



Clinical trial results:

A Phase IIb, 24 week, randomized, double-blind, 3 arm parallel group study, comparing the efficacy, safety and tolerability of two doses of umecclidinium bromide administered once-daily via a dry powder inhaler, versus placebo, in participants with asthma.

Summary

EudraCT number	2016-002843-40
Trial protocol	PL
Global end of trial date	30 May 2018

Results information

Result version number	v1 (current)
This version publication date	13 June 2019
First version publication date	13 June 2019

Trial information

Trial identification

Sponsor protocol code	205832
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 September 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of Umeclidinium bromide (UMEC) 62.5 mcg and UMEC 31.25 mcg on lung function (trough Forced expiratory volume in 1 second [FEV1]) versus placebo after 24 weeks of treatment.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Poland: 107
Country: Number of subjects enrolled	Romania: 58
Country: Number of subjects enrolled	Russian Federation: 170
Country: Number of subjects enrolled	United States: 69
Worldwide total number of subjects	421
EEA total number of subjects	165

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	365

From 65 to 84 years	56
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at different centers in Russia, United States, Canada, Poland and Romania to compare the efficacy, safety and tolerability of two doses of umeclidinium bromide (UMEC) administered once-daily (OD) via a dry powder inhaler, versus placebo.

Pre-assignment

Screening details:

Total 421 participants were included in the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo QD

Arm description:

Participants received placebo once daily (QD) via the ELLIPTA dry powder inhaler (DPI) for 24 weeks. Participants also received Fluticasone Furoate (FF) 100 micrograms (mcg) once daily as background therapy, in the morning from a separate ELLIPTA DPI for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Placebo is a white powder administered using ELLIPTA DPI which hold two individual blister strips, both of which contains lactose monohydrate blended with magnesium stearate.

Investigational medicinal product name	Fluticasone furoate (FF)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

FF is a white powder administered using ELLIPTA DPI which hold two individual blister strips, one of which contains GW685698 blended with lactose monohydrate and another one contains lactose monohydrate with magnesium stearate. This was given 100 mcg once daily as background therapy.

Arm title	UMEC 31.25 mcg QD
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Arm description:

Participants received UMEC 31.25 mcg once daily via the ELLIPTA DPI for 24 weeks. Participants also received FF 100 mcg once daily as background therapy, in the morning from a separate ELLIPTA DPI for 24 weeks.

Arm type	Experimental
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Investigational medicinal product name	FF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

FF is a white powder administered using ELLIPTA DPI which hold two individual blister strips, one of which contains GW685698 blended with lactose monohydrate and another one contains lactose monohydrate with magnesium stearate. This was given 100 mcg once daily as background therapy.

Investigational medicinal product name	UMEC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

UMEC is a white powder administered using ELLIPTA DPI which hold two individual blister strips, one of which contains GSK573719 blended with lactose blended with magnesium stearate and another one contains lactose monohydrate blended with magnesium stearate.

Arm title	UMEC 62.5 mcg QD
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Arm description:

Participants received UMEC 62.5 mcg once daily via the ELLIPTA DPI for 24 weeks. Participants also received FF 100 mcg once daily as background therapy, in the morning from a separate ELLIPTA DPI for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	UMEC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

UMEC is a white powder administered using ELLIPTA DPI which hold two individual blister strips, one of which contains GSK573719 blended with lactose blended with magnesium stearate and another one contains lactose monohydrate blended with magnesium stearate.

Investigational medicinal product name	FF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

FF is a white powder administered using ELLIPTA DPI which hold two individual blister strips, one of which contains GW685698 blended with lactose monohydrate and another one contains lactose monohydrate with magnesium stearate. This was given 100 mcg once daily as background therapy.

