ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 03/27/2014

ClinicalTrials.gov ID: NCT00515502

Study Identification

Unique Protocol ID:	AC4108123
Brief Title:	Safety Study Using GSK573719 And Tiotropium In Patients With Chronic Obstructive Pulmonary Disease
Official Title:	See Detailed Description
Secondary IDs:	

Study Status

Record Verification:	February 2014
Overall Status:	Completed
Study Start:	June 2007
Primary Completion:	November 2007 [Actual]
Study Completion:	November 2007 [Actual]

Sponsor/Collaborators

Sponsor:	GlaxoSmithKline
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	
IND/IDE Protocol?:	No

Review Board:	Approval Status: Approved Approval Number: EK 5 125/07 Board Name: Ethikkommission des Landes Berlin Board Affiliation: Landesamt für Gesundheit und Soziales Berlin Phone: +49 30 9012 7637 Email: ethik-kommission@lageso.verwalt-berlin.de
Data Monitoring?:	No
Plan to Share Data?:	
Oversight Authorities:	Germany: Federal Institute for Drugs and Medical Devices

Study Description

Brief Summary:	GSK573719 is a high-affinity specific muscarinic receptor (mAChR) antagonist which is being developed for once daily treatment of chronic obstructive pulmonary disease (COPD). The long duration of action of GSK573719 when administered via inhalation in animal models supports the potential for use as a once-daily bronchodilator for COPD.
Detailed Description:	A randomised, double blind, placebo-controlled, double dummy, 4-way cross-over, dose ascending study to assess the safety, tolerability, pharmacodynamics and pharmacokinetics of single inhaled doses of GSK573719 (3 escalating mcg doses will be used) and tiotropium bromide (18µg) via DPI in COPD patients

Conditions

Conditions:	Pulmonary Disease, Chronic Obstructive
Keywords:	chronic obstructive pulmonary disease, GSK573719, muscarinic receptor antagonist

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Intervention Model:	Crossover Assignment
Number of Arms:	
Masking:	Double Blind
Allocation:	Randomized

Endpoint Classification: Safety Study

Enrollment: 24 [Actual]

Arms and Interventions

Intervention Details:

Drug: GSK573719

Other Names:

- GSK573719

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 40 Years

Maximum Age: 75 Years

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Caucasian male or female subjects aged 40-75 years inclusive. The need to recruit only Caucasian subjects is related to the need to rigorously exclude 2D6 poor metabolisers based on genotype.
- Female subjects must be of non-childbearing potential.
- An established clinical history of COPD (ATS/ERS definition).
- ‘Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.’
- Subject is a smoker or an ex-smoker with a smoking history of at least 10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or equivalent).
- Subject has FEV1/FVC < 0.7 post-bronchodilator (salbutamol) dose.
- Subject has 40 ≥ FEV1 ≤ 80% of predicted normal for height, age and gender after inhalation of salbutamol dose.
- Response to ipratropium bromide.
- Subject is able and has given written informed consent to take part in the study.
- Subject is available to complete all study measurements and procedures.
- Subject’s BMI is 18.0 – 32.0 kg/m2.
- Subjects have a 24hr Holter recording that is within normal limits 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

Exclusion Criteria:

- Subjects who have a past or present disease of any organ system, which as judged by the Investigator, may affect the outcome of this study.
- The subject has a positive pre-study drug screen. A minimum list of drugs that will be screened for include Amphetamines, Barbiturates, Cannabis, Cocaine and Opiates. The detection of drugs with a legitimate medical use would not be an exclusion to study participation.
- The subject has a positive pre-study alcohol screen. The detection of alcohol would not be an exclusion at screening but would need to be negative pre-dose and during the study.
- A suspected history of alcohol abuse within the six months previous to the screening visit.
- The subject has tested positive for hepatitis C antibody, hepatitis B surface antigen or HIV (if determined by local SOP's).
- Subject has received an investigational drug within 30 days of screening.
- The subject is currently taking medication which is known to be a CYP 2D6 inhibitor/substrate.
- The subject has donated a unit (400ml) of blood within 60 days of screening, or, intends to donate during the study.
- The subject has a known allergy or hypersensitivity to ipratropium bromide, tiotropium bromide, atropine and any of its derivatives or lactose/milk protein.
- Subject is unable to use the DISKUS™/HandiHaler devices correctly.
- Subject has prostatic hypertrophy, bladder outlet obstruction, or narrow angle glaucoma.
- Subjects with a 2D6 poor metaboliser genotype (Caucasian).
- The subject has claustrophobia that may be aggravated by entering the plethysmography cabinet (American Association of Respiratory Care 2001 guidelines for body plethysmography)
- Received antibiotic therapy for either a lower respiratory tract infection or for COPD exacerbation within the 4 weeks prior to Screening.

Respiratory criteria

- Subject has a diagnosis of active tuberculosis, lung cancer, clinically overt bronchiectasis, allergic rhinitis, or asthma.
- Subject has poorly controlled COPD, defined as either: acute worsening of COPD that is managed by the subject at home by treatment with corticosteroids in the 6 weeks prior to screening visit Or more than two exacerbations in the previous 6 months prior to screening that required a course of oral corticosteroids or antibiotics, or, for which the subject was hospitalised.
- Subject has participated in a Pulmonary Rehabilitation Program within 4 weeks prior to screening visit or will enter a program during the study.
- Subject has had a respiratory tract infection in the 4 weeks prior to the screening visit.

Cardiovascular criteria

- Current congestive heart failure (greater than NYHA I), myocardial infarction (within 3-years of the screening date) or ischaemic heart disease requiring regular therapy (such as β blockers, long-acting nitrates, calcium antagonists or nicorandil). Aspirin, Clopidogrel and statins are allowed.
- A history of clinically significant arrhythmia or clinically important 24hr 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, the QTc(B) of all 3 screening ECGs are not within 10% of the mean, or an ECG that is not suitable for QT measurements (e.g. poorly defined termination of the T wave)
- Mobitz type II or third degree heart block.
- Risk factors for torsades de pointes (heart failure NYHA II-IV, chronic hypokalaemia, familial long QT syndrome).

- Elevated resting blood pressure or a mean blood pressure equal to or higher than 150/95 mmHg at screening. A history of hypertension is acceptable provided control has been achieved for > 3 months prior to screening with diuretic only.
- A mean heart rate outside the range 50-100 bpm at screening (from vital signs measurement).

Concurrent medication criteria

- Subject requires treatment with inhaled cromolyn sodium or nedocromil, oral β2-agonists, nebulised β2-agonists, nebulised anticholinergics or leukotriene modifiers.
- Subject is unable to abstain from xanthines (other than caffeine) 13-15 days prior to the first dose of study medication until completion of the study (last study-related procedure at the follow-up visit).
- Subject is unable to abstain from short-acting inhaled bronchodilators from 6hrs prior to screening until after completion of screening, or, from 6hrs prior to the administration of study medication until after completion of any given treatment period (i.e. the last assessment in a dosing period).
- Subject is unable to abstain from long-acting inhaled bronchodilators from 72hrs prior to the screening until after completion of all treatment periods (i.e. the last assessment in the final dosing period).
- Subject has changed dose of inhaled corticosteroids within the last 4 weeks, or, will be unable to maintain a constant dose of inhaled corticosteroids during the study.
- Subject is receiving treatment with long term or short-term oxygen therapy or requires nocturnal positive pressure ventilation (CPAP or NIPPV).
- Subject is receiving treatment with beta-blockers, except eye drops, Diltiazem or Verapamil.
- Subject is receiving co-medication with drugs which are commonly recognised to prolong the QTc interval (e.g. quinolones, amiodarone, disopyramide, quinidine, sotalol, chlorpromazine, haloperidol, ketoconazole, terfenadine, cisapride and terodiline).

Contacts/Locations

Study Officials: GSK Clinical Trials
Study Director
GlaxoSmithKline

Locations: Germany
GSK Investigational Site
Hamburg, Hamburg, Germany, 22291

GSK Investigational Site
Berlin, Berlin, Germany, 14050

GSK Investigational Site
Hannover, Niedersachsen, Germany, 30625

References

Citations: 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.

Links:

Study Data/Documents:

Study Results

Participant Flow

Pre-Assignment Details	Participants were randomized to receive a sequence of 4 of 5 possible treatments over 4 treatment periods each separated by a washout period of at least 14 days. Participants were randomized to receive treatments in 12 possible sequences.

Reporting Groups

	Description
Seq 1: UMEC 250 µg, UMEC 500 µg, Tiotropium 18 µg, Placebo	Participants received single doses of 4 treatments, over 4 treatment periods, in the following sequence: umeclidinium bromide (UMEC) 250 micrograms (µg), UMEC 500 µg, Tiotropium 18 µg and placebo. Treatment periods were seperated by a washout period of at least 14 days.
Seq 2: UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg, Placebo	Participants received single doses of 4 treatments, over 4 treatment periods, in the following sequence: UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg and placebo. Treatment periods were seperated by a washout period of at least 14 days.
Seq 3: UMEC 250 µg, Placebo, UMEC 500 µg, UMEC 1000 µg	Participants received single doses of 4 treatments, over 4 treatment periods, in the following sequence: UMEC 250 µg, placebo, UMEC 500 µg and UMEC 1000 µg. Treatment periods were seperated by a washout period of at least 14 days.
Seq 4: UMEC 250 µg, UMEC 500 µg, Placebo, UMEC 1000 µg	Participants received single doses of 4 treatments, over 4 treatment periods, in the following sequence: UMEC 250 µg, UMEC 500 µg, placebo and UMEC 1000 µg. Treatment periods were seperated by a washout period of at least 14 days.
Seq 5: Placebo, UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg	Participants received single doses of 4 treatments, over 4 treatment periods, in the following sequence: Placebo, UMEC 250 µg, UMEC 500 µg and UMEC 1000 µg. Treatment periods were seperated by a washout period of at least 14 days.

	Description
Seq 6: UMEC 250 µg, Placebo, Tiotropium 18 µg, UMEC 500 µg	Participants received single doses of 4 treatments, over 4 treatment periods, in the following sequence: UMEC 250 µg, placebo, Tiotropium 18 µg and UMEC 500 µg. Treatment periods were seperated by a washout period of at least 14 days.
Seq 7: Placebo, Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg	Participants received single doses of 4 treatments, over 4 treatment periods, in the following sequence: Placebo, Tiotropium 18 µg, UMEC 250 µg and UMEC 500 µg. Treatment periods were seperated by a washout period of at least 14 days.
Seq 8: Tiotropium 18 µg, Placebo, UMEC 250 µg, UMEC 500 µg	Participants received single doses of 4 treatments, over 4 treatment periods, in the following sequence: Tiotropium 18 µg, placebo, UMEC 250 µg and UMEC 500 µg. Treatment periods were seperated by a washout period of at least 14 days.
Seq 9: Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg, Placebo	Participants received single doses of 4 treatments, over 4 treatment periods, in the following sequence: Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg and placebo. Treatment periods were seperated by a washout period of at least 14 days.
Seq 10: Tiotropium 18 µg, UMEC 250 µg, Placebo, UMEC 500 µg	Participants received single doses of 4 treatments, over 4 treatment periods, in the following sequence: Tiotropium 18 µg, UMEC 250 µg, placebo and UMEC 500 µg. Treatment periods were seperated by a washout period of at least 14 days.
Seq 11: Placebo, UMEC 250 µg, Tiotropium 18 µg, UMEC 500 µg	Participants received single doses of 4 treatments, over 4 treatment periods, in the following sequence: Placebo, UMEC 250 µg, Tiotropium 18 µg and UMEC 500 µg. Treatment periods were seperated by a washout period of at least 14 days.
Seq 12: UMEC 250 µg, Placebo, UMEC 500 µg, Tiotropium 18 µg	Participants received single doses of 4 treatments, over 4 treatment periods, in the following sequence: UMEC 250 µg, placebo, UMEC 500 µg and Tiotropium 18 µg. Treatment periods were seperated by a washout period of at least 14 days.

