Clinical trial results:
A 24-week treatment, multi-center, randomized, double-blind, double-dummy, parallel group study to compare Umeclidinium/Vilanterol, Umeclidinium, and Salmeterol in subjects with chronic obstructive pulmonary disease (COPD)

Summary

EudraCT number	2016-002513-22
Trial protocol	SE ES DE FR NL IT
Global end of trial date	18 June 2018

Results information

Result version number	v1 (current)
This version publication date	03 July 2019
First version publication date	03 July 2019

Trial information

Trial identification

Sponsor protocol code	201749

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, TW8 9GS
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	15 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of Umeclidinium/Vilanterol [(UMEC/VI) 62.5/25 mcg once daily] with Umeclidinium [UMEC (62.5 mcg once daily)] on lung function.

Protection of trial subjects:

The protection of trial participants was enhanced by excluding participants with unstable liver and cardiac disease, pneumonia and/or moderate COPD exacerbation that had not resolved at least 14 days prior to screening, had >1 moderate exacerbation in the 12 months prior Screening, or 1 severe exacerbation requiring hospitalisation in the 12 months prior screening or other respiratory tract infections that had not resolved at least 7 days prior to screening. Female participants were only eligible to participate if they were not pregnant (as confirmed by a negative urine human chorionic gonadotrophin [hCG] test) and not lactating. Protocol-defined stopping criteria were put in place to safeguard participants and included: • Elevated liver chemistry • Positive urine pregnancy test. Unstable or life-threatening cardiac events (myocardial infarction, hospitalisation for unstable angina, stroke, and other CV events considered life- or intensively health-threatening by the study physician). • Participants with 2 moderate or 1 severe COPD exacerbation during the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 June 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	Argentina: 549
Country: Number of subjects enrolled	Australia: 35
Country: Number of subjects enrolled	Canada: 83
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Germany: 645
Country: Number of subjects enrolled	Italy: 77
Country: Number of subjects enrolled	Mexico: 35
Country: Number of subjects enrolled	Netherlands: 37
Country: Number of subjects enrolled	South Africa: 63
Country: Number of subjects enrolled	Spain: 78
Country: Number of subjects enrolled	Sweden: 109
Country: Number of subjects enrolled	United States: 678
Worldwide total number of subjects	2425
EEA total number of subjects	982

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)	1198
From 65 to 84 years	1208
85 years and over	19

Subject disposition

Recruitment

Recruitment details:

In this randomized, double-blind, double dummy, 3-arm parallel group study, eligible participants received Umeclidinium/Vilanterol (UMEC/VI) 62.5/25 microgram (mcg) once daily via the ELLIPTA dry powder inhaler (DPI), or UMEC 62.5 mcg once daily via ELLIPTA DPI, or Salmeterol (SAL) 50 mcg twice daily via the DISKUS DPI (1:1:1) for 24 weeks.

Pre-assignment

Screening details:

A total of 3591 participants who met the eligibility criteria were screened; 2431 participants were randomized and 2425 comprised the Intent to Treat (ITT) population (6 participants randomized in error and did not receive any treatment).The study consisted of a run-in period (4 weeks), treatment period (24 weeks) and follow up period (7+/-3 days).

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	UMEC/VI 62.5/25 mcg+ Placebo

Arm description:

Participants with COPD received UMEC/VI 62.5/25 mcg once daily via the ELLIPTA DPI along with placebo twice daily via the DISKUS DPI for 24 weeks. In addition albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the study. Participants were followed up 7 days after the last dose of study medication.

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

Dosage and administration details:

Participants received UMEC/VI, 62.5 mcg/25 mcg inhalation powder via ELLIPTA, once daily in the morning.

Investigational medicinal product name	Placebo via DISKUS
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received placebo inhalation powder via DISKUS, one dose in the morning and one in the evening.

Investigational medicinal product name	Albuterol/salbutamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received albuterol/salbutamol as a rescue medication via metered-dose inhaler (MDI) with a

spacer which was used when needed during the study

Arm title	UMEC 62.5 mcg + Placebo

Arm description:

Participants with COPD received UMEC 62.5mcg once daily via the ELLIPTA DPI along with placebo twice daily via DISKUS DPI for 24 weeks. In addition albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the study. Participants were followed up 7 days after the last dose of study medication.

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:

Participants received UMEC 62.5 mcg inhalation powder via ELLIPTA, once daily in the morning.

Investigational medicinal product name	Placebo via DISKUS
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received placebo inhalation powder via DISKUS, one dose in the morning and one in the evening.

Investigational medicinal product name	Albuterol/salbutamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received albuterol/salbutamol as a rescue medication via metered-dose inhaler (MDI) with a spacer which was used when needed during the study

Arm title	Salmeterol 50 mcg+Placebo

Arm description:

Participants with COPD received salmeterol 50 mcg twice daily via the DISKUS DPI along with placebo once daily via ELLIPTA DPI for 24 weeks. In addition albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the study. Participants were followed up 7 days after the last dose of study medication.