Number of subjects in period 1	Placebo QD	UMEC 31.25 mcg QD	UMEC 62.5 mcg QD
Started	143	139	139
Completed	137	130	131
Not completed	6	9	8
Consent withdrawn by subject	1	5	4
Adverse event, non-fatal	2	-	-
Investigator Site Closed	1	2	-

Lost to follow-up	2	1	-
Protocol-Specified Withdrawal Criterion	-	-	1
Study closed/ Terminated	-	-	1
Lack of efficacy	-	1	-
Protocol deviation	-	-	2

Baseline characteristics

Reporting groups

Reporting group title	Placebo QD
Reporting group description:	
Participants received placebo once daily (QD) via the ELLIPTA dry powder inhaler (DPI) for 24 weeks. Participants also received Fluticasone Furoate (FF) 100 micrograms (mcg) once daily as background therapy, in the morning from a separate ELLIPTA DPI for 24 weeks.	
Reporting group title	UMEC 31.25 mcg QD
Reporting group description:	
Participants received UMEC 31.25 mcg once daily via the ELLIPTA DPI for 24 weeks. Participants also received FF 100 mcg once daily as background therapy, in the morning from a separate ELLIPTA DPI for 24 weeks.	
Reporting group title	UMEC 62.5 mcg QD
Reporting group description:	
Participants received UMEC 62.5 mcg once daily via the ELLIPTA DPI for 24 weeks. Participants also received FF 100 mcg once daily as background therapy, in the morning from a separate ELLIPTA DPI for 24 weeks.	

Reporting group values	Placebo QD	UMEC 31.25 mcg QD	UMEC 62.5 mcg QD
Number of subjects	143	139	139
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	126	118	121
From 65-84 years	17	21	18
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	49.3	48.7	48.5
standard deviation	± 13.93	± 15.83	± 14.21
Sex: Female, Male Units: Subjects			
Female	106	94	98
Male	37	45	41
Race/Ethnicity, Customized Units: Subjects			
Black or African American	10	8	8
Asian, Central/South Asian Heritage	1	1	1
Asian, East Asian Heritage	0	1	0
Asian, South East Asian Heritage	0	1	1
Native Hawaiian or other Pacific Islander	1	0	0
White: Arabic/North African Heritage	0	1	0

White: White/Caucasian/European Heritage	131	126	129
Black or African American & White	0	1	0

Reporting group values	Total		
Number of subjects	421		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	365		
From 65-84 years	56		
85 years and over	0		
Age Continuous Units: Years arithmetic mean standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	298		
Male	123		
Race/Ethnicity, Customized Units: Subjects			
Black or African American	26		
Asian, Central/South Asian Heritage	3		
Asian, East Asian Heritage	1		
Asian, South East Asian Heritage	2		
Native Hawaiian or other Pacific Islander	1		
White: Arabic/North African Heritage	1		
White: White/Caucasian/European Heritage	386		
Black or African American & White	1		

End points

End points reporting groups

Reporting group title	Placebo QD
Reporting group description: Participants received placebo once daily (QD) via the ELLIPTA dry powder inhaler (DPI) for 24 weeks. Participants also received Fluticasone Furoate (FF) 100 micrograms (mcg) once daily as background therapy, in the morning from a separate ELLIPTA DPI for 24 weeks.	
Reporting group title	UMEC 31.25 mcg QD
Reporting group description: Participants received UMEC 31.25 mcg once daily via the ELLIPTA DPI for 24 weeks. Participants also received FF 100 mcg once daily as background therapy, in the morning from a separate ELLIPTA DPI for 24 weeks.	
Reporting group title	UMEC 62.5 mcg QD
Reporting group description: Participants received UMEC 62.5 mcg once daily via the ELLIPTA DPI for 24 weeks. Participants also received FF 100 mcg once daily as background therapy, in the morning from a separate ELLIPTA DPI for 24 weeks.	

Primary: Mean change from Baseline in clinic trough Forced expiratory volume in 1 second (FEV1) at Week 24

End point title	Mean change from Baseline in clinic trough Forced expiratory volume in 1 second (FEV1) at Week 24
End point description: FEV1 is measure of lung function, defined as maximal amount of air, can be forcefully exhaled in 1 second. Highest of 3 technically acceptable measurements were recorded at each Visit. Baseline value of clinic FEV1 was last acceptable/borderline acceptable (pre-dose) FEV1 value obtained prior to randomized treatment start date. Change from Baseline was calculated as FEV1 value at Week 24 minus FEV1 value at Baseline. Treatment policy estimand was assessed, including all on-/post-treatment data. Intent-to-Treat Population was comprised all randomized participants, excluding who were randomized in error, did not receive the study drug. Different participants may have been analyzed at different timepoints; overall number of participants analyzed reflects everyone in ITT Population without missing covariate information, with Baseline, at least 1 post-Baseline measurement. Participants with available data at Baseline, at least 1 timepoint post-Baseline were analyzed. All on-/post-treatment data was included.	
End point type	Primary
End point timeframe: Baseline (Day 1 pre-dose) and Week 24	