Treatment Period 1

	Seq 1: UMEC 250 µg, UMEC 500 µg, Tiotropium 18 µg, Placebo	Seq 2: UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg, Placebo	Seq 3: UMEC 250 µg, Placebo, UMEC 500 µg, UMEC 1000 µg	Seq 4: UMEC 250 µg, UMEC 500 µg, Placebo, UMEC 1000 µg	Seq 5: Placebo, UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg	Seq 6: UMEC 250 µg, Placebo, Tiotropium 18 µg, UMEC 500 µg
Started	1	4	4	3	3	1
Completed	1	4	4	3	3	1
Not Completed	0	0	0	0	0	0
Adverse Event	0	0	0	0	0	0

	Seq 7: Placebo, Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg	Seq 8: Tiotropium 18 µg, Placebo, UMEC 250 µg, UMEC 500 µg	Seq 9: Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg, Placebo	Seq 10: Tiotropium 18 µg, UMEC 250 µg, Placebo, UMEC 500 µg	Seq 11: Placebo, UMEC 250 µg, Tiotropium 18 µg, UMEC 500 µg	Seq 12: UMEC 250 µg, Placebo, UMEC 500 µg, Tiotropium 18 µg
Started	2	1	1	2	1	1
Completed	1	1	0	2	1	0
Not Completed	1	0	1	0	0	1
Adverse Event	1	0	1	0	0	1

Washout Period 1

	Seq 1: UMEC 250 µg, UMEC 500 µg, Tiotropium 18 µg, Placebo	Seq 2: UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg, Placebo	Seq 3: UMEC 250 µg, Placebo, UMEC 500 µg, UMEC 1000 µg	Seq 4: UMEC 250 µg, UMEC 500 µg, Placebo, UMEC 1000 µg	Seq 5: Placebo, UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg	Seq 6: UMEC 250 µg, Placebo, Tiotropium 18 µg, UMEC 500 µg
Started	1	4	4	3	3	1
Completed	1	4	4	3	3	1
Not Completed	0	0	0	0	0	0

	Seq 7: Placebo, Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg	Seq 8: Tiotropium 18 µg, Placebo, UMEC 250 µg, UMEC 500 µg	Seq 9: Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg, Placebo	Seq 10: Tiotropium 18 µg, UMEC 250 µg, Placebo, UMEC 500 µg	Seq 11: Placebo, UMEC 250 µg, Tiotropium 18 µg, UMEC 500 µg	Seq 12: UMEC 250 µg, Placebo, UMEC 500 µg, Tiotropium 18 µg
Started	1	1	0	2	1	0
Completed	1	1	0	2	1	0
Not Completed	0	0	0	0	0	0

Treatment Period 2

	Seq 1: UMEC 250 µg, UMEC 500 µg, Tiotropium 18 µg, Placebo	Seq 2: UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg, Placebo	Seq 3: UMEC 250 µg, Placebo, UMEC 500 µg, UMEC 1000 µg	Seq 4: UMEC 250 µg, UMEC 500 µg, Placebo, UMEC 1000 µg	Seq 5: Placebo, UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg	Seq 6: UMEC 250 µg, Placebo, Tiotropium 18 µg, UMEC 500 µg
Started	1	4	4	3	3	1
Completed	1	3	4	3	3	1
Not Completed	0	1	0	0	0	0
Adverse Event	0	1	0	0	0	0

	Seq 7: Placebo, Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg	Seq 8: Tiotropium 18 µg, Placebo, UMEC 250 µg, UMEC 500 µg	Seq 9: Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg, Placebo	Seq 10: Tiotropium 18 µg, UMEC 250 µg, Placebo, UMEC 500 µg	Seq 11: Placebo, UMEC 250 µg, Tiotropium 18 µg, UMEC 500 µg	Seq 12: UMEC 250 µg, Placebo, UMEC 500 µg, Tiotropium 18 µg
Started	1	1	0	2	1	0
Completed	1	1	0	2	1	0
Not Completed	0	0	0	0	0	0
Adverse Event	0	0	0	0	0	0

Washout Period 2

	Seq 1: UMEC 250 µg, UMEC 500 µg, Tiotropium 18 µg, Placebo	Seq 2: UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg, Placebo	Seq 3: UMEC 250 µg, Placebo, UMEC 500 µg, UMEC 1000 µg	Seq 4: UMEC 250 µg, UMEC 500 µg, Placebo, UMEC 1000 µg	Seq 5: Placebo, UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg	Seq 6: UMEC 250 µg, Placebo, Tiotropium 18 µg, UMEC 500 µg
Started	1	3	4	3	3	1
Completed	1	3	4	3	3	1
Not Completed	0	0	0	0	0	0

	Seq 7: Placebo, Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg	Seq 8: Tiotropium 18 µg, Placebo, UMEC 250 µg, UMEC 500 µg	Seq 9: Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg, Placebo	Seq 10: Tiotropium 18 µg, UMEC 250 µg, Placebo, UMEC 500 µg	Seq 11: Placebo, UMEC 250 µg, Tiotropium 18 µg, UMEC 500 µg	Seq 12: UMEC 250 µg, Placebo, UMEC 500 µg, Tiotropium 18 µg
Started	1	1	0	2	1	0
Completed	1	1	0	2	1	0
Not Completed	0	0	0	0	0	0

Treatment Period 3

	Seq 1: UMEC 250 µg, UMEC 500 µg, Tiotropium 18 µg, Placebo	Seq 2: UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg, Placebo	Seq 3: UMEC 250 µg, Placebo, UMEC 500 µg, UMEC 1000 µg	Seq 4: UMEC 250 µg, UMEC 500 µg, Placebo, UMEC 1000 µg	Seq 5: Placebo, UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg	Seq 6: UMEC 250 µg, Placebo, Tiotropium 18 µg, UMEC 500 µg
Started	1	3	4	3	3	1
Completed	1	3	4	3	3	1
Not Completed	0	0	0	0	0	0

	Seq 7: Placebo, Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg	Seq 8: Tiotropium 18 µg, Placebo, UMEC 250 µg, UMEC 500 µg	Seq 9: Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg, Placebo	Seq 10: Tiotropium 18 µg, UMEC 250 µg, Placebo, UMEC 500 µg	Seq 11: Placebo, UMEC 250 µg, Tiotropium 18 µg, UMEC 500 µg	Seq 12: UMEC 250 µg, Placebo, UMEC 500 µg, Tiotropium 18 µg
Started	1	1	0	2	1	0
Completed	1	1	0	2	1	0
Not Completed	0	0	0	0	0	0

Washout Period 3

	Seq 1: UMEC 250 µg, UMEC 500 µg, Tiotropium 18 µg, Placebo	Seq 2: UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg, Placebo	Seq 3: UMEC 250 µg, Placebo, UMEC 500 µg, UMEC 1000 µg	Seq 4: UMEC 250 µg, UMEC 500 µg, Placebo, UMEC 1000 µg	Seq 5: Placebo, UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg	Seq 6: UMEC 250 µg, Placebo, Tiotropium 18 µg, UMEC 500 µg
Started	1	3	4	3	3	1
Completed	1	3	4	3	3	1
Not Completed	0	0	0	0	0	0

	Seq 7: Placebo, Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg	Seq 8: Tiotropium 18 µg, Placebo, UMEC 250 µg, UMEC 500 µg	Seq 9: Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg, Placebo	Seq 10: Tiotropium 18 µg, UMEC 250 µg, Placebo, UMEC 500 µg	Seq 11: Placebo, UMEC 250 µg, Tiotropium 18 µg, UMEC 500 µg	Seq 12: UMEC 250 µg, Placebo, UMEC 500 µg, Tiotropium 18 µg
Started	1	1	0	2	1	0
Completed	1	1	0	2	1	0
Not Completed	0	0	0	0	0	0

Treatment Period 4

	Seq 1: UMEC 250 µg, UMEC 500 µg, Tiotropium 18 µg, Placebo	Seq 2: UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg, Placebo	Seq 3: UMEC 250 µg, Placebo, UMEC 500 µg, UMEC 1000 µg	Seq 4: UMEC 250 µg, UMEC 500 µg, Placebo, UMEC 1000 µg	Seq 5: Placebo, UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg	Seq 6: UMEC 250 µg, Placebo, Tiotropium 18 µg, UMEC 500 µg
Started	1	3	4	3	3	1
Completed	1	3	4	3	3	1
Not Completed	0	0	0	0	0	0

	Seq 7: Placebo, Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg	Seq 8: Tiotropium 18 µg, Placebo, UMEC 250 µg, UMEC 500 µg	Seq 9: Tiotropium 18 µg, UMEC 250 µg, UMEC 500 µg, Placebo	Seq 10: Tiotropium 18 µg, UMEC 250 µg, Placebo, UMEC 500 µg	Seq 11: Placebo, UMEC 250 µg, Tiotropium 18 µg, UMEC 500 µg	Seq 12: UMEC 250 µg, Placebo, UMEC 500 µg, Tiotropium 18 µg
Started	1	1	0	2	1	0
Completed	1	1	0	2	1	0
Not Completed	0	0	0	0	0	0

Baseline Characteristics

Reporting Groups

	Description
All Study Treatments	Participants received a sequence containing 4 of the following 5 possible treatments: placebo, UMEC 250 µg, UMEC 500 µg, UMEC 1000 µg and Tiotropium 18 µg. Participants received each of the treatments in 1 of 4 single dose treatment periods, each of which was followed by a washout period. Treatment periods 1, 2, and 3 were followed by at least a 14-day washout period; Treatment period 4 was followed by a Follow-up visit within 10 days.