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

Dosage and administration details:

Participants received salmeterol 50 mcg administered one dose in the morning and one in the evening via DISKUS

Investigational medicinal product name	Placebo via ELLIPTA
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received placebo inhalation powder via ELLIPTA, once daily in the morning.

Investigational medicinal product name	Albuterol/salbutamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received albuterol/salbutamol as a rescue medication via metered-dose inhaler (MDI) with a spacer which was used when needed during the study

Number of subjects in period 1	UMEC/VI 62.5/25 mcg+ Placebo	UMEC 62.5 mcg + Placebo	Salmeterol 50 mcg+Placebo
Started	812	804	809
Completed	717	650	683
Not completed	95	154	126
Adverse event, serious fatal	5	2	2
Consent withdrawn by subject	29	46	41
Physician decision	1	5	2
Adverse event, non-fatal	24	30	20
Protocol Deviation	2	14	7
Protocol-defined withdrawal criteria met	19	26	29
Site closed	2	2	4
Lost to follow-up	5	13	3
Lack of efficacy	8	16	18

Baseline characteristics

Reporting groups	
Reporting group title	UMEC/VI 62.5/25 mcg+ Placebo
Reporting group description:	
Participants with COPD received UMEC/VI 62.5/25 mcg once daily via the ELLIPTA DPI along with placebo twice daily via the DISKUS DPI for 24 weeks. In addition albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the study. Participants were followed up 7 days after the last dose of study medication.	
Reporting group title	UMEC 62.5 mcg + Placebo
Reporting group description:	
Participants with COPD received UMEC 62.5mcg once daily via the ELLIPTA DPI along with placebo twice daily via DISKUS DPI for 24 weeks. In addition albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the study. Participants were followed up 7 days after the last dose of study medication.	
Reporting group title	Salmeterol 50 mcg+Placebo
Reporting group description:	
Participants with COPD received salmeterol 50 mcg twice daily via the DISKUS DPI along with placebo once daily via ELLIPTA DPI for 24 weeks. In addition albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the study. Participants were followed up 7 days after the last dose of study medication.	

Reporting group values	UMEC/VI 62.5/25 mcg+ Placebo	UMEC 62.5 mcg + Placebo	Salmeterol 50 mcg+Placebo
Number of subjects	812	804	809
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)	400	398	400
From 65-84 years	402	399	407
85 years and over	10	7	2
Age Continuous Units: Years			
arithmetic mean	64.6	64.9	64.4
standard deviation	± 8.37	± 8.48	± 8.53
Sex: Female, Male Units: Subjects			
Female	319	327	342
Male	493	477	467
Race/Ethnicity, Customized Units: Subjects			
Black or African American	24	23	25
American Indian or Alaska Native	13	12	12
Asian - Central/South Asian Heritage	5	0	0
Asian - Japanese Heritage	0	1	0

Asian - East Asian Heritage	0	0	1
White – Arabic/North African Heritage	3	1	1
White – White/Caucasian/European Heritage	764	763	765
American Indian or Alaska Native & White	1	0	0
Black or African American & White	2	4	4
Native Hawaiian or other Pacific Islander & White	0	0	1

Reporting group values	Total		
Number of subjects	2425		
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)	1198		
From 65-84 years	1208		
85 years and over	19		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Subjects			
Female	988		
Male	1437		
Race/Ethnicity, Customized			
Units: Subjects			
Black or African American	72		
American Indian or Alaska Native	37		
Asian - Central/South Asian Heritage	5		
Asian - Japanese Heritage	1		
Asian - East Asian Heritage	1		
White – Arabic/North African Heritage	5		
White – White/Caucasian/European Heritage	2292		
American Indian or Alaska Native & White	1		
Black or African American & White	10		
Native Hawaiian or other Pacific Islander & White	1		

End points

End points reporting groups

Reporting group title	UMEC/VI 62.5/25 mcg+ Placebo

Reporting group description:

Participants with COPD received UMEC/VI 62.5/25 mcg once daily via the ELLIPTA DPI along with placebo twice daily via the DISKUS DPI for 24 weeks. In addition albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the study. Participants were followed up 7 days after the last dose of study medication.

Reporting group title	UMEC 62.5 mcg + Placebo

Reporting group description:

Participants with COPD received UMEC 62.5mcg once daily via the ELLIPTA DPI along with placebo twice daily via DISKUS DPI for 24 weeks. In addition albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the study. Participants were followed up 7 days after the last dose of study medication.

Reporting group title	Salmeterol 50 mcg+Placebo

Reporting group description:

Participants with COPD received salmeterol 50 mcg twice daily via the DISKUS DPI along with placebo once daily via ELLIPTA DPI for 24 weeks. In addition albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the study. Participants were followed up 7 days after the last dose of study medication.

