once daily (QD) for 7 days via a dry powder inhaler (DPI).

	Description
Cohort 1 UMEC 250 µg	Participants received a single inhaled dose of umeclidinium (UMEC) 250 micrograms (µg) formulated with magnesium stearate (MgSt) QD for 7 days via a DPI.
Cohort 2 UMEC 250 µg in Error	Participants received a single inhaled dose of UMEC 250 µg formulated with MgSt QD for 7 days via a DPI. These participants were to have been randomized to receive UMEC 1000 µg; however, they received UMEC 250 µg in error.
Cohort 3 UMEC 1000 µg	Participants received four inhaled doses of UMEC 250 µg (equivalent to 1000 µg) formulated with MgSt QD for 7 days via a DPI.

Time Frame

On-treatment serious adverse events (SAEs) and non-serious AEs (events occurring between the start of investigational product and follow-up contact) were collected from the start of study medication to the end of the treatment period (up to study day 12).

Additional Description

On-treatment SAEs and non-serious AEs were collected in members of the All Subjects Population, comprised of all participants who received at least one dose of study medication.

Serious Adverse Events

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Total # participants affected/at risk	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/9 (0%)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 0%

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
Total # participants affected/at risk	6/9 (66.67%)	2/10 (20%)	8/10 (80%)	5/9 (55.56%)
Cardiac disorders				
Arrhythmia † [A]				
# participants affected/at risk	0/9 (0%)	0/10 (0%)	1/10 (10%)	0/9 (0%)
# events				
Atrioventricular block second degree † [A]				
# participants affected/at risk	0/9 (0%)	0/10 (0%)	1/10 (10%)	0/9 (0%)
# events				
Ear and labyrinth disorders				
Ear pain † [A]				
# participants affected/at risk	1/9 (11.11%)	0/10 (0%)	0/10 (0%)	0/9 (0%)
# events				
Gastrointestinal disorders				
Dry mouth † [A]				
# participants affected/at	0/9 (0%)	0/10 (0%)	0/10 (0%)	1/9 (11.11%)

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
risk				
# events				
General disorders				
Chest discomfort † [A]				
# participants affected/at risk	1/9 (11.11%)	0/10 (0%)	0/10 (0%)	0/9 (0%)
# events				
Chest pain † [A]				
# participants affected/at risk	0/9 (0%)	1/10 (10%)	0/10 (0%)	0/9 (0%)
# events				
Feeling abnormal † [A]				
# participants affected/at risk	0/9 (0%)	0/10 (0%)	0/10 (0%)	1/9 (11.11%)
# events				
Thirst † [A]				
# participants affected/at risk	0/9 (0%)	0/10 (0%)	0/10 (0%)	2/9 (22.22%)
# events				
Infections and infestations				
Absess jaw † [A]				

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
# participants affected/at risk	1/9 (11.11%)	0/10 (0%)	0/10 (0%)	0/9 (0%)
# events				
Gastroenteritis † [A]				
# participants affected/at risk	0/9 (0%)	0/10 (0%)	0/10 (0%)	1/9 (11.11%)
# events				
Lower respiratory tract infection † [A]				
# participants affected/at risk	0/9 (0%)	0/10 (0%)	0/10 (0%)	1/9 (11.11%)
# events				
Respiratory tract infection † [A]				
# participants affected/at risk	0/9 (0%)	0/10 (0%)	1/10 (10%)	0/9 (0%)
# events				
Rhinitis † [A]				
# participants affected/at risk	0/9 (0%)	0/10 (0%)	1/10 (10%)	0/9 (0%)
# events				
Investigations				
Blood glucose abnormal † [A]				

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
# participants affected/at risk	0/9 (0%)	0/10 (0%)	0/10 (0%)	1/9 (11.11%)
# events				
Blood pressure increased † [A]				
# participants affected/at risk	0/9 (0%)	0/10 (0%)	1/10 (10%)	1/9 (11.11%)
# events				
Metabolism and nutrition disorders				
Decreased appetite † [A]				
# participants affected/at risk	1/9 (11.11%)	0/10 (0%)	0/10 (0%)	0/9 (0%)
# events				
Impaired fasting glucose † [A]				
# participants affected/at risk	1/9 (11.11%)	0/10 (0%)	0/10 (0%)	0/9 (0%)
# events				
Nervous system disorders				
Dizziness † [A]				
# participants affected/at	1/9 (11.11%)	0/10 (0%)	0/10 (0%)	0/9 (0%)

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
risk				
# events				
Dysgeusia † [A]				
# participants affected/at risk	0/9 (0%)	0/10 (0%)	1/10 (10%)	0/9 (0%)
# events				
Headache † [A]				
# participants affected/at risk	1/9 (11.11%)	1/10 (10%)	4/10 (40%)	1/9 (11.11%)
# events				
Hypoaesthesia † [A]				
# participants affected/at risk	1/9 (11.11%)	0/10 (0%)	0/10 (0%)	0/9 (0%)
# events				
Respiratory, thoracic and mediastinal disorders				
Bronchospasm † [A]				
# participants affected/at risk	0/9 (0%)	0/10 (0%)	1/10 (10%)	0/9 (0%)
# events				
Cough † [A]				
# participants affected/at	1/9 (11.11%)	0/10 (0%)	2/10 (20%)	0/9 (0%)

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
risk				
# events				
Dyspnoea † [A]				
# participants affected/at risk	2/9 (22.22%)	0/10 (0%)	0/10 (0%)	1/9 (11.11%)
# events				
Oropharyngeal pain † [A]				
# participants affected/at risk	0/9 (0%)	0/10 (0%)	0/10 (0%)	1/9 (11.11%)
# events				
Skin and subcutaneous tissue disorders				
Pruritus † [A]				
# participants affected/at risk	1/9 (11.11%)	0/10 (0%)	0/10 (0%)	0/9 (0%)
# events				
Vascular disorders				
Flushing † [A]				
# participants affected/at risk	1/9 (11.11%)	0/10 (0%)	0/10 (0%)	0/9 (0%)
# events				
Hypertension † [A]				

	Placebo	Cohort 1 UMEC 250 µg	Cohort 2 UMEC 250 µg in Error	Cohort 3 UMEC 1000 µg
# participants affected/at risk	0/9 (0%)	0/10 (0%)	1/10 (10%)	0/9 (0%)
# events				

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

GSK agreements may vary with individual investigators, but will not prohibit any investigator from publishing. GSK supports the publication of results from all centers of a multi-center trial but requests that reports based on single-site data not precede the primary publication of the entire clinical trial.

Limitations and Caveats:

Subject 303 and Subject 317 correspond to the same participant who was randomized and dosed on two separate occasions. This participant has been counted as two separate participants on all the outputs.

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