End point values	Placebo QD	UMEC 31.25 mcg QD	UMEC 62.5 mcg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	141 ^[1]	136 ^[2]	139 ^[3]	
Units: Liters				
least squares mean (standard error)	0.1289 (± 0.0298)	0.3046 (± 0.0304)	0.3130 (± 0.0302)	

Notes:

[1] - ITT Population.

[2] - ITT Population.

[3] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: UMEC 31.25 mcg versus placebo	
Comparison groups	Placebo QD v UMEC 31.25 mcg QD
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed-model repeated measures (MMRM)
Parameter estimate	Mean difference (net)
Point estimate	0.1758
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.092
upper limit	0.2595
Variability estimate	Standard error of the mean
Dispersion value	0.0426

Statistical analysis title	Statistical analysis 2
Statistical analysis description: UMEC 62.5 mcg versus placebo	
Comparison groups	Placebo QD v UMEC 62.5 mcg QD
Number of subjects included in analysis	280
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.1841
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1008
upper limit	0.2675
Variability estimate	Standard error of the mean
Dispersion value	0.0424

Secondary: Mean change from Baseline in clinic FEV1 at 3 hours post dose at Week 24

End point title	Mean change from Baseline in clinic FEV1 at 3 hours post dose at Week 24
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End point description:

FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. The highest of 3 technically acceptable measurements were recorded at each Visit. The Baseline value of clinic FEV1 was the last acceptable/borderline acceptable (pre-dose) FEV1 value obtained prior to randomization (either from Visit 2 pre-dose or from Visit 1 pre-bronchodilator). Change from Baseline was calculated as FEV1 value at Week 24 (recorded at 3 hours post dose) minus

FEV1 value at Baseline. The analysis only included data collected on-treatment. LS mean change and SE data is presented. Only those participants with available on-treatment data at the specified time points were analyzed.

End point type	Secondary
End point timeframe:	
Baseline (Day 1 pre-dose) and Week 24	

End point values	Placebo QD	UMEC 31.25 mcg QD	UMEC 62.5 mcg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133 ^[4]	127 ^[5]	129 ^[6]	
Units: Liters				
least squares mean (standard error)	0.1768 (± 0.0318)	0.3663 (± 0.0325)	0.3744 (± 0.0322)	

Notes:

[4] - ITT Population.

[5] - ITT Population.

[6] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
UMEC 31.25 mcg vs Placebo	
Comparison groups	Placebo QD v UMEC 31.25 mcg QD
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.1895
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.2789
Variability estimate	Standard error of the mean
Dispersion value	0.0455

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
UMEC 62.5 mcg vs Placebo	
Comparison groups	Placebo QD v UMEC 62.5 mcg QD

Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[7]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.1976
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1086
upper limit	0.2866
Variability estimate	Standard error of the mean
Dispersion value	0.0453

Notes:

[7] - Analysis of covariance (ANCOVA)

Secondary: Number of participants with on-treatment adverse events (AE), serious adverse events (SAE) and non-serious adverse events (non-SAE)

End point title	Number of participants with on-treatment adverse events (AE), serious adverse events (SAE) and non-serious adverse events (non-SAE)
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End point description:

An AE is 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. Any untoward event resulting in death, life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, congenital anomaly/birth defect, any other situation according to medical or scientific judgment or all events of possible drug-induced liver injury with hyperbilirubinemia were categorized as SAE. Number of participants with on-treatment AEs and SAEs and common ($\geq 3\%$) non-SAEs have been reported.

End point type	Secondary
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End point timeframe:

Up to Week 24

End point values	Placebo QD	UMEC 31.25 mcg QD	UMEC 62.5 mcg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	143 ^[8]	139 ^[9]	139 ^[10]	
Units: Participants				
Any AE	65	73	57	
Any SAE	5	4	3	
Any non-SAE	39	47	33	

Notes:

[8] - ITT population.

[9] - ITT population.