Baseline Measures

	All Study Treatments
Number of Participants	24
Age, Continuous [units: Years] Mean (Standard Deviation)	56.0 (5.32)
Gender, Male/Female [units: Participants]	
Female	5
Male	19

	All Study Treatments
Race/Ethnicity, Customized White - White/Caucasian/European [units: Participants]	24

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants With Any Adverse Event (AE) or Any Serious Adverse Event (SAE)
Measure Description	An AE is defined as any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, or is an event of possible drug-induced liver injury. Refer to the general AE/SAE module for a list of AEs and SAEs.
Time Frame	From Day 1 of Treatment Period 1until Follow-up (up to 10 weeks)
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 a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 micrograms (µg) via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Number of Participants With Any Adverse Event (AE) or Any Serious Adverse Event (SAE) [units: Participants]					
Any AE	6	9	8	4	3
Any SAE	0	0	0	0	0

2. Primary Outcome Measure:

Measure Title	Maximum (0-4 Hours) Heart Rate on Day 1 of Each Treatment Period
Measure Description	Resting heart rate was measured at pre-dose and 15 minutes (min), 45min, 1.5 hour (h) 4 h, 8 h, and 24 h post-dose of each treatment period and the maximum value for heart rate (0-4hours) was derived at rest. Baseline is the mean of the 3 pre-dose measurements for each period. Participant level Baseline is the mean of the Baselines for each participant and period level Baseline is the difference between the Baseline and the participant level Baseline in each treatment period for each participant. Analysis was performed using a mixed model with participant level Baseline, period level Baseline, period and treatment group were fitted as fixed effects and participant as a random effect.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

	Description
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Maximum (0-4 Hours) Heart Rate on Day 1 of Each Treatment Period [units: Beats per minute (bpm)] Least Squares Mean (Standard Error)	69.1 (1.01)	68.7 (1.14)	69.5 (1.04)	71.2 (1.54)	66.4 (1.69)

Statistical Analysis 1 for Maximum (0-4 Hours) Heart Rate on Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 250 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.4
	Confidence Interval	(2-Sided) 95% -3.0 to 2.2
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.31
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Maximum (0-4 Hours) Heart Rate on Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 500 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.4
	Confidence Interval	(2-Sided) 95% -2.1 to 2.9
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.25
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Maximum (0-4 Hours) Heart Rate on Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 1000 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	2.1

	Confidence Interval	(2-Sided) 95% -1.4 to 5.7
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.77
	Estimation Comments	[Not specified]

Statistical Analysis 4 for Maximum (0-4 Hours) Heart Rate on Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-2.7
	Confidence Interval	(2-Sided) 95% -6.2 to 0.9
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.79
	Estimation Comments	[Not specified]

Statistical Analysis 5 for Maximum (0-4 Hours) Heart Rate on Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 250 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	2.3
	Confidence Interval	(2-Sided) 95% -1.3 to 5.8
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.78
	Estimation Comments	[Not specified]

Statistical Analysis 6 for Maximum (0-4 Hours) Heart Rate on Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 500 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	3.1
	Confidence Interval	(2-Sided) 95% -0.7 to 6.9
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.89
	Estimation Comments	[Not specified]

Statistical Analysis 7 for Maximum (0-4 Hours) Heart Rate on Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 1000 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	4.8
	Confidence Interval	(2-Sided) 95% -0.1 to 9.7
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.46
	Estimation Comments	[Not specified]

3. Primary Outcome Measure:

Measure Title	Weighted Mean (0-4 Hours) Heart Rate at Day 1 of Each Treatment Period
Measure Description	Resting heart rate was measured at pre-dose and 15 minutes (min), 45 min, 1.5 hours (h), 4 h, 8 h and 24 h post-dose of each treatment period and the weighted mean value for heart rate (0-4 hours) was derived. Baseline is the mean of the 3 pre-dose measurements for each period. Participant level Baseline is the mean of the Baselines for each participant and period level Baseline is the difference between the Baseline and the participant level Baseline in each treatment period for each participant. Analysis was performed using a mixed model with participant level Baseline, period level Baseline, period and treatment group were fitted as fixed effects and participant as a random effect.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Weighted Mean (0-4 Hours) Heart Rate at Day 1 of Each Treatment Period [units: Beats per minute (bpm)] Least Squares Mean (Standard Error)	64.66 (0.882)	63.88 (0.953)	65.69 (0.894)	66.61 (1.177)	62.93 (1.275)

Statistical Analysis 1 for Weighted Mean (0-4 Hours) Heart Rate at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 250 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.78
	Confidence Interval	(2-Sided) 95% -2.47 to 0.92
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.844
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Weighted Mean (0-4 Hours) Heart Rate at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 500 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	1.04
	Confidence Interval	(2-Sided) 95% -0.57 to 2.64
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.798
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Weighted Mean (0-4 Hours) Heart Rate at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 1000 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	1.95
	Confidence Interval	(2-Sided) 95% -0.35 to 4.26
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.151
	Estimation Comments	[Not specified]

Statistical Analysis 4 for Weighted Mean (0-4 Hours) Heart Rate at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-1.72
	Confidence Interval	(2-Sided) 95% -4.11 to 0.67
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.193
	Estimation Comments	[Not specified]

Statistical Analysis 5 for Weighted Mean (0-4 Hours) Heart Rate at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 250 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.95
	Confidence Interval	(2-Sided) 95% -1.44 to 3.33
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.190
	Estimation Comments	[Not specified]

Statistical Analysis 6 for Weighted Mean (0-4 Hours) Heart Rate at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 500 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)

	Estimated Value	2.76
	Confidence Interval	(2-Sided) 95% 0.24 to 5.28
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.257
	Estimation Comments	[Not specified]

Statistical Analysis 7 for Weighted Mean (0-4 Hours) Heart Rate at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 1000 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	3.68
	Confidence Interval	(2-Sided) 95% 0.34 to 7.02
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.670
	Estimation Comments	[Not specified]

4. Primary Outcome Measure:

Measure Title	Maximum (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period

Measure Description	Resting systolic blood pressure was measured at pre-dose and 15 minutes (min), 45 min, 1.5 hours (h), 4 h, 8 h and 24 h post-dose of each treatment period and the maximum value for systolic blood pressure (0-4 hours) was derived. Baseline is the mean of the 3 pre-dose measurements for each period. Participant level Baseline is the mean of the Baselines for each participant and period level Baseline is the difference between the Baseline and the participant level Baseline in each treatment period for each participant. Analysis was performed using a mixed model with participant level Baseline, period level Baseline, period and treatment group were fitted as fixed effects and participant as a random effect.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Maximum (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period [units: Millimeters of mercury (mmHg)] Least Squares Mean (Standard Error)	129.7 (1.59)	129.0 (1.84)	126.2 (1.65)	133.0 (2.41)	131.0 (2.78)

Statistical Analysis 1 for Maximum (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 250 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.8
	Confidence Interval	(2-Sided) 95% -5.0 to 3.4
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.11
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Maximum (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 500 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-3.5

	Confidence Interval	(2-Sided) 95% -7.6 to 0.6
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.03
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Maximum (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 1000 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	3.3
	Confidence Interval	(2-Sided) 95% -2.2 to 8.7
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.74
	Estimation Comments	[Not specified]

Statistical Analysis 4 for Maximum (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	1.3
	Confidence Interval	(2-Sided) 95% -4.7 to 7.2
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.98
	Estimation Comments	[Not specified]

Statistical Analysis 5 for Maximum (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 250 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-2.0
	Confidence Interval	(2-Sided) 95% -7.7 to 3.6
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.83
	Estimation Comments	[Not specified]

Statistical Analysis 6 for Maximum (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 500 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-4.8
	Confidence Interval	(2-Sided) 95% -11.2 to 1.6
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.20
	Estimation Comments	[Not specified]

Statistical Analysis 7 for Maximum (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 1000 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	2.0

	Confidence Interval	(2-Sided) 95% -5.9 to 10.0
	Parameter Dispersion	Type: Standard Error of the mean Value: 4.00
	Estimation Comments	[Not specified]

5. Primary Outcome Measure:

Measure Title	Weighted Mean (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period
Measure Description	Resting systolic blood pressure was measured at pre-dose and 15 minutes (min), 45 min, 1.5 hours (h), 4 h, 8 h and 24 h post-dose of each treatment period and the weighted mean value for systolic blood pressure (0-4 hours) was derived. Baseline is the mean of the 3 pre-dose measurements for each period. Participant level Baseline is the mean of the Baselines for each participant and period level Baseline is the difference between the Baseline and the participant level Baseline in each treatment period for each participant. Analysis was performed using a mixed model with participant level Baseline, period level Baseline, period and treatment group were fitted as fixed effects and participant as a random effect.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Weighted Mean (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period [units: Millimeters of mercury (mmHg)] Least Squares Mean (Standard Error)	124.49 (1.445)	122.07 (1.670)	122.61 (1.503)	125.61 (2.190)	124.80 (2.517)

Statistical Analysis 1 for Weighted Mean (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 250 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-2.42
	Confidence Interval	(2-Sided) 95% -6.23 to 1.39
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.902
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Weighted Mean (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 500 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-1.88
	Confidence Interval	(2-Sided) 95% -5.56 to 1.79
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.834
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Weighted Mean (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 1000 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	1.12
	Confidence Interval	(2-Sided) 95% -3.82 to 6.07
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.474
	Estimation Comments	[Not specified]

Statistical Analysis 4 for Weighted Mean (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.31
	Confidence Interval	(2-Sided) 95% -5.07 to 5.69
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.697
	Estimation Comments	[Not specified]

Statistical Analysis 5 for Weighted Mean (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 250 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)

	Estimated Value	-2.73
	Confidence Interval	(2-Sided) 95% -7.84 to 2.38
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.562
	Estimation Comments	[Not specified]

Statistical Analysis 6 for Weighted Mean (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 500 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-2.19
	Confidence Interval	(2-Sided) 95% -7.97 to 3.59
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.898
	Estimation Comments	[Not specified]

Statistical Analysis 7 for Weighted Mean (0-4 Hours) Systolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 1000 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.82
	Confidence Interval	(2-Sided) 95% -6.39 to 8.02
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.618
	Estimation Comments	[Not specified]

6. Primary Outcome Measure:

Measure Title	Maximum (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period
Measure Description	Resting diastolic blood pressure was measured at pre-dose and 15 minutes (min), 45 min, 1.5 hours (h), 4 h, 8 h and 24 h post-dose of each treatment period and the maximum value for diastolic blood pressure (0-4 hours) was derived. Baseline is the mean of the 3 pre-dose measurements for each period. Participant level Baseline is the mean of the Baselines for each participant and period level Baseline is the difference between the Baseline and the participant level Baseline in each treatment period for each participant. Analysis was performed using a mixed model with participant level Baseline, period level Baseline, period and treatment group were fitted as fixed effects and participant as a random effect.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

	Description
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Maximum (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period [units: Millimeters of mercury (mmHg)] Least Squares Mean (Standard Error)	82.7 (0.96)	80.2 (1.14)	80.6 (1.01)	86.0 (1.46)	80.3 (1.63)

Statistical Analysis 1 for Maximum (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 250 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-2.5
	Confidence Interval	(2-Sided) 95% -5.1 to 0.2
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.31

	Estimation Comments	[Not specified]