Primary: Change from Baseline in trough Forced Expiratory Volume in One Second (FEV1) at Week 24

End point title	Change from Baseline in trough Forced Expiratory Volume in One Second (FEV1) at Week 24

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. Trough FEV1 at Week 24 is defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on the previous day. Baseline trough FEV1 is the mean of the values measured at 30 minutes and 5 minutes pre-dose on Day 1. Change from Baseline was calculated as the trough FEV1 value on Week 24 minus the Baseline value. Analysis was performed using a repeated measures model (MMRM) with covariates of Baseline FEV1, geographical region, stratum (number of bronchodilators per day during run-in), visit, treatment, visit by Baseline and visit by treatment interaction. ITT population comprised of all randomized participants (excluding those who were randomized in error) who received at least one dose of study medication.

End point type	Primary

End point timeframe:

Baseline (Pre-dose on Day 1) and Week 24

End point values	UMEC/VI 62.5/25 mcg+ Placebo	UMEC 62.5 mcg + Placebo	Salmeterol 50 mcg+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	691[1]	621[2]	654[3]	
Units: Liters				
least squares mean (standard error)	0.122 (± 0.0081)	0.056 (± 0.0085)	-0.019 (± 0.0083)	

Notes:

[1] - ITT Population. Participants represents those with data available at the time point being presented

[2] - ITT Population. Participants represents those with data available at the time point being presented

[3] - ITT Population. Participants represents those with data available at the time point being presented

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: LS Mean difference comparing UMEC/VI versus UMEC at Week 24.	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v UMEC 62.5 mcg + Placebo
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.066
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.043
upper limit	0.089
Variability estimate	Standard error of the mean
Dispersion value	0.0118

Statistical analysis title	Statistical analysis 2
Statistical analysis description: LS Mean difference comparing UMEC/VI versus salmeterol at Week 24.	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1345
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.141
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.118
upper limit	0.164
Variability estimate	Standard error of the mean
Dispersion value	0.0117

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
LS Mean difference comparing UMEC versus salmeterol at Week 24.	
Comparison groups	UMEC 62.5 mcg + Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1275
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.075
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.051
upper limit	0.098
Variability estimate	Standard error of the mean
Dispersion value	0.0119

Secondary: Self administered computerized (SAC) transient dyspnea index (TDI) Focal score at Week 24

End point title	Self administered computerized (SAC) transient dyspnea index (TDI) Focal score at Week 24
End point description:	
TDI focal score comprises of 3 individual scales (Functional Impairment, Magnitude of Task, Magnitude of Effort). Each of these scales had a possible score ranging from -6 to +6, lower scores indicates impairment. TDI focal score was calculated as the sum of 3 individual scores (range is -18 to +18). Lower score indicates deterioration of dyspnea. If a score is missing for any of the three scales, then the TDI focal score was set to missing. Analysis was performed using mixed model repeated measures (MMRM) with covariates of SAC BDI focal score, geographical region, stratum (no. of bronchodilators per day during run-in), visit, treatment, visit by SAC BDI and visit by treatment interactions.	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	UMEC/VI 62.5/25 mcg+ Placebo	UMEC 62.5 mcg + Placebo	Salmeterol 50 mcg+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	704[4]	636[5]	673[6]	
Units: Scores on a scale				
least squares mean (standard error)	1.68 (± 0.109)	1.30 (± 0.114)	1.22 (± 0.111)	

Notes:

[4] - ITT Population. Participants represents those with data available at the time point being presented

[5] - ITT Population. Participants represents those with data available at the time point being presented

[6] - ITT Population. Participants represents those with data available at the time point being presented

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
LS Mean difference comparing UMEC/VI versus UMEC at Week 24.	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v UMEC 62.5 mcg + Placebo
Number of subjects included in analysis	1340
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.018
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.68
Variability estimate	Standard error of the mean
Dispersion value	0.157

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
LS Mean difference comparing UMEC/VI versus salmeterol at Week 24.	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1377
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.004
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.76
Variability estimate	Standard error of the mean
Dispersion value	0.155

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
LS Mean difference comparing UMEC versus salmeterol at Week 24.	
Comparison groups	UMEC 62.5 mcg + Placebo v Salmeterol 50 mcg+Placebo

Number of subjects included in analysis	1309
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.61
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.39
Variability estimate	Standard error of the mean
Dispersion value	0.159

Secondary: Percentage of TDI responders according to SAC TDI Focal score

End point title	Percentage of TDI responders according to SAC TDI Focal score

End point description:

TDI focal score comprises of 3 individual scales (Functional Impairment, Magnitude of Task, Magnitude of Effort). Each of these scales had a possible score ranging from -6 to +6, lower scores indicates impairment. TDI focal score was calculated as the sum of 3 individual scores (range is -18 to +18). Lower score indicates deterioration of dyspnea. If a score is missing for any of the three scales, then TDI focal score was set to missing. A participant was considered as a responder if the on-treatment TDI focal score was at least 1 unit at that visit. Non-response was SAC TDI focal score of less than 1 unit or a missing SAC TDI focal score with no subsequent non-missing on-treatment scores. Analysis was performed using a generalized linear mixed model with treatment as an explanatory variable and visit, SAC BDI focal score, stratum (no. of bronchodilators per day during run-in), geographical region, visit by SAC BDI and visit by treatment interactions included as covariates.