[10] - ITT population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with on-treatment abnormal Electrocardiograms (ECG) Findings

End point title	Number of participants with on-treatment abnormal Electrocardiograms (ECG) Findings
End point description: A single 12-lead ECG and rhythm strip was recorded after measurement of vital signs and spirometry at given time points. All ECG measurements were measured with participants in supine position after ≥ 5 minutes rest. All ECGs were electronically transmitted to an independent and treatment-blinded cardiologist for the measurement. ECG was obtained 15 minutes to 45 minutes after the administration of study treatment. Data for number of participants with abnormal ECG Findings have been reported. Only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles).	
End point type	Secondary
End point timeframe: Week 4 and Week 24	

End point values	Placebo QD	UMEC 31.25 mcg QD	UMEC 62.5 mcg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	143 ^[11]	139 ^[12]	139 ^[13]	
Units: Participants				
Week 4, n=139, 135, 138	23	26	35	
Week 24, n=133, 129, 129	26	23	39	

Notes:

[11] - ITT population.

[12] - ITT population.

[13] - ITT population.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in on-treatment systolic blood pressure (SBP) and diastolic blood pressure (DBP)

End point title	Mean Change from Baseline in on-treatment systolic blood pressure (SBP) and diastolic blood pressure (DBP)
End point description: Blood pressure was measured at every clinic visit, starting at Visit 1, and prior to conducting spirometry. Blood pressure was measured with participant in sitting position after approximately 5 minutes rest. Baseline value was defined as the latest vital signs assessment prior to randomized treatment start, including unscheduled visits. Change from Baseline was calculated by subtracting Baseline value from the value at specified time point. LS mean and SE data is presented. Different participants may have data available at different time points; thus, the overall number of participants analyzed reflects everyone in the ITT Population without missing covariate information and with a Baseline and at least one post-Baseline measurement. Participants with available data at Baseline and at least one time point post-baseline were analyzed. Participants with data available at the specified time points are represented by n=X in the category titles.	
End point type	Secondary
End point timeframe: Baseline (Day 1 pre-dose), Weeks 4, 12 and 24	

End point values	Placebo QD	UMEC 31.25 mcg QD	UMEC 62.5 mcg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	139 ^[14]	137 ^[15]	139 ^[16]	
Units: Millimeters of mercury				
least squares mean (standard error)				
SBP, Week 4, n=139, 137, 139	-0.7 (± 0.70)	1.1 (± 0.71)	0.3 (± 0.70)	
SBP, Week 12, n=139, 133, 135	0.3 (± 0.78)	-0.2 (± 0.79)	0.6 (± 0.79)	
SBP, Week 24, n=135, 131, 130	-0.6 (± 0.77)	1.1 (± 0.78)	-0.1 (± 0.79)	
DBP, Week 4, n=139, 137, 139	0.4 (± 0.55)	1.2 (± 0.56)	0.6 (± 0.55)	
DBP, Week 12, n=139, 133, 135	0.7 (± 0.57)	0.2 (± 0.59)	1.8 (± 0.58)	
DBP, Week 24, n=135, 131, 130	-0.1 (± 0.57)	1.6 (± 0.58)	1.4 (± 0.58)	

Notes:

[14] - ITT population.

[15] - ITT population.

[16] - ITT population.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: UMEC 31.25 mcg vs Placebo, SBP, Week 4	
Comparison groups	Placebo QD v UMEC 31.25 mcg QD
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.083
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	3.7
Variability estimate	Standard error of the mean
Dispersion value	1

Statistical analysis title	Statistical analysis 2
Statistical analysis description: UMEC 31.25 mcg vs Placebo, SBP, Week 12	
Comparison groups	Placebo QD v UMEC 31.25 mcg QD
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.636
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	1.7
Variability estimate	Standard error of the mean
Dispersion value	1.11

Statistical analysis title	Statistical analysis 3
Statistical analysis description: UMEC 31.25 mcg vs Placebo, SBP, Week 24	
Comparison groups	Placebo QD v UMEC 31.25 mcg QD
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.115
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	3.9
Variability estimate	Standard error of the mean
Dispersion value	1.1