Statistical Analysis 2 for Maximum (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 500 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-2.1
	Confidence Interval	(2-Sided) 95% -4.6 to 0.4
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.25
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Maximum (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 1000 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	3.3
	Confidence Interval	(2-Sided) 95% -0.0 to 6.6
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.67
	Estimation Comments	[Not specified]

Statistical Analysis 4 for Maximum (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-2.4
	Confidence Interval	(2-Sided) 95% -5.9 to 1.2
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.77
	Estimation Comments	[Not specified]

Statistical Analysis 5 for Maximum (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 250 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.1
	Confidence Interval	(2-Sided) 95% -3.5 to 3.3
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.71
	Estimation Comments	[Not specified]

Statistical Analysis 6 for Maximum (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 500 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.3
	Confidence Interval	(2-Sided) 95% -3.5 to 4.1
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.90
	Estimation Comments	[Not specified]

Statistical Analysis 7 for Maximum (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 1000 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	5.7
	Confidence Interval	(2-Sided) 95% 1.0 to 10.4
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.35
	Estimation Comments	[Not specified]

7. Primary Outcome Measure:

Measure Title	Weighted Mean (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period
Measure Description	Resting diastolic blood pressure was measured at pre-dose and 15 minutes (min), 45 min, 1.5 hours (h), 4 h, 8 h and 24 h post-dose of each treatment period and the weighted mean value for diastolic blood pressure (0-4 hours) was derived. Baseline is the mean of the 3 pre-dose measurements for each period. Participant level Baseline is the mean of the Baselines for each participant and period level Baseline is the difference between the Baseline and the participant level Baseline in each treatment period for each participant. Analysis was performed using a mixed model with participant level Baseline, period level Baseline, period and treatment group were fitted as fixed effects and participant as a random effect.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Weighted Mean (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period [units: Millimeters of mercury (mmHg)] Least Squares Mean (Standard Error)	79.21 (0.759)	76.23 (0.902)	77.69 (0.798)	81.42 (1.156)	75.89 (1.293)

Statistical Analysis 1 for Weighted Mean (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 250 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis

	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-2.97
	Confidence Interval	(2-Sided) 95% -5.08 to -0.87
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.051
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Weighted Mean (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 500 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-1.51
	Confidence Interval	(2-Sided) 95% -3.53 to 0.50
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.006
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Weighted Mean (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 1000 µg
	Comments	[Not specified]

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	2.21
	Confidence Interval	(2-Sided) 95% -0.46 to 4.88
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.335
	Estimation Comments	[Not specified]

Statistical Analysis 4 for Weighted Mean (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-3.32
	Confidence Interval	(2-Sided) 95% -6.13 to -0.50
	Parameter Dispersion	Type: Standard Error of the mean

		Value: 1.409
	Estimation Comments	[Not specified]

Statistical Analysis 5 for Weighted Mean (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 250 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.35
	Confidence Interval	(2-Sided) 95% -2.38 to 3.07
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.366
	Estimation Comments	[Not specified]

Statistical Analysis 6 for Weighted Mean (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 500 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	1.80
	Confidence Interval	(2-Sided) 95% -1.22 to 4.82
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.514
	Estimation Comments	[Not specified]

Statistical Analysis 7 for Weighted Mean (0-4 Hours) Diastolic Blood Pressure at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 1000 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	5.53
	Confidence Interval	(2-Sided) 95% 1.81 to 9.25
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.867
	Estimation Comments	[Not specified]

8. Primary Outcome Measure:

Measure Title	Maximum (0-4 Hours) QTcB at Day 1 of Each Treatment Period

Measure Description	Twelve-lead ECGs (electrocardiograms) were performed to measure QT interval corrected according to Bazzet's formula (QTcB) at pre-dose and 15 minutes (min), 45 min, 1.5 hours (h), 4 h, 8 h and 24 h post-dose of each treatment period and the maximum value for QTcB (0-4 hours) was derived. Baseline is the mean of the 3 pre-dose measurements for each period. Participant level Baseline is the mean of the Baselines for each participant and period level Baseline is the difference between the Baseline and the participant level Baseline in each treatment period for each participant. Analysis was performed using a mixed model with participant level Baseline, period level Baseline, period and treatment group were fitted as fixed effects and participant as a random effect.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Maximum (0-4 Hours) QTcB at Day 1 of Each Treatment Period [units: Milliseconds (msec)] Least Squares Mean (Standard Error)	402.79 (2.263)	399.48 (2.621)	404.48 (2.396)	401.25 (3.579)	397.62 (3.867)

Statistical Analysis 1 for Maximum (0-4 Hours) QTcB at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 250 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-3.31
	Confidence Interval	(2-Sided) 95% -9.82 to 3.21
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.256
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Maximum (0-4 Hours) QTcB at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 500 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	1.69

	Confidence Interval	(2-Sided) 95% -4.70 to 8.09
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.193
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Maximum (0-4 Hours) QTcB at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 1000 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-1.54
	Confidence Interval	(2-Sided) 95% -10.06 to 6.98
	Parameter Dispersion	Type: Standard Error of the mean Value: 4.268
	Estimation Comments	[Not specified]

Statistical Analysis 4 for Maximum (0-4 Hours) QTcB at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-5.17
	Confidence Interval	(2-Sided) 95% -13.84 to 3.50
	Parameter Dispersion	Type: Standard Error of the mean Value: 4.347
	Estimation Comments	[Not specified]

Statistical Analysis 5 for Maximum (0-4 Hours) QTcB at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 250 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	1.86
	Confidence Interval	(2-Sided) 95% -6.65 to 10.37
	Parameter Dispersion	Type: Standard Error of the mean Value: 4.264
	Estimation Comments	[Not specified]

Statistical Analysis 6 for Maximum (0-4 Hours) QTcB at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 500 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	6.86
	Confidence Interval	(2-Sided) 95% -2.35 to 16.08
	Parameter Dispersion	Type: Standard Error of the mean Value: 4.622
	Estimation Comments	[Not specified]

Statistical Analysis 7 for Maximum (0-4 Hours) QTcB at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 1000 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	3.63

	Confidence Interval	(2-Sided) 95% -7.59 to 14.85
	Parameter Dispersion	Type: Standard Error of the mean Value: 5.634
	Estimation Comments	[Not specified]

9. Primary Outcome Measure:

Measure Title	Weighted Mean (0-4 Hours) QTcB at Day 1 of Each Treatment Period
Measure Description	Twelve-lead ECGs were performed to measure QTcB at pre-dose and 15 minutes (min), 45 min, 1.5 hours (h), 4 h, 8 h and 24 h post-dose of each treatment period and the weighted mean value for QTcB (0-4 hours) was derived. Baseline is the mean of the 3 pre-dose measurements for each period. Participant level Baseline is the mean of the Baselines for each participant and period level Baseline is the difference between the Baseline and the participant level Baseline in each treatment period for each participant. Analysis was performed using a mixed model with participant level Baseline, period level Baseline, period and treatment group were fitted as fixed effects and participant as a random effect.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Weighted Mean (0-4 Hours) QTcB at Day 1 of Each Treatment Period [units: Milliseconds (msec)] Least Squares Mean (Standard Error)	391.266 (1.7582)	390.968 (2.0079)	392.332 (1.8401)	389.204 (2.7044)	391.628 (2.9378)

Statistical Analysis 1 for Weighted Mean (0-4 Hours) QTcB at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 250 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.298
	Confidence Interval	(2-Sided) 95% -4.961 to 4.365
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.3297
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Weighted Mean (0-4 Hours) QTcB at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 500 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	1.066
	Confidence Interval	(2-Sided) 95% -3.495 to 5.627
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.2776
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Weighted Mean (0-4 Hours) QTcB at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 1000 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-2.062
	Confidence Interval	(2-Sided) 95% -8.247 to 4.122
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.0952
	Estimation Comments	[Not specified]

Statistical Analysis 4 for Weighted Mean (0-4 Hours) QTcB at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.362
	Confidence Interval	(2-Sided) 95% -6.003 to 6.726
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.1891
	Estimation Comments	[Not specified]

Statistical Analysis 5 for Weighted Mean (0-4 Hours) QTcB at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 250 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)

	Estimated Value	-0.660
	Confidence Interval	(2-Sided) 95% -6.873 to 5.554
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.1121
	Estimation Comments	[Not specified]

Statistical Analysis 6 for Weighted Mean (0-4 Hours) QTcB at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 500 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.704
	Confidence Interval	(2-Sided) 95% -6.064 to 7.473
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.3916
	Estimation Comments	[Not specified]

Statistical Analysis 7 for Weighted Mean (0-4 Hours) QTcB at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 1000 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-2.424
	Confidence Interval	(2-Sided) 95% -10.84 to 5.993
	Parameter Dispersion	Type: Standard Error of the mean Value: 4.2233
	Estimation Comments	[Not specified]

10. Primary Outcome Measure:

Measure Title	Maximum (0-4 Hours) QTcF at Day 1 of Each Treatment Period
Measure Description	Twelve-lead ECGs were performed to measure QT interval corrected according to Fredericia's formula (QTcF) at pre-dose and 15 minutes (min), 45 min, 1.5 hours (h), 4 h, 8 h and 24 h post-dose of each treatment period and the maximum value for QTcF (0-4 hours) was derived. Baseline is the mean of the 3 pre-dose measurements for each period. Participant level Baseline is the mean of the Baselines for each participant and period level Baseline is the difference between the Baseline and the participant level Baseline in each treatment period for each participant. Analysis was performed using a mixed model with participant level Baseline, period level Baseline, period and treatment group were fitted as fixed effects and participant as a random effect.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

	Description
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Maximum (0-4 Hours) QTcF at Day 1 of Each Treatment Period [units: Milliseconds (msec)] Least Squares Mean (Standard Error)	394.25 (1.699)	394.34 (1.977)	395.60 (1.802)	393.10 (2.604)	393.93 (2.873)

Statistical Analysis 1 for Maximum (0-4 Hours) QTcF at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 250 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.08
	Confidence Interval	(2-Sided) 95% -4.98 to 5.15
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.542

	Estimation Comments	[Not specified]

Statistical Analysis 2 for Maximum (0-4 Hours) QTcF at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 500 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	1.34
	Confidence Interval	(2-Sided) 95% -3.65 to 6.34
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.507
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Maximum (0-4 Hours) QTcF at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 1000 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-1.15
	Confidence Interval	(2-Sided) 95% -7.49 to 5.19
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.182
	Estimation Comments	[Not specified]

Statistical Analysis 4 for Maximum (0-4 Hours) QTcF at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.32
	Confidence Interval	(2-Sided) 95% -6.89 to 6.24
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.296
	Estimation Comments	[Not specified]

Statistical Analysis 5 for Maximum (0-4 Hours) QTcF at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 250 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.41
	Confidence Interval	(2-Sided) 95% -6.13 to 6.94
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.279
	Estimation Comments	[Not specified]