End point type	Secondary

End point timeframe:

Week 24

End point values	UMEC/VI 62.5/25 mcg+ Placebo	UMEC 62.5 mcg + Placebo	Salmeterol 50 mcg+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	806[7]	799[8]	807[9]	
Units: Percentage of responders	50	42	41	

Notes:

[7] - ITT Population. Participants represents those with data available at the time point being presented

[8] - ITT Population. Participants represents those with data available at the time point being presented

[9] - ITT Population. Participants represents those with data available at the time point being presented

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Odds Ratio (responder vs. a non-responder) comparing UMEC/VI versus UMEC at Week 24.

Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v UMEC 62.5 mcg + Placebo

Number of subjects included in analysis	1605
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	generalized linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.17
upper limit	1.75

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Odds Ratio (responder vs. a non-responder) comparing UMEC/VI versus salmeterol at Week 24.	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1613
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	generalized linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.21
upper limit	1.81

Statistical analysis title	Statistical analysis 3
Statistical analysis description: Odds Ratio (responder vs. a non-responder) comparing UMEC versus salmeterol at Week 24.	
Comparison groups	UMEC 62.5 mcg + Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1606
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.755
Method	generalized linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.27

Secondary: Mean change from Baseline in Evaluating Respiratory Symptoms (E-RS) total score

End point title	Mean change from Baseline in Evaluating Respiratory Symptoms (E-RS) total score

End point description:

The E-RS is intended to capture information related to respiratory symptoms. A daily symptom score for E-RS is derived by summing 11 item-scores. The domains include: respiratory symptoms (RS)-breathlessness (RS-BRL comprised of 5 items, score range [0-17]), RS-cough and sputum (RS-CSP comprised of 3 items, score range [0-11]), and RS-chest symptoms (RS-CSY comprised of 3 items, score range [0-12]). Total score ranged between 0-40 and higher values indicates severe respiratory symptoms. The instrument was completed each night prior to going to bed. Baseline E-RS score is the mean within-participant daily score over 7 days prior to randomization. Change from Baseline is the difference at Week 21-Week 24 value and Baseline value. Analysis was performed using MMRM with covariates of Baseline score, geographical region, stratum (no. of bronchodilators per day during run-in), 4-weekly period, treatment, 4-weekly period by Baseline and 4-weekly period by treatment interactions.

End point type	Secondary

End point timeframe:

Baseline (Pre-dose on Day 1) and Week 21 to Week 24

End point values	UMEC/VI 62.5/25 mcg+ Placebo	UMEC 62.5 mcg + Placebo	Salmeterol 50 mcg+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	677[10]	621[11]	653[12]	
Units: Scores on a scale				
least squares mean (standard error)	-1.52 (± 0.148)	-0.99 (± 0.152)	-0.69 (± 0.150)	

Notes:

[10] - ITT Population. Participants represents those with data available at the time point being presented

[11] - ITT Population. Participants represents those with data available at the time point being presented

[12] - ITT Population. Participants represents those with data available at the time point being presented

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

LS Mean difference comparing UMEC/VI versus UMEC at Week 21 to Week 24

Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v UMEC 62.5 mcg + Placebo
Number of subjects included in analysis	1298
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.013
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	-0.11
Variability estimate	Standard error of the mean
Dispersion value	0.213

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
LS Mean difference comparing UMEC/VI versus salmeterol at Week 21 to Week 24	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1330
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	-0.42
Variability estimate	Standard error of the mean
Dispersion value	0.211

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
LS Mean difference comparing UMEC versus Salmeterol at Week 21 to Week 24	
Comparison groups	UMEC 62.5 mcg + Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1274
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.159
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.214

Secondary: Mean change from Baseline in E-RS Subscale Score

End point title	Mean change from Baseline in E-RS Subscale Score

End point description:

The E-RS is intended to capture information related to respiratory symptoms. A daily symptom score for E-RS is derived by summing 11 item-scores. The domains include: respiratory symptoms (RS)-breathlessness (RS-BRL comprised of 5 items, score range [0-17]), RS-cough and sputum (RS-CSP comprised of 3 items, score range [0-11]), and RS-chest symptoms (RS-CSY comprised of 3 items, score range [0-12]). Total score ranged between 0-40 and higher values indicates severe respiratory symptoms. The instrument was completed each night prior to going to bed. Baseline E-RS score is the mean within-participant daily score over 7 days prior to randomization. Change from Baseline is the difference at Week 21-Week 24 value and Baseline value. Analysis was performed using MMRM with covariates of Baseline score, geographical region, stratum (no. of bronchodilators per day during run-in), 4-weekly period, treatment, 4-weekly period by Baseline and 4-weekly period by treatment interactions.