Statistical analysis title	Statistical analysis 4
Statistical analysis description: UMEC 62.5 mcg vs Placebo, SBP, Week 4	
Comparison groups	Placebo QD v UMEC 62.5 mcg QD
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.336
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	2.9
Variability estimate	Standard error of the mean
Dispersion value	0.99

Statistical analysis title	Statistical analysis 5
Statistical analysis description: UMEC 62.5 mcg vs Placebo, SBP, Week 12	
Comparison groups	Placebo QD v UMEC 62.5 mcg QD
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.787
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	2.5
Variability estimate	Standard error of the mean
Dispersion value	1.11

Statistical analysis title	Statistical analysis 6
Statistical analysis description: UMEC 62.5 mcg vs Placebo, SBP, Week 24	
Comparison groups	Placebo QD v UMEC 62.5 mcg QD
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.625
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	2.7
Variability estimate	Standard error of the mean
Dispersion value	1.1

Statistical analysis title	Statistical analysis 7
Statistical analysis description: UMEC 31.25 mcg vs Placebo, DBP, Week 4	
Comparison groups	Placebo QD v UMEC 31.25 mcg QD

Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.309
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	2.3
Variability estimate	Standard error of the mean
Dispersion value	0.79

Statistical analysis title	Statistical analysis 8
Statistical analysis description: UMEC 31.25 mcg vs Placebo, DBP, Week 12	
Comparison groups	Placebo QD v UMEC 31.25 mcg QD
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.521
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	0.82

Statistical analysis title	Statistical analysis 9
Statistical analysis description: UMEC 31.25 mcg vs Placebo, DBP, Week 24	
Comparison groups	Placebo QD v UMEC 31.25 mcg QD
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	3.2
Variability estimate	Standard error of the mean
Dispersion value	0.81

Statistical analysis title	Statistical analysis 10
Statistical analysis description: UMEC 62.5 mcg versus placebo, DBP, Week 4	
Comparison groups	Placebo QD v UMEC 62.5 mcg QD
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.779
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	1.8
Variability estimate	Standard error of the mean
Dispersion value	0.78

Statistical analysis title	Statistical analysis 11
Statistical analysis description: UMEC 62.5 mcg versus placebo, DBP, Week 12	
Comparison groups	Placebo QD v UMEC 62.5 mcg QD
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.204
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	2.6
Variability estimate	Standard error of the mean
Dispersion value	0.82

Statistical analysis title	Statistical analysis 12
Statistical analysis description: UMEC 62.5 mcg versus placebo, DBP, Week 24	
Comparison groups	Placebo QD v UMEC 62.5 mcg QD
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.066
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	3.1
Variability estimate	Standard error of the mean
Dispersion value	0.81

Secondary: Mean change from Baseline in on-treatment pulse rate

End point title	Mean change from Baseline in on-treatment pulse rate
End point description: Pulse rate was measured at every clinic visit, starting at Visit 1, and prior to conducting spirometry. Pulse rate was measured with participant in sitting position after approximately 5 minutes rest. Baseline value was defined as the latest vital signs assessment prior to randomized treatment start, including unscheduled visits. Change from Baseline was calculated by subtracting Baseline value from the value at specified time point. LS mean and SE data is presented. Participants with available data at baseline and at least one time point post-baseline were analyzed. Participants with data available at the specified time points are represented by n=X in the category titles.	
End point type	Secondary
End point timeframe: Baseline (Day 1 pre-dose), Weeks 4, 12 and 24	

End point values	Placebo QD	UMEC 31.25 mcg QD	UMEC 62.5 mcg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	139 ^[17]	137 ^[18]	139 ^[19]	
Units: Beats per minute				
least squares mean (standard error)				
Week 4, n=139, 137, 139	-2.3 (± 0.69)	-1.0 (± 0.69)	-0.8 (± 0.69)	
Week 12, n=139, 133, 135	-0.9 (± 0.59)	-0.3 (± 0.60)	0.8 (± 0.60)	
Week 24, n=135, 131, 130	-1.8 (± 0.75)	-0.7 (± 0.76)	1.5 (± 0.76)	

Notes:

[17] - ITT population.

[18] - ITT population.