Statistical Analysis 6 for Maximum (0-4 Hours) QTcF at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 500 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	1.67
	Confidence Interval	(2-Sided) 95% -5.34 to 8.67
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.516
	Estimation Comments	[Not specified]

Statistical Analysis 7 for Maximum (0-4 Hours) QTcF at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 1000 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.83
	Confidence Interval	(2-Sided) 95% -8.97 to 7.32
	Parameter Dispersion	Type: Standard Error of the mean Value: 4.087
	Estimation Comments	[Not specified]

11. Primary Outcome Measure:

Measure Title	Weighted Mean (0-4 Hours) QTcF at Day 1 of Each Treatment Period
Measure Description	Twelve-lead ECGs were performed to measure QTcF at pre-dose and 15 minutes (min), 45 min, 1.5 hours (h), 4 h, 8 h and 24 h post-dose of each treatment period and the weighted mean value for QTcF (0-4 hours) was derived. Baseline is the mean of the 3 pre-dose measurements for each period. Participant level Baseline is the mean of the Baselines for each participant and period level Baseline is the difference between the Baseline and the participant level Baseline in each treatment period for each participant. Analysis was performed using a mixed model with participant level Baseline, period level Baseline, period and treatment group were fitted as fixed effects and participant as a random effect.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Weighted Mean (0-4 Hours) QTcF at Day 1 of Each Treatment Period [units: Milliseconds (msec)] Least Squares Mean (Standard Error)	386.501 (1.3698)	387.965 (1.5869)	386.750 (1.4414)	383.856 (2.1160)	389.086 (2.3515)

Statistical Analysis 1 for Weighted Mean (0-4 Hours) QTcF at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 250 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	1.464
	Confidence Interval	(2-Sided) 95% -2.492 to 5.419
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.9766
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Weighted Mean (0-4 Hours) QTcF at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 500 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.248
	Confidence Interval	(2-Sided) 95% -3.647 to 4.144
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.9457
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Weighted Mean (0-4 Hours) QTcF at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 1000 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-2.645
	Confidence Interval	(2-Sided) 95% -7.687 to 2.396
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.5254
	Estimation Comments	[Not specified]

Statistical Analysis 4 for Weighted Mean (0-4 Hours) QTcF at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	2.585
	Confidence Interval	(2-Sided) 95% -2.671 to 7.840
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.6352
	Estimation Comments	[Not specified]

Statistical Analysis 5 for Weighted Mean (0-4 Hours) QTcF at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 250 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-1.121
	Confidence Interval	(2-Sided) 95% -6.308 to 4.067
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.5993
	Estimation Comments	[Not specified]

Statistical Analysis 6 for Weighted Mean (0-4 Hours) QTcF at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 500 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)

	Estimated Value	-2.336
	Confidence Interval	(2-Sided) 95% -7.952 to 3.280
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.8164
	Estimation Comments	[Not specified]

Statistical Analysis 7 for Weighted Mean (0-4 Hours) QTcF at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 1000 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-5.230
	Confidence Interval	(2-Sided) 95% -11.96 to 1.504
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.3802
	Estimation Comments	[Not specified]

12. Primary Outcome Measure:

Measure Title	Maximum (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period
Measure Description	Twenty-four hour Holter monitoring was conducted to measure heart rate for the 24-hour period following dosing at each treatment period and the maximum value for heart rate (0-24 hours) was derived. Analysis was performed using a mixed model of period and treatment group fitted as fixed effects and participant as a random effect.
Time Frame	Day 1 of each treatment period (up to Study Day 46)

Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Maximum (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period [units: Beats per minute (bpm)] Least Squares Mean (Standard Error)	116.7 (2.92)	111.5 (3.06)	112.1 (2.96)	109.0 (3.53)	111.4 (3.79)

Statistical Analysis 1 for Maximum (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 250 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-5.2
	Confidence Interval	(2-Sided) 95% -9.7 to -0.7
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.24
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Maximum (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 500 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-4.6
	Confidence Interval	(2-Sided) 95% -8.9 to -0.3
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.15
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Maximum (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 1000 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-7.7
	Confidence Interval	(2-Sided) 95% -13.5 to -1.8
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.91
	Estimation Comments	[Not specified]

Statistical Analysis 4 for Maximum (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-5.3

	Confidence Interval	(2-Sided) 95% -11.8 to 1.1
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.21
	Estimation Comments	[Not specified]

Statistical Analysis 5 for Maximum (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 250 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.1
	Confidence Interval	(2-Sided) 95% -6.1 to 6.4
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.12
	Estimation Comments	[Not specified]

Statistical Analysis 6 for Maximum (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 500 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.7
	Confidence Interval	(2-Sided) 95% -6.1 to 7.5
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.38
	Estimation Comments	[Not specified]

Statistical Analysis 7 for Maximum (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 1000 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-2.4
	Confidence Interval	(2-Sided) 95% -10.9 to 6.2
	Parameter Dispersion	Type: Standard Error of the mean Value: 4.29
	Estimation Comments	[Not specified]

13. Primary Outcome Measure:

Measure Title	Mean (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period
Measure Description	Twenty-four-hour Holter monitoring was conducted to measure heart rate for the 24-h period following dosing of each treatment period and the mean value for heart rate (0-24 hours) was derived. Analysis was performed using a mixed model of period and treatment group fitted as fixed effects and participant as a random effect.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Mean (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period [units: Beats per minute (bpm)] Least Squares Mean (Standard Error)	77.1 (1.61)	75.3 (1.66)	76.8 (1.62)	75.5 (1.80)	76.1 (1.89)

Statistical Analysis 1 for Mean (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 250 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-1.8
	Confidence Interval	(2-Sided) 95% -3.6 to 0.0
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.90
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Mean (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 500 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.3

	Confidence Interval	(2-Sided) 95% -2.0 to 1.4
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.86
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Mean (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, UMEC 1000 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-1.6
	Confidence Interval	(2-Sided) 95% -3.9 to 0.8
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.17
	Estimation Comments	[Not specified]

Statistical Analysis 4 for Mean (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	Placebo, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-1.0
	Confidence Interval	(2-Sided) 95% -3.6 to 1.6
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.30
	Estimation Comments	[Not specified]

Statistical Analysis 5 for Mean (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 250 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.8
	Confidence Interval	(2-Sided) 95% -3.3 to 1.7
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.26
	Estimation Comments	[Not specified]

Statistical Analysis 6 for Mean (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 500 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.7
	Confidence Interval	(2-Sided) 95% -2.0 to 3.4
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.37
	Estimation Comments	[Not specified]

Statistical Analysis 7 for Mean (0-24 Hours) Heart Rate as Measured From Holter Monitoring at Day 1 of Each Treatment Period

Statistical Analysis Overview	Comparison Groups	UMEC 1000 µg, Tiotropium 18 µg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.6

	Confidence Interval	(2-Sided) 95% -4.1 to 2.9
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.74
	Estimation Comments	[Not specified]

14. Primary Outcome Measure:

Measure Title	Basophils, Eosinophils, Lymphocytes, Monocytes, and Total Neutrophils Values at the Indicated Time Points on Day 1 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of basophils, eosinophils, lymphocytes, monocytes, and total neutrophils at pre-dose and 24 hour (h) post-dose of each treatment period.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

All Subjects Population

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Basophils, Eosinophils, Lymphocytes, Monocytes, and Total Neutrophils Values at the Indicated Time Points on Day 1 of Each Treatment Period [units: Percentage] Mean (Standard Deviation)					
Basophils, Pre-dose	0.65 (0.284)	0.73 (0.366)	0.74 (0.396)	0.87 (0.275)	0.71 (0.314)
Basophils, 24 h Post-dose	0.70 (0.434)	0.65 (0.313)	0.56 (0.292)	0.58 (0.344)	0.76 (0.558)
Eosinophils, Pre-dose	3.30 (2.336)	3.46 (2.249)	3.67 (2.813)	4.03 (2.679)	3.05 (1.562)
Eosinophils, 24 h Post-dose	3.34 (1.914)	3.25 (1.839)	3.30 (2.164)	3.49 (2.437)	3.38 (1.552)
Lymphocytes, Pre-dose	29.23 (6.820)	30.66 (7.355)	28.91 (9.279)	33.70 (7.161)	27.99 (7.637)
Lymphocytes, 24 h Post-dose	31.60 (6.387)	30.86 (6.749)	30.99 (6.558)	31.72 (4.920)	30.86 (6.298)
Monocytes, Pre-dose	8.53 (1.842)	8.50 (2.467)	8.60 (2.179)	8.10 (1.626)	9.33 (2.582)
Monocytes, 24 h Post-dose	8.10 (1.975)	7.62 (1.934)	8.23 (1.985)	7.45 (1.406)	9.40 (2.084)
Total neutrophils, Pre-dose	58.30 (8.159)	56.64 (9.081)	58.10 (10.941)	53.32 (7.825)	58.88 (9.403)
Total neutrophils, 24 h Post-dose	56.26 (7.166)	57.62 (7.740)	56.94 (7.164)	56.78 (6.204)	55.63 (7.699)

15. Primary Outcome Measure:

Measure Title	Hemoglobin, Mean Corpuscle Hemoglobin Concentration (MCHC), Albumin and Total Protein Values at the Indicated Time Points on Day 1 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of hemoglobin, MCHC, albumin and total protein at pre-dose and 24 hour (h) post-dose of each treatment period.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description
All Subjects Population

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.

	Description
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Hemoglobin, Mean Corpuscle Hemoglobin Concentration (MCHC), Albumin and Total Protein Values at the Indicated Time Points on Day 1 of Each Treatment Period [units: Grams per liter (G/L)] Mean (Standard Deviation)					
Hemoglobin, Pre-dose	146.1 (11.80)	146.6 (10.31)	145.4 (11.27)	143.8 (12.34)	152.0 (7.23)
Hemoglobin, 24 h Post-dose	147.0 (12.53)	145.5 (11.01)	144.1 (10.97)	143.5 (14.77)	148.9 (5.59)
MCHC, Pre-dose	347.2 (7.03)	343.3 (5.78)	344.1 (7.87)	346.8 (4.62)	343.0 (5.04)
MCHC, 24 h Post-dose	344.9 (6.35)	344.0 (7.02)	344.9 (8.50)	345.2 (6.57)	342.9 (3.91)
Albumin, Pre-dose	39.16 (2.020)	39.24 (2.109)	39.33 (1.955)	39.10 (1.545)	39.49 (2.775)
Albumin, 24 h Post-dose	39.36 (1.682)	38.75 (1.742)	38.76 (1.744)	39.30 (1.750)	38.38 (2.930)
Total protein, Pre-dose	66.05 (4.120)	66.04 (4.245)	66.19 (3.987)	66.15 (3.576)	65.35 (2.931)
Total protein, 24 h Post-dose	66.37 (3.584)	65.40 (3.933)	65.62 (2.945)	66.44 (3.448)	64.14 (3.349)

16. Primary Outcome Measure:

Measure Title	Hematocrit Values at the Indicated Time Points on Day 1 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of hematocrit at pre-dose and 24 hour (h) post-dose of each treatment period.

Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description
All Subjects Population

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Hematocrit Values at the Indicated Time Points on Day 1 of Each Treatment Period [units: Proportion of red blood cells in blood] Mean (Standard Deviation)					
Pre-dose	0.421 (0.0335)	0.428 (0.0321)	0.423 (0.0326)	0.416 (0.0345)	0.445 (0.0193)
24 h Post-dose	0.427 (0.0352)	0.424 (0.0361)	0.418 (0.0322)	0.417 (0.0419)	0.434 (0.0192)

17. Primary Outcome Measure:

Measure Title	Mean Corpuscle Hemoglobin Values at the Indicated Time Points on Day 1 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of the mean corpuscle hemoglobin at pre-dose and 24 hour (h) post-dose of each treatment period.

Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description
All Subjects Population

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Mean Corpuscle Hemoglobin Values at the Indicated Time Points on Day 1 of Each Treatment Period [units: picograms/cell (pg)] Mean (Standard Deviation)					
Pre-dose	32.56 (1.402)	32.36 (1.365)	32.36 (1.513)	32.29 (1.393)	32.86 (0.971)
24 Hour Post-dose	32.41 (1.354)	32.36 (1.208)	32.36 (1.359)	32.15 (1.309)	32.79 (1.018)

18. Primary Outcome Measure:

Measure Title	Mean Corpuscle Volume Values at the Indicated Time Points on Day 1 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of the mean corpuscle volume at pre-dose and 24 hour (h) post-dose of each treatment period.

Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description
All Subjects Population

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Mean Corpuscle Volume Values at the Indicated Time Points on Day 1 of Each Treatment Period [units: Femtoliters (FL)] Mean (Standard Deviation)					
Pre-dose	93.78 (3.701)	94.23 (3.547)	94.04 (3.734)	93.11 (3.840)	95.83 (3.310)
24 h Post-dose	93.99 (3.597)	94.09 (3.763)	93.85 (3.955)	93.15 (3.652)	95.65 (2.946)

19. Primary Outcome Measure:

Measure Title	Red Blood Cells Count Values at the Indicated Time Points on Day 1 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of the red blood cells count at pre-dose and 24 hour (h) post-dose of each treatment period.

Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description
All Subjects Population

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Red Blood Cells Count Values at the Indicated Time Points on Day 1 of Each Treatment Period [units: 10^12 cells per liter (TI/L)] Mean (Standard Deviation)					
Pre-dose	4.493 (0.3992)	4.537 (0.3487)	4.498 (0.3758)	4.456 (0.3987)	4.625 (0.2469)
24 h Post-dose	4.539 (0.3960)	4.498 (0.3760)	4.457 (0.3614)	4.464 (0.4511)	4.543 (0.2232)

20. Primary Outcome Measure:

Measure Title	Platelets Count and White Blood Cells (WBC) Count Values at the Indicated Time Points on Day 1 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of platelets count and WBC count at pre-dose and 24 hour (h) post-dose of each treatment period.

Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description
All Subjects Population

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Platelets Count and White Blood Cells (WBC) Count Values at the Indicated Time Points on Day 1 of Each Treatment Period [units: 10^9 cells per liter (GI/L)] Mean (Standard Deviation)					
Platelets count, Pre-dose	247.2 (70.84)	245.0 (71.33)	250.7 (69.06)	235.9 (47.15)	243.4 (104.43)
Platelets count, 24 h Post-dose	248.8 (69.53)	245.4 (76.18)	250.3 (63.51)	237.9 (46.30)	237.6 (101.59)
WBC count, Pre-dose	7.623 (1.7271)	7.130 (1.6116)	7.560 (1.6860)	7.121 (1.2807)	6.763 (1.0249)
WBC count, 24 h Post-dose	7.520 (1.3103)	7.385 (1.7548)	7.218 (1.4426)	7.999 (1.6531)	6.623 (1.2366)

21. Primary Outcome Measure:

Measure Title	Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Creatine Phosphokinase (CPK), and Gamma Glutamyl Transferase (GGT) Values at the Indicated Time Points on Day 1 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of ALP, ALT, AST, CPK, and GGT at pre-dose and 24 hour (h) post-dose of each treatment period.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Creatine Phosphokinase (CPK), and Gamma Glutamyl Transferase (GGT) Values at the Indicated Time Points on Day 1 of Each Treatment Period [units: International units per liter (IU/L)] Mean (Standard Deviation)					

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
ALP, Pre-dose, n=21, 22, 21, 13, 8	67.04 (17.260)	65.32 (12.687)	66.60 (13.127)	63.37 (13.469)	71.06 (19.304)
ALP, 24 h Post-dose, n=21, 22, 21, 13, 8	67.20 (18.388)	65.04 (15.289)	64.96 (14.933)	61.76 (12.253)	71.84 (21.099)
ALT, Pre-dose,n=21, 22, 21, 13, 8	23.6 (11.67)	24.1 (9.80)	21.3 (8.37)	26.2 (10.53)	19.1 (5.36)
ALT, 24 h Post-dose,n=21, 22, 21, 13, 8	23.3 (12.29)	23.0 (9.36)	20.5 (7.56)	25.6 (9.69)	17.8 (5.39)
AST, Pre-dose, n=21, 22, 20, 13, 8	21.98 (7.525)	24.55 (6.689)	22.13 (5.358)	23.03 (6.923)	22.09 (4.995)
AST, 24 h Post-dose, n=21, 22, 21, 13, 8	21.68 (8.625)	22.01 (7.048)	20.58 (5.761)	20.75 (6.947)	19.23 (5.473)
CPK, Pre-dose, n=21, 22, 21, 13, 8	124.33 (89.568)	101.88 (49.410)	104.39 (42.381)	100.16 (44.497)	117.08 (61.189)
CPK, 24 h Post-dose, n=21, 22, 21, 13, 8	99.97 (61.307)	82.81 (30.913)	83.77 (29.233)	87.78 (37.566)	109.36 (90.411)
GGT, Pre-dose, n=21, 22, 21, 13, 8	27.81 (18.287)	26.41 (14.704)	26.41 (17.573)	29.86 (21.391)	19.94 (6.369)
GGT, 24 h Post-dose, n=21, 22, 21, 13, 8	27.14 (16.806)	25.33 (13.962)	25.89 (18.218)	29.38 (19.277)	19.59 (6.431)

22. Primary Outcome Measure:

Measure Title	Total Bilirubin, Creatinine and Uric Acid Values at the Indicated Time Points on Day 1 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of total bilirubin, creatinine, and uric acid at pre-dose and 24 hour (h) post-dose of each treatment period.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description
All Subjects Population

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

	Description
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Total Bilirubin, Creatinine and Uric Acid Values at the Indicated Time Points on Day 1 of Each Treatment Period [units: Micromoles per liter (µmol/L)] Mean (Standard Deviation)					
Total bilirubin, Pre-dose	7.92 (2.457)	8.33 (2.234)	8.66 (3.387)	8.68 (2.238)	7.69 (1.549)
Total bilirubin, 24 h Post-dose	8.70 (2.602)	8.26 (2.955)	9.48 (3.523)	10.27 (3.086)	6.83 (2.036)
Creatinine, Pre-dose	78.55 (7.589)	80.50 (8.012)	80.24 (10.079)	78.64 (8.296)	79.79 (8.333)
Creatinine, 24 h Post-dose	78.02 (6.451)	79.08 (8.324)	78.14 (9.684)	76.44 (7.241)	76.29 (8.999)
Uric acid, Pre-dose	295.86 (64.155)	301.24 (77.192)	303.18 (77.389)	317.09 (76.125)	281.19 (67.657)
Uric acid, 24 h Post-dose	285.55 (63.350)	293.21 (65.637)	296.28 (70.307)	306.26 (72.701)	268.64 (61.525)

23. Primary Outcome Measure:

Measure Title	Calcium, Bicarbonate, Chloride, Glucose, Inorganic Phosphorus (IP), Potassium, Sodium, and Urea Values at the Indicated Time Points on Day 1 of Each Treatment Period
Measure Description	Blood samples were collected for the measurement of the calcium, bicarbonate, chloride, glucose, IP, potassium, sodium, and urea at pre-dose and 24 hour (h) post-dose of each treatment period.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

All Subjects Population. Only those participants available at the specified time points were analyzed (represented by n=X, X, X in the category titles). Different participants may have been analyzed for different parameters/at different time points, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Calcium, Bicarbonate, Chloride, Glucose, Inorganic Phosphorus (IP), Potassium, Sodium, and Urea Values at the Indicated Time Points on Day 1 of Each Treatment Period [units: Millimoles per liter (mmol/L)] Mean (Standard Deviation)					
Calcium, Pre-dose, n=21, 22, 21, 13, 8	2.283 (0.0729)	2.277 (0.0861)	2.267 (0.0809)	2.242 (0.0625)	2.278 (0.0547)
Calcium, 24 h Post-dose, n=21, 22, 21, 13, 8	2.270 (0.0891)	2.290 (0.0713)	2.265 (0.0704)	2.244 (0.0864)	2.280 (0.0428)
Chloride, Pre-dose, n=21, 22, 21, 13, 8	106.88 (2.727)	107.11 (1.972)	106.42 (1.857)	107.26 (2.738)	106.49 (2.255)
Chloride, 24 h Post-dose, n=21, 22, 21, 13, 8	107.18 (1.875)	107.10 (2.457)	106.94 (2.002)	107.17 (2.830)	106.59 (1.460)
Glucose, Pre-dose, n=21, 22, 21, 13, 8	5.225 (0.5294)	5.046 (0.5583)	5.082 (0.5882)	5.098 (0.4362)	5.326 (0.6739)
Glucose, 24 h Post-dose, n=21, 22, 21, 13, 8	5.278 (0.5800)	5.203 (0.6391)	5.224 (0.5500)	5.031 (0.3691)	5.291 (0.5350)
Bicarbonate, Pre-dose, n=21, 22, 21, 13, 8	22.41 (2.609)	22.95 (2.295)	23.28 (2.698)	23.08 (2.401)	22.98 (4.179)
Bicarbonate, 24 h Post-dose, n=21, 22, 21, 13, 7	22.98 (2.414)	22.62 (2.995)	23.30 (2.600)	23.80 (2.822)	25.14 (2.738)
Potassium, Pre-dose, n=21, 22, 21, 13, 8	4.283 (0.3178)	4.177 (0.2537)	4.209 (0.2255)	4.248 (0.2717)	4.193 (0.1896)
Potassium, 24 h Post-dose, n=21, 22, 21, 13, 8	4.270 (0.2340)	4.274 (0.3311)	4.266 (0.3065)	4.279 (0.3587)	4.359 (0.3642)
Sodium, Pre-dose,n=21, 22, 21, 13, 8	140.45 (2.253)	140.95 (1.932)	140.84 (1.551)	141.07 (0.825)	140.86 (2.458)