End point type	Secondary

End point timeframe:

Baseline (Pre-dose on Day 1) and Week 21 to Week 24

End point values	UMEC/VI 62.5/25 mcg+ Placebo	UMEC 62.5 mcg + Placebo	Salmeterol 50 mcg+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	677[13]	621[14]	653[15]	
Units: Scores on a scale				
least squares mean (standard error)				
RS-BRL	-0.67 (± 0.080)	-0.40 (± 0.082)	-0.22 (± 0.081)	
RS-CSP	-0.45 (± 0.044)	-0.38 (± 0.045)	-0.32 (± 0.044)	
RS-CSY	-0.39 (± 0.049)	-0.22 (± 0.050)	-0.15 (± 0.049)	

Notes:

[13] - ITT Population. Participants represents those with data available at the time point being presented

[14] - ITT Population. Participants represents those with data available at the time point being presented

[15] - ITT Population. Participants represents those with data available at the time point being presented

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

LS Mean difference comparing UMEC/VI versus UMEC at Week 21 to Week 24

Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v UMEC 62.5 mcg + Placebo

Number of subjects included in analysis	1298
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.016 [16]
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.114

Notes:

[16] - E-RS Breathlessness Score

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

LS Mean difference comparing UMEC/VI versus salmeterol at Week 21 to Week 24

Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1330
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [17]
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	-0.23
Variability estimate	Standard error of the mean
Dispersion value	0.113

Notes:

[17] - E-RS Breathlessness Score

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

LS Mean difference comparing UMEC versus salmeterol at Week 21 to Week 24

Comparison groups	UMEC 62.5 mcg + Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1274
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.115 [18]
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.115

Notes:
[18] - E-RS Breathlessness Score

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
LS Mean difference comparing UMEC/VI versus UMEC at Week 21 to Week 24	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v UMEC 62.5 mcg + Placebo
Number of subjects included in analysis	1298
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.247 [19]
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.063

Notes:
[19] - E-RS Cough and Sputum Score

Statistical analysis title	Statistical analysis 5
Statistical analysis description:	
LS Mean difference comparing UMEC/VI versus salmeterol at Week 21 to Week 24	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1330
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.042 [20]
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.063

Notes:
[20] - E-RS Cough and Sputum Score

Statistical analysis title	Statistical analysis 6
Statistical analysis description:	
LS Mean difference comparing UMEC versus salmeterol at Week 21 to Week 24	
Comparison groups	UMEC 62.5 mcg + Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1274
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.391 [21]
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.07
Variability estimate	Standard error of the mean
Dispersion value	0.063

Notes:
[21] - E-RS Cough and Sputum Score

Statistical analysis title	Statistical analysis 7
Statistical analysis description:	
LS Mean difference comparing UMEC/VI versus UMEC at Week 21 to Week 24	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v UMEC 62.5 mcg + Placebo
Number of subjects included in analysis	1298
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.014 [22]
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:
[22] - E-RS Chest Symptoms Score

Statistical analysis title	Statistical analysis 8
Statistical analysis description:	
LS Mean difference comparing UMEC/VI versus salmeterol at Week 21 to Week 24	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v Salmeterol 50 mcg+Placebo

Number of subjects included in analysis	1330
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [23]
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.069

Notes:

[23] - E-RS Chest Symptoms Score

Statistical analysis title	Statistical analysis 9

Statistical analysis description:

LS Mean difference comparing UMEC versus salmeterol at Week 21 to Week 24

Comparison groups	UMEC 62.5 mcg + Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1274
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.34 [24]
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.07
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

[24] - E-RS Chest Symptoms Score

Secondary: Percentage of E-RS responders according to E-RS total score

End point title	Percentage of E-RS responders according to E-RS total score

End point description:

The E-RS is intended to capture information related to respiratory symptoms. A daily symptom score for E-RS is derived by summing 11 item-scores. The domains include: RS-BRL comprised of 5 items, score range (0-17); RS-CSP comprised of 3 items, score range (0-11); and RS-CSY comprised of 4 items, score range (0-12). Total score ranged between 0-40 and higher values indicates severe respiratory symptoms. The instrument was completed each night prior to going to bed. Response is defined as an E-RS total score of at least 2 or 3.35 below Baseline. Participants with a Baseline but all missing post-Baseline data are also considered a non-responder. Analysis was performed using a generalized linear mixed model with treatment as an explanatory variable and four-weekly period, Baseline score, stratum (no. of bronchodilators per day during run-in), geographical region, four-weekly period by baseline and four-weekly period by treatment interactions included as covariates.