[19] - ITT population.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: UMEC 31.25 mcg vs Placebo, Week 4	
Comparison groups	Placebo QD v UMEC 31.25 mcg QD
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.195
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	3.2
Variability estimate	Standard error of the mean
Dispersion value	0.97

Statistical analysis title	Statistical analysis 2
Statistical analysis description: UMEC 31.25 mcg vs Placebo, Week 12	
Comparison groups	Placebo QD v UMEC 31.25 mcg QD
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.457
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	2.3
Variability estimate	Standard error of the mean
Dispersion value	0.84

Statistical analysis title	Statistical analysis 3
Statistical analysis description: UMEC 31.25 mcg vs Placebo, Week 24	
Comparison groups	Placebo QD v UMEC 31.25 mcg QD
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	3.2
Variability estimate	Standard error of the mean
Dispersion value	1.07

Statistical analysis title	Statistical analysis 4
Statistical analysis description: UMEC 62.5 mcg vs Placebo, Week 4	
Comparison groups	Placebo QD v UMEC 62.5 mcg QD
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	3.3
Variability estimate	Standard error of the mean
Dispersion value	0.97

Statistical analysis title	Statistical analysis 5
Statistical analysis description: UMEC 62.5 mcg versus Placebo, Week 12	
Comparison groups	Placebo QD v UMEC 62.5 mcg QD

Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	3.3
Variability estimate	Standard error of the mean
Dispersion value	0.84

Statistical analysis title	Statistical analysis 6
Statistical analysis description: UMEC 62.5 mcg versus Placebo, Week 24	
Comparison groups	Placebo QD v UMEC 62.5 mcg QD
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	5.5
Variability estimate	Standard error of the mean
Dispersion value	1.07

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events and non-serious adverse events were collected up to 25 weeks.

Adverse event reporting additional description:

Intent-to-Treat Population was used to collect adverse events.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Placebo QD
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Reporting group description:

Participants received placebo once daily (QD) via the ELLIPTA dry powder inhaler (DPI) for 24 weeks. Participants also received Fluticasone Furoate (FF) 100 micrograms (mcg) once daily as background therapy, in the morning from a separate ELLIPTA DPI for 24 weeks.

Reporting group title	UMEC 31.25 mcg QD
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Reporting group description:

Participants received UMEC 31.25 mcg once daily via the ELLIPTA DPI for 24 weeks. Participants also received FF 100 mcg once daily as background therapy, in the morning from a separate ELLIPTA DPI for 24 weeks.

Reporting group title	UMEC 62.5 mcg QD
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Reporting group description:

Participants received UMEC 62.5 mcg once daily via the ELLIPTA DPI for 24 weeks. Participants also received FF 100 mcg once daily as background therapy, in the morning from a separate ELLIPTA DPI for 24 weeks.

Serious adverse events	Placebo QD	UMEC 31.25 mcg QD	UMEC 62.5 mcg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 143 (3.50%)	4 / 139 (2.88%)	3 / 139 (2.16%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 143 (1.40%)	0 / 139 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis superficial			
subjects affected / exposed	0 / 143 (0.00%)	1 / 139 (0.72%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 143 (0.00%)	1 / 139 (0.72%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient Ischemic attack			
subjects affected / exposed	1 / 143 (0.70%)	0 / 139 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 143 (0.00%)	0 / 139 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 143 (1.40%)	0 / 139 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 143 (0.00%)	1 / 139 (0.72%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary infarction			
subjects affected / exposed	0 / 143 (0.00%)	1 / 139 (0.72%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 143 (0.00%)	1 / 139 (0.72%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis			

subjects affected / exposed	0 / 143 (0.00%)	0 / 139 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 143 (0.00%)	1 / 139 (0.72%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Placebo QD	UMEC 31.25 mcg QD	UMEC 62.5 mcg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 143 (27.27%)	47 / 139 (33.81%)	33 / 139 (23.74%)
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 143 (7.69%)	9 / 139 (6.47%)	12 / 139 (8.63%)
occurrences (all)	22	14	17
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	4 / 143 (2.80%)	1 / 139 (0.72%)	5 / 139 (3.60%)
occurrences (all)	5	1	5
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 143 (1.40%)	6 / 139 (4.32%)	4 / 139 (2.88%)
occurrences (all)	2	6	6
Dysphonia			
subjects affected / exposed	2 / 143 (1.40%)	6 / 139 (4.32%)	0 / 139 (0.00%)
occurrences (all)	2	7	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 143 (3.50%)	3 / 139 (2.16%)	1 / 139 (0.72%)
occurrences (all)	5	3	1
Arthralgia			
subjects affected / exposed	1 / 143 (0.70%)	5 / 139 (3.60%)	2 / 139 (1.44%)
occurrences (all)	1	6	2