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Sodium, 24 h Post-dose, n=21, 22, 21, 13, 8	140.90 (1.674)	140.68 (1.864)	140.93 (1.610)	141.13 (1.165)	140.56 (1.749)
IP, Pre-dose, n=21, 22, 21, 13, 8	1.153 (0.1271)	1.095 (0.1026)	1.135 (0.1406)	1.105 (0.1490)	1.161 (0.1763)
IP, 24 h Post-dose, n=21, 22, 21, 13, 8	1.131 (0.1455)	1.118 (0.1391)	1.143 (0.1486)	1.121 (0.1735)	1.158 (0.1179)
Urea, Pre-dose, n=21, 22, 21, 13, 8	4.905 (1.2041)	4.629 (0.9289)	5.002 (1.1933)	4.904 (0.9358)	4.820 (1.2474)
Urea, 24 h Post-dose, n=21, 22, 21, 13, 8	4.700 (0.8093)	4.721 (0.9688)	4.710 (0.9958)	4.579 (0.8701)	4.764 (1.6021)

24. Primary Outcome Measure:

Measure Title	Forced Expiratory Volume in 1 Second (FEV1) and Forced Vital Capacity (FVC) at the Indicated Time Points on Day 1 of Each Treatment Period
Measure Description	FEV1 and FVC are measures of lung function. FEV1 is defined as the maximal amount of air that can be forcefully exhaled in one second. FVC is defined as the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible. FEV1 and FVC measurements were taken at pre-dose and 1 hour (h), 2 h, 6 h, 9 h, 12 h and 24 h post-dose of each treatment period.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

	Description
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Forced Expiratory Volume in 1 Second (FEV1) and Forced Vital Capacity (FVC) at the Indicated Time Points on Day 1 of Each Treatment Period [units: Liters] Mean (Standard Deviation)					
FEV1, Pre-dose, n= 21, 22, 21, 13, 8	1.637 (0.3991)	1.559 (0.2867)	1.589 (0.2871)	1.732 (0.2080)	1.400 (0.2545)
FEV1, 1h, n=21, 20, 21, 13, 8	1.670 (0.4130)	1.874 (0.3414)	1.905 (0.3574)	1.966 (0.3781)	1.663 (0.3250)
FEV1, 2h, n= 21, 20, 21, 13, 8	1.689 (0.4172)	1.969 (0.3760)	2.015 (0.3512)	2.123 (0.3757)	1.696 (0.3311)
FEV1, 6h, n=21, 22, 21, 13, 8	1.700 (0.4055)	2.000 (0.4251)	2.073 (0.3343)	2.198 (0.3329)	1.841 (0.4372)
FEV1, 9h, n=21, 19, 21, 13, 7	1.754 (0.3664)	1.984 (0.3554)	2.010 (0.3113)	2.135 (0.2850)	1.767 (0.4555)
FEV1, 12h, n=21, 22, 21, 13,8	1.688 (0.3797)	1.933 (0.3756)	1.988 (0.3463)	2.103 (0.3633)	1.619 (0.4182)
FEV1, 24h, =21, 22, 21, 13, 8	1.612 (0.3189)	1.830 (0.4033)	1.817 (0.3569)	1.978 (0.3416)	1.454 (0.3135)
FVC, Pre-dose, n=21, 22, 21, 13, 8	3.438 (0.8138)	3.247 (0.7574)	3.337 (0.7139)	3.640 (0.7869)	3.080 (0.6682)
FVC, 1h, n=21, 20, 21, 13, 8	3.490 (0.8721)	3.751 (0.8688)	3.845 (0.7974)	4.006 (0.9430)	3.631 (0.7223)
FVC, 2h, n=21, 20, 21, 13, 8	3.545 (0.8796)	3.877 (0.9571)	3.976 (0.8479)	4.205 (0.9935)	3.674 (0.7766)
FVC, 6h, n=21, 22, 21, 13, 8	3.572 (0.8555)	3.940 (0.9583)	4.064 (0.8822)	4.257 (1.0390)	3.780 (0.8023)
FVC, 9h, n=21, 19, 21, 13, 7	3.662 (0.8436)	4.015 (0.8461)	3.969 (0.8783)	4.184 (0.9694)	3.544 (0.7176)
FVC, 12h, n=21, 22, 21, 13, 8	3.595 (0.8178)	3.841 (0.9190)	3.923 (0.8966)	4.130 (1.0544)	3.563 (0.7816)
FVC, 24h, n=21, 22, 21, 13, 8	3.389 (0.7272)	3.712 (0.9878)	3.705 (0.8597)	3.993 (0.9759)	3.280 (0.6741)

25. Secondary Outcome Measure:

Measure Title	Area Under Concentration-time Curve From Time 0 to 2 Hours [AUC(0-2)] and Area Under Concentration-time Curve From Time 0 to Time of Last Quantifiable Concentration [AUC(0-t)] of UMEC

Measure Description	Blood samples were collected to determine the plasma concentrations of UMEC from pre-dose up to 24 hour post-dose of each treatment period to derive the AUC(0-2) and AUC(0-t). Blood samples for PK analysis of UMEC were obtained on Day 1at pre-dose and 5 minutes (min), 15 min, 30 min, 1 hour (h), 2 h, 4 h, 6 h, 8 h, 12 h, 16 h, and 24 h post UMEC dose administration.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

Pharmacokinetic (PK) Population:all participants in the All Subjects Population for whom a PK sample was obtained and analyzed.

Reporting Groups

	Description
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg
Number of Participants Analyzed	22	21	13
Area Under Concentration-time Curve From Time 0 to 2 Hours [AUC(0-2)] and Area Under Concentration-time Curve From Time 0 to Time of Last Quantifiable Concentration [AUC(0-t)] of UMEC [units: hr * nanograms per milliliter (ng/mL)] Geometric Mean (Geometric Coefficient of Variation)			
AUC(0-2)	0.10264 (58.9%)	0.27099 (58.5%)	0.71522 (21.8%)
AUC(0-t)	0.10271 (70.0%)	0.35491 (65.2%)	0.96100 (27.7%)

26. Secondary Outcome Measure:

Measure Title	Maximum Observed Plasma Concentration (Cmax) of UMEC

Measure Description	Blood samples were collected to determine the plasma concentrations of UMEC from pre-dose up to 24 hour post-dose of each treatment period to derive the Cmax. Blood samples for PK analysis of UMEC were obtained on Day 1at pre-dose and 5 minutes (min), 15 min, 30 min, 1 hour (h), 2 h, 4 h, 6 h, 8 h, 12 h, 16 h, and 24 h post UMEC dose administration.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description
PK Population

Reporting Groups

	Description
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg
Number of Participants Analyzed	22	21	13
Maximum Observed Plasma Concentration (Cmax) of UMEC [units: ng/mL] Geometric Mean (Geometric Coefficient of Variation)	0.12615 (43.4%)	0.30389 (40.7%)	0.83228 (22.9%)

27. Secondary Outcome Measure:

Measure Title	Time of Maximum Observed Plasma Concentration (Tmax), Last Time Point Where the Concentration is Above the Limit of Quantification (Tlast), and Plasma Half-life (t1/2) of UMEC
Measure Description	Blood samples were collected to determine the plasma concentrations of UMEC from pre-dose up to 24 hour post-dose of each treatment period to derive tmax, tlast and t1/2. Blood samples for PK analysis of UMEC were obtained on Day 1at pre-dose and 5 minutes (min), 15 min, 30 min, 1 hour (h), 2 h, 4 h, 6 h, 8 h, 12 h, 16 h, and 24 h post UMEC dose administration.
Time Frame	Day 1 of each treatment period (up to Study Day 46)

Safety Issue?	No

Analysis Population Description

PK Population. Only those participants with non-missing observations (including non-calculable values) were analyzed (represented by n=X, X, X in the category titles). Different participants may have been analyzed for different parameters/at different time points, so the overall number of participants analyzed reflects everyone in the PK Population

Reporting Groups

	Description
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg
Number of Participants Analyzed	22	21	13
Time of Maximum Observed Plasma Concentration (Tmax), Last Time Point Where the Concentration is Above the Limit of Quantification (Tlast), and Plasma Half-life (t1/2) of UMEC [units: Hours] Median (Full Range)			
tmax, n=22, 21, 13	0.090 (0.08 to 0.50)	0.100 (0.07 to 0.27)	0.250 (0.08 to 0.28)
tlast, n=22, 21, 13	1.975 (0.47 to 4.07)	4.030 (1.00 to 24.00)	6.000 (4.00 to 15.95)
t1/2, n=22, 21, 13	NA (NA to NA) [1]	1.24490 (0.7079 to 3.6743)	1.19780 (0.7889 to 20.2309)

[1] Due to the large amount of non-quantifiable (NQ) data in the distribution and elimination phase at 250mcg dose level, all t½ values could not be calculated and median and the confidence interval (CI) could not be estimated.

28. Secondary Outcome Measure:

Measure Title	Amount of Drug Excreted Unchanged in Urine From Time Zero to: 2h [Ae(0-2)] , 8h [Ae(0-8)], 12h [Ae(0-12)], 24h [Ae(0-24)], and 48h [Ae(0-48)]; and Area Under the Excretion Rate Curve From Time Zero to: 18h [AUER(0-18)] and 36h [AUER(0-36)] for UMEC

Measure Description	Urine samples were collected to determine the urine concentrations of UMEC from 0 min up to 48 hours post-dose of each treatment period to derive Ae(0-2), Ae(0-8), Ae(0-12), Ae(0-24), Ae(0-48), AUER(0-18) and AUER(0-36). Urine samples for PK analysis of UMEC were obtained on Day 1; a single sample was collected at each of the following timepoints: 0–2 h, 2–8 h, 8–12 h, 12–24 h and 24–48 h post UMEC dose administration.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description
PK Population

Reporting Groups

	Description
UMEC 250 µg	
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg
Number of Participants Analyzed	22	21	13
Amount of Drug Excreted Unchanged in Urine From Time Zero to: 2h [Ae(0-2)] , 8h [Ae(0-8)], 12h [Ae(0-12)], 24h [Ae(0-24)], and 48h [Ae(0-48)]; and Area Under the Excretion Rate Curve From Time Zero to: 18h [AUER(0-18)] and 36h [AUER(0-36)] for UMEC [units: ng] Geometric Mean (Geometric Coefficient of Variation)			
Ae(0-2)	734.525 (56.0%)	1793.951 (40.5%)	4456.582 (43.5%)
Ae(0-8)	1676.101 (54.7%)	4146.206 (50.6%)	9935.792 (33.4%)
Ae(0-12)	1987.910 (50.0%)	4712.376 (50.1%)	10983.771 (34.5%)
Ae(0-24)	2352.662 (47.5%)	5486.724 (48.3%)	12401.722 (33.7%)
Ae(0-48)	2729.434 (45.0%)	6361.233 (47.0%)	13671.981 (34.7%)
AUER(0-18)	2119.916 (48.4%)	4830.401 (47.9%)	10919.838 (34.6%)
AUER(0-36)	2487.288 (48.8%)	5752.880 (49.3%)	12363.246 (35.0%)

29. Secondary Outcome Measure:

Measure Title	Renal Clearance (CLr) of UMEC Following Dose Administration on Day 1
Measure Description	The CLr is defined as the apparent total clearance of the drug from plasma after oral administration. Blood samples for PK analysis of UMEC were obtained on Day 1at pre-dose and 5 minutes (min), 15 min, 30 min, 1 hour (h), 2 h, 4 h, 6 h, 8 h, 12 h, 16 h, and 24 h post UMEC dose administration.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description
PK Population

Reporting Groups

	Description
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg
Number of Participants Analyzed	22	21	13
Renal Clearance (CLr) of UMEC Following Dose Administration on Day 1 [units: Liters per hour (L/hr)] Geometric Mean (Geometric Coefficient of Variation)	5.317 (56.2%)	6.395 (36.9%)	6.831 (56.8%)

30. Secondary Outcome Measure:

Measure Title	Half-life for Renal Excretion of UMEC on Day 1

Measure Description	The terminal half-life (t1/2) of UMEC is defined as the time required for the urine concentration of UMEC to reach half of its original concentration. Urine samples for PK analysis of UMEC were obtained on Day 1; a single sample was collected at each of the following timepoints: 0–2 h, 2–8 h, 8–12 h, 12–24 h and 24–48 h post UMEC dose administration.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description
PK Population

Reporting Groups

	Description
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg
Number of Participants Analyzed	22	21	13
Half-life for Renal Excretion of UMEC on Day 1 [units: Hours] Geometric Mean (Geometric Coefficient of Variation)	10.679 (37.2%)	12.023 (44.9%)	10.821 (32.8%)

31. Secondary Outcome Measure:

Measure Title	Fraction of Dose Excreted Unchanged in Urine From Time Zero to: 24 Hours [Fe(0-24)] and 48 Hours [Fe(0-48)] for UMEC
Measure Description	Urine samples were collected to determine the urine concentrations of UMEC from 0 min up to 48 hours post-dose of each treatment period to derive Fe(0-24) and Fe(0-48). Urine samples for PK analysis of UMEC were obtained on Day 1; a single sample was collected at each of the following timepoints: 0–2 h, 2–8 h, 8–12 h, 12–24 h and 24–48 h post UMEC dose administration.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description
PK Population

Reporting Groups

	Description
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg
Number of Participants Analyzed	22	21	13
Fraction of Dose Excreted Unchanged in Urine From Time Zero to: 24 Hours [Fe(0-24)] and 48 Hours [Fe(0-48)] for UMEC [units: Percentage of total dose administered] Median (Full Range)			
Fe(0-24)	0.993 (0.32 to 2.56)	1.253 (0.46 to 2.73)	1.360 (0.68 to 1.94)
Fe(0-48)	1.142 (0.42 to 2.88)	1.413 (0.48 to 2.95)	1.512 (0.77 to 2.10)

32. Secondary Outcome Measure:

Measure Title	Mean Serial FEV1over 24 Hours After Dosing on Day 1 of Each Treatment Period
Measure Description	Serial spirometry assessments were conducted on Day 1 of each treatment period over the course of 24 hours and were taken at 1 hour (h), 2 h, 6 h, 9 h, 12 h and 24 h post-dose. The maximum of the 3 FEV1 measurements for each participant, treatment period and timepoint were used in the calculation of the mean for each treatment group at each timepoint.
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Mean Serial FEV1over 24 Hours After Dosing on Day 1 of Each Treatment Period [units: Liters] Least Squares Mean (Standard Error)					
FEV1, 1 h, n= 21, 20, 21, 13, 8	1.638 (0.0410)	1.861 (0.0437)	1.915 (0.0408)	1.834 (0.0542)	1.880 (0.0644)
FEV1, 2h, n= 21, 20, 21, 13, 8	1.654 (0.0433)	1.951 (0.0456)	2.027 (0.0431)	1.992 (0.0570)	1.910 (0.0684)
FEV1, 6h, n=21, 22, 21, 13, 8	1.669 (0.0497)	1.991 (0.0510)	2.083 (0.0492)	2.070 (0.0648)	2.050 (0.0793)
FEV1, 9h, n=21, 19, 21, 13, 7	1.721 (0.0418)	1.938 (0.0446)	2.021 (0.0416)	2.024 (0.0553)	1.927 (0.0673)
FEV1, 12h, n=21, 22, 21, 13, 7	1.662 (0.0501)	1.917 (0.0514)	1.996 (0.0497)	1.988 (0.0654)	1.812 (0.0801)
FEV1, 24h, n=21, 22, 21, 13, 8	1.583 (0.0411)	1.818 (0.0431)	1.827 (0.0410)	1.856 (0.0544)	1.655 (0.0646)

33. Secondary Outcome Measure:

Measure Title	Mean Serial Specific Airway Resistance (sGaw) Over 24 Hours After Dosing on Day 1 of Each Treatment Period
Measure Description	sGaw is the specific airways resistance (mid) which was assessed by whole body plethysmography. Values used were the mean of the 3 readings recorded at each timepoint. sGaw measurements were taken at 2 hour (h), 6 h, 12 h and 24 h post-dose of each treatment period. 1/kPa.s=1(the inverses)/kPa (kilopascal).s (second)
Time Frame	Day 1 of each treatment period (up to Study Day 46)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Measured Values

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
Number of Participants Analyzed	21	22	21	13	8
Mean Serial Specific Airway Resistance (sGaw) Over 24 Hours After Dosing on Day 1 of Each Treatment Period [units: 1/kPa*s] Geometric Mean (Standard Error)					
sGaw, 2h, n= 21, 20, 21, 13, 8	0.400 (0.0598)	0.652 (0.0631)	0.699 (0.0602)	0.714 (0.0753)	0.648 (0.0893)
sGaw, 6h, n=21, 21, 21, 13, 8	0.426 (0.0574)	0.734 (0.0603)	0.806 (0.0578)	0.778 (0.0720)	0.711 (0.0848)

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
sGaw, 12h, n=21, 21, 21, 13, 8	0.403 (0.0661)	0.637 (0.0692)	0.735 (0.0665)	0.730 (0.0836)	0.550 (0.1008)
sGaw, 24h, n=21, 21, 21, 13, 8	0.379 (0.0627)	0.514 (0.0662)	0.501 (0.0630)	0.514 (0.0790)	0.440 (0.0945)

Reported Adverse Events

Time Frame	Serious adverse events (SAEs) and non-serious AEs were collected from Day 1 of Treatment Period 1 until Follow-up visit (up to 10 weeks)
Additional Description	AEs and SAEs were collected in the members of All Subjects Population comprised of all participants who received at least one dose of study medication.

Reporting Groups

	Description
Placebo	Participants received a single inhaled dose of matching placebo via a dry powder inhaler (DPI) in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 250 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 250 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 500 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 500 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
UMEC 1000 µg	Participants received a single inhaled dose of a dry powder formulation of UMEC 1000 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.
Tiotropium 18 µg	Participants received a single inhaled dose of a dry powder formulation of tiotropium 18 µg via a DPI in one of the 4 treatment periods, separated by a washout period of at least 14 days.

Serious Adverse Events

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	0/21 (0%)	0/22 (0%)	0/21 (0%)	0/13 (0%)	0/8 (0%)

Other Adverse Events

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

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	6/21 (28.57%)	9/22 (40.91%)	8/21 (38.1%)	4/13 (30.77%)	3/8 (37.5%)
Cardiac disorders					
Atrial fibrillation [A] †	0/21 (0%)	0/22 (0%)	1/21 (4.76%)	1/13 (7.69%)	0/8 (0%)
Supraventricular tachycardia [A] †	0/21 (0%)	0/22 (0%)	0/21 (0%)	0/13 (0%)	1/8 (12.5%)
Ventricular tachycardia [A] †	0/21 (0%)	0/22 (0%)	1/21 (4.76%)	0/13 (0%)	0/8 (0%)
Gastrointestinal disorders					
Dyspepsia [A] †	0/21 (0%)	0/22 (0%)	1/21 (4.76%)	0/13 (0%)	0/8 (0%)
Gingivitis [A] †	0/21 (0%)	1/22 (4.55%)	0/21 (0%)	0/13 (0%)	0/8 (0%)
Tooth loss [A] †	0/21 (0%)	0/22 (0%)	1/21 (4.76%)	0/13 (0%)	0/8 (0%)
Vomiting [A] †	0/21 (0%)	1/22 (4.55%)	0/21 (0%)	0/13 (0%)	0/8 (0%)
General disorders					
Asthenia [A] †	1/21 (4.76%)	0/22 (0%)	0/21 (0%)	0/13 (0%)	0/8 (0%)
Infections and infestations					
Infected insect bite [A] †	0/21 (0%)	1/22 (4.55%)	0/21 (0%)	0/13 (0%)	0/8 (0%)
Nasopharyngitis [A] †	1/21 (4.76%)	1/22 (4.55%)	0/21 (0%)	0/13 (0%)	0/8 (0%)
Respiratory tract infection [A] †	0/21 (0%)	1/22 (4.55%)	1/21 (4.76%)	0/13 (0%)	0/8 (0%)
Sinusitis [A] †	1/21 (4.76%)	0/22 (0%)	0/21 (0%)	0/13 (0%)	0/8 (0%)
Urinary tract infection [A] †	1/21 (4.76%)	0/22 (0%)	0/21 (0%)	0/13 (0%)	1/8 (12.5%)
Musculoskeletal and connective tissue disorders					
Back pain [A] †	0/21 (0%)	0/22 (0%)	1/21 (4.76%)	1/13 (7.69%)	0/8 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Gammopathy [A] †	1/21 (4.76%)	0/22 (0%)	0/21 (0%)	0/13 (0%)	0/8 (0%)

	Placebo	UMEC 250 µg	UMEC 500 µg	UMEC 1000 µg	Tiotropium 18 µg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Nervous system disorders					
Dizziness [A] †	1/21 (4.76%)	0/22 (0%)	2/21 (9.52%)	1/13 (7.69%)	0/8 (0%)
Headache [A] †	4/21 (19.05%)	4/22 (18.18%)	4/21 (19.05%)	1/13 (7.69%)	0/8 (0%)
Tension headache [A] †	0/21 (0%)	1/22 (4.55%)	0/21 (0%)	0/13 (0%)	0/8 (0%)
Respiratory, thoracic and mediastinal disorders					
Chronic obstructive pulmonary disease [A] †	0/21 (0%)	0/22 (0%)	0/21 (0%)	0/13 (0%)	1/8 (12.5%)
Pharyngolaryngeal pain [A] †	0/21 (0%)	0/22 (0%)	0/21 (0%)	2/13 (15.38%)	0/8 (0%)
Respiratory distress [A] †	1/21 (4.76%)	1/22 (4.55%)	0/21 (0%)	0/13 (0%)	0/8 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA

Limitations and Caveats

[Not specified]

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.

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