End point type	Secondary

End point timeframe:
Week 21 to Week 24

End point values	UMEC/VI 62.5/25 mcg+ Placebo	UMEC 62.5 mcg + Placebo	Salmeterol 50 mcg+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	809[25]	800[26]	808[27]	
Units: Percentage of responders	36	27	27	

Notes:

[25] - ITT Population. Participants represents those with data available at the time point being presented
[26] - ITT Population. Participants represents those with data available at the time point being presented
[27] - ITT Population. Participants represents those with data available at the time point being presented

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Odds Ratio (responder vs. a non-responder) comparing UMEC/VI vs UMEC at Week 21 to Week 24	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v UMEC 62.5 mcg + Placebo
Number of subjects included in analysis	1609
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	generalized linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.22
upper limit	1.89

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Odds Ratio (responder vs. a non-responder) comparing UMEC/VI vs salmeterol at Week 21 to Week 24	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1617
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	generalized linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	1.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	1.9

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
Odds Ratio (responder vs. a non-responder) comparing UMEC vs salmeterol at Week 21 to Week 24	
Comparison groups	UMEC 62.5 mcg + Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1608
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.969
Method	generalized linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.26

Secondary: Change from Baseline in St George's Respiratory Questionnaire (SGRQ) total score

End point title	Change from Baseline in St George's Respiratory Questionnaire (SGRQ) total score

End point description:

SGRQ is a disease-specific questionnaire designed to measure impact of respiratory disease and its treatment on HRQoL of participants with COPD. It contains 14 questions with a total of 40 items grouped into domains (Symptoms, Activity and Impacts). SGRQ total score was calculated as 100 multiplied by summed weights from all positive items divided by sum of weights for all items in questionnaire. It ranges from 0 to 100, higher score indicates poor HRQoL. Baseline is last non-missing score recorded prior to dosing on Day 1. Change from Baseline was calculated by subtracting Baseline value from the value at Week 24. Analysis was performed using mixed model repeated measures (MMRM) with covariates of Baseline SGRQ total score, geographical region, stratum (no. of bronchodilators per day during run-in), visit, treatment, visit by Baseline and visit by treatment interactions.

End point type	Secondary

End point timeframe:

Baseline (Pre-dose on Day 1) and Week 24

End point values	UMEC/VI 62.5/25 mcg+ Placebo	UMEC 62.5 mcg + Placebo	Salmeterol 50 mcg+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	704[28]	636[29]	674[30]	
Units: Scores on a scale				
least squares mean (standard error)	-4.98 (± 0.465)	-5.23 (± 0.484)	-3.29 (± 0.475)	

Notes:

[28] - ITT Population. Participants represents those with data available at the time point being presented
[29] - ITT Population. Participants represents those with data available at the time point being presented
[30] - ITT Population. Participants represents those with data available at the time point being presented

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: LS Mean difference comparing UMEC/VI versus UMEC at Week 24.	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v UMEC 62.5 mcg + Placebo
Number of subjects included in analysis	1340
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.709
Method	mixed model repeated measure
Parameter estimate	Mean difference (net)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.07
upper limit	1.57
Variability estimate	Standard error of the mean
Dispersion value	0.672

Statistical analysis title	Statistical analysis 2
Statistical analysis description: LS Mean difference comparing UMEC/VI versus salmeterol at Week 24.	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1378
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.011
Method	mixed model repeated measure
Parameter estimate	Mean difference (net)
Point estimate	-1.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.99
upper limit	-0.39
Variability estimate	Standard error of the mean
Dispersion value	0.665

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
LS Mean difference comparing UMEC versus salmeterol at Week 24.	
Comparison groups	UMEC 62.5 mcg + Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1310
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.004
Method	mixed model repeated measure
Parameter estimate	Mean difference (net)
Point estimate	-1.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.27
upper limit	-0.61
Variability estimate	Standard error of the mean
Dispersion value	0.678

Secondary: Change from Baseline in COPD assessment test (CAT)

End point title	Change from Baseline in COPD assessment test (CAT)

End point description:

The CAT is a participant-completed instrument designed to provide a simple and reliable measure of health status in COPD for the assessment and long-term follow-up of the individual participant. The CAT consists of eight items, each formatted on a differential scale. Participants rated their experience on a 6-point scale for each question, ranging from 0 (no impact) to 5 (high impact). A total CAT score was calculated by summing the non-missing scores on the eight items ranging from 0 to 40 with higher scores indicating greater disease impact. Baseline is defined as the last non-missing score recorded prior to dosing on Day 1. Change from Baseline was calculated by subtracting Baseline value from the value at Week 24. Analysis was performed using mixed model repeated measures (MMRM) with covariates of Baseline CAT score, geographical region, stratum (no. of bronchodilators per day during run-in), visit, treatment, visit by Baseline and visit by treatment interactions.

End point type	Secondary

End point timeframe:

Baseline (Pre-dose on Day 1) and Week 24

End point values	UMEC/VI 62.5/25 mcg+ Placebo	UMEC 62.5 mcg + Placebo	Salmeterol 50 mcg+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	703[31]	633[32]	669[33]	
Units: Scores on a scale				
least squares mean (standard error)	-3.5 (± 0.21)	-3.4 (± 0.22)	-2.9 (± 0.21)	

Notes:

[31] - ITT Population. Participants represents those with data available at the time point being presented

[32] - ITT Population. Participants represents those with data available at the time point being presented

[33] - ITT Population. Participants represents those with data available at the time point being presented

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: LS Mean difference comparing UMEC/VI versus UMEC at Week 24.	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v UMEC 62.5 mcg + Placebo
Number of subjects included in analysis	1336
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.891
Method	mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.3

Statistical analysis title	Statistical analysis 2
Statistical analysis description: LS Mean difference comparing UMEC/VI versus salmeterol at Week 24.	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1372
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.074
Method	mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.3

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
LS Mean difference comparing UMEC versus salmeterol at Week 24.	
Comparison groups	UMEC 62.5 mcg + Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1302
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.107
Method	mixed model repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.31

Secondary: Percentage of responders according to CAT

End point title	Percentage of responders according to CAT

End point description:

The CAT is a participant-completed instrument designed to provide a simple and reliable measure of health status in COPD for the assessment and long-term follow-up of the individual participant. The CAT consists of eight items. Participants rated their experience on a 6-point scale for each question, ranging from 0 (no impact) to 5 (high impact). A total CAT score was calculated by summing the non-missing scores on the eight items ranging from 0 to 40 with higher scores indicating greater disease impact. Response was defined as an CAT score of >=2 below Baseline. Non response was defined as CAT score <2 units below Baseline or a missing CAT score with no subsequent on treatment scores. Analysis was performed using a generalized linear mixed model with treatment as an explanatory variable and visit, baseline CAT score, stratum (no. of bronchodilators per day during run-in), geographical region, visit by baseline and visit by treatment interactions included as covariates.

End point type	Secondary

End point timeframe:

Week 24

End point values	UMEC/VI 62.5/25 mcg+ Placebo	UMEC 62.5 mcg + Placebo	Salmeterol 50 mcg+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	812[34]	804[35]	809[36]	
Units: Percentage of responders	55	48	50	

Notes:

[34] - ITT Population.

[35] - ITT Population.

[36] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: Odds Ratio (responder vs. a non-responder) comparing UMEC/VI versus UMEC at Week 24.	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v UMEC 62.5 mcg + Placebo
Number of subjects included in analysis	1616
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.003
Method	generalized linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	1.65

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Odds Ratio (responder vs. a non-responder) comparing UMEC/VI versus salmeterol at Week 24.	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1621
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.037
Method	generalized linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.5

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Odds Ratio (responder vs. a non-responder) comparing UMEC versus salmeterol at Week 24.

Comparison groups	UMEC 62.5 mcg + Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1613
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.363
Method	generalized linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.11

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

End point title	Number of participants with on treatment adverse events (AE) and serious adverse events (SAE)

End point description:

An AE is any untoward medical occurrence in a participant or 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 associated with liver injury and impaired liver function based on pre-defined criteria were categorized as SAE.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	UMEC/VI 62.5/25 mcg+ Placebo	UMEC 62.5 mcg + Placebo	Salmeterol 50 mcg+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	812[37]	804[38]	809[39]	
Units: Participants				
Any AE	315	316	314	
Any SAE	49	35	38	

Notes:

[37] - ITT Population.

[38] - ITT Population.

[39] - ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of responders based on the Saint (St) George Respiratory Questionnaire COPD specific (SGRQ-C) Total Score

End point title	Percentage of responders based on the Saint (St) George Respiratory Questionnaire COPD specific (SGRQ-C) Total Score

End point description:

SGRQ-C is a disease-specific questionnaire designed to measure impact of respiratory disease and its treatment on HRQoL of participants with COPD. It contains 14 questions with a total of 40 items grouped into domains (Symptoms, Activity and Impacts). SGRQ-C total score was calculated as 100 multiplied by summed weights from all positive items divided by sum of weights for all items in questionnaire. It ranges from 0 to 100, higher score indicates poor HRQoL. SGRQ-C total score was converted to SGRQ total score by multiplying (SGRQ-Cx0.90) + 3.10 units. Analysis was performed using a generalized linear mixed model with treatment as an explanatory variable and visit, Baseline SGRQ score, stratum (no. of bronchodilators per day during run-in), geographical region, visit by Baseline and visit by treatment interactions included as covariates. Response was defined as an SGRQ total score of 4 or more units below Baseline.

End point type	Secondary

End point timeframe:

Week 24

End point values	UMEC/VI 62.5/25 mcg+ Placebo	UMEC 62.5 mcg + Placebo	Salmeterol 50 mcg+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	811[40]	802[41]	809[42]	
Units: Percentage of responders	45	41	36	

Notes:

[40] - ITT Population. Participants represents those with data available at the time point being presented
[41] - ITT Population. Participants represents those with data available at the time point being presented
[42] - ITT Population. Participants represents those with data available at the time point being presented

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Odds Ratio (responder vs. a non-responder) comparing UMEC/VI versus UMEC at Week 24.

Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v UMEC 62.5 mcg + Placebo
Number of subjects included in analysis	1613
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.063
Method	generalized linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.48

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Odds Ratio (responder vs. a non-responder) comparing UMEC/VI versus salmeterol at Week 24.	
Comparison groups	UMEC/VI 62.5/25 mcg+ Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1620
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	generalized linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.22
upper limit	1.83

Statistical analysis title	Statistical analysis 3
Statistical analysis description: Odds Ratio (responder vs. a non-responder) comparing UMEC versus salmeterol at Week 24.	
Comparison groups	UMEC 62.5 mcg + Placebo v Salmeterol 50 mcg+Placebo
Number of subjects included in analysis	1611
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.045
Method	generalized linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.51

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-Treatment serious adverse events (SAEs) and non-serious AEs (nSAEs) were collected from start of study treatment until Week 24.

Adverse event reporting additional description:

On-Treatment SAEs and nSAEs were reported for ITT Population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	UMEC/VI 62.5/25 mcg+ Placebo

Reporting group description:

Participants with COPD received UMEC/VI 62.5/25 mcg once daily via the ELLIPTA DPI along with placebo BID via the DISKUS DPI for 24 weeks. In addition albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the study. Participants were followed up 7 days after the last dose of study medication.

Reporting group title	Salmeterol 50 mcg+Placebo

Reporting group description:

Participants with COPD received salmeterol 50 mcg twice daily via the DISKUS DPI along with placebo once daily via ELLIPTA DPI for 24 weeks. In addition albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the study. Participants were followed up 7 days after the last dose of study medication.

Reporting group title	UMEC 62.5 mcg + Placebo

Reporting group description:

Participants with COPD received UMEC 62.5mcg once daily via the ELLIPTA DPI along with placebo twice daily via DISKUS DPI for 24 weeks. In addition albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the study. Participants were followed up 7 days after the last dose of study medication.

Serious adverse events	UMEC/VI 62.5/25 mcg+ Placebo	Salmeterol 50 mcg+Placebo	UMEC 62.5 mcg + Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 812 (6.03%)	38 / 809 (4.70%)	35 / 804 (4.35%)
number of deaths (all causes)	4	0	4
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	1 / 812 (0.12%)	1 / 809 (0.12%)	0 / 804 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer			

subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 812 (0.12%)	1 / 809 (0.12%)	0 / 804 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenosquamous cell lung cancer			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Benign lung neoplasm			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Lung neoplasm malignant			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Malignant melanoma			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Meningioma			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Non-small cell lung cancer metastatic			

subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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
Papillary cystadenoma lymphomatosum			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 812 (0.12%)	1 / 809 (0.12%)	2 / 804 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	2 / 812 (0.25%)	0 / 809 (0.00%)	0 / 804 (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
Aortic stenosis			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive emergency			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Hypotension			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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
Subclavian artery stenosis			

subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Varicose vein			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	7 / 812 (0.86%)	9 / 809 (1.11%)	7 / 804 (0.87%)
occurrences causally related to treatment / all	0 / 7	0 / 9	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Pneumothorax			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute respiratory failure			

subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypoxia			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Pulmonary oedema			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	1 / 812 (0.12%)	1 / 809 (0.12%)	0 / 804 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Craniocerebral injury			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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

Fibula fracture			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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
Post-thoracotomy pain syndrome			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Spinal compression fracture			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Tendon rupture			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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	2 / 812 (0.25%)	2 / 809 (0.25%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	2 / 804 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			

subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardio-respiratory arrest			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Acute coronary syndrome			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Angina pectoris			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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
Angina unstable			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Atrioventricular block complete			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			

subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Ventricular fibrillation			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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 ischaemic attack			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basilar artery stenosis			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain stem stroke			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar infarction			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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
Encephalopathy			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			

subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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
Status epilepticus			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tethered cord syndrome			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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
Microcytic anaemia			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	2 / 812 (0.25%)	0 / 809 (0.00%)	0 / 804 (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

Abdominal pain			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Duodenal ulcer			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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
Enterocolitis haemorrhagic			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral hernia strangulated			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Gastric polyps			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Gastric ulcer			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Intestinal obstruction			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	2 / 812 (0.25%)	0 / 809 (0.00%)	0 / 804 (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
Back pain			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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
Spinal pain			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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

Synovial cyst			