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	17 / 143 (11.89%) 21	14 / 139 (10.07%) 20	13 / 139 (9.35%) 15
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 143 (2.10%) 3	8 / 139 (5.76%) 13	6 / 139 (4.32%) 8
Respiratory tract infection viral subjects affected / exposed occurrences (all)	5 / 143 (3.50%) 5	7 / 139 (5.04%) 9	4 / 139 (2.88%) 4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 November 2016	Amendment 2: Schedule of Activities (SOA): Included Line item "X" in the box for inclusion/exclusion criteria at Visit 2 (randomization). Section 2: Schedule of Activities (SOA): Included row for "Exacerbation history" and Line item "X" at "screening". Section 2: Schedule of Activities (SOA): Included row for Exacerbation assessment and line item "X" in the boxes from Visit 2 (randomization) to "end of study (EOS)/early withdrawal (EW)". Section 2: Schedule of Activities (SOA) [Study Treatment] Included row for dispensing Albuterol/Salbutamol and line item "X" at Visit 1 (screening) until Visit 4. Section 3.3.1 Risk Assessments: Updated the information of hypothalamic pituitary axis (HPA) study (Mentioned 24 hour urinary cortisol excretion [Previously mentioned as 24 hour serum cortisol excretion]). Section 6.2 Exclusion Criteria: Example of tobacco products has been added to Exclusion criteria #14 Tobacco Use (electronic-cigarettes/vaping). Section 6.2 Exclusion Criteria: Example of a drug has been added to Exclusion criteria 15 Drug/alcohol abuse (marijuana is considered an abused drug). Section 9, Study Assessments and Procedures: Removed: Healthcare Resource Utilization (HRU) from the additional critical Baseline assessments (Screening [Visit 1]). Section 9, Study Assessments and Procedures: Removed: Questionnaires (St. George's Respiratory Questionnaire ([SGRQ]; Asthma Quality of Life Questionnaire [AQLQ]) from the additional critical Baseline assessments (Screening [Visit 1]). Section 9, Study Assessments and Procedures: Added: Letters "AE" to the additional critical Baseline assessments (Screening [Visit 1]). Section 9.2.1, Time Period and Frequency for collecting adverse event (AE) and serious adverse event (SAE) Information: Updated the information in the second bullet; (Stated AEs will be collected from the start of Study Screening [Previously mentioned AEs will be collected from the start of Study Treatment]).
06 July 2017	Amendment 2: Table of Contents: Section 7.1.3- Updated Section 7.1.3 to include albuterol/salbutamol medication for Return process, Section 2: Schedule of Activities (SOA) Removed the Screen Run-in "Window" day "-7d", also added language to clarify when electrocardiogram (ECG) completed: ECG was obtained after the vital signs assessment but prior to performing the pre-bronchodilator spirometry assessment. At all post randomization visits the ECG was to be obtained 15 minutes to 45 minutes after the administration of study treatment. Section 6.1: Inclusion Criteria; inclusion criteria #5: Updated best pre-bronchodilator morning Forced expiratory volume in 1 second (FEV1) to <=90%. Section 6.2.2: Inclusion Criteria for Randomization; inclusion criteria #2: Updated Spirometry: best pre-bronchodilator morning FEV1 to <=90%, Section 6.4 Pre-Screening/Screening/Run-In/Randomization Failures: Updated to Include re-screening language- Re screening of participants will be permitted; however, advance written approval to proceed with rescreening a participant must be obtained from the Medical Monitor. Section 7.1.3: Study Treatment, albuterol/salbutamol, and fluticasone furoate (FF) 100 mcg, Return: Updated to include specifically the medication name, albuterol/salbutamol to the return process. Section 9.1.4: Asthma Exacerbation: Added "moderate" to the last sentence in the paragraph. Section 9.4.3: Electrocardiograms: Added language ("but prior to performing pre-bronchodilator spirometry, assessment") to clarify when the ECG is to be done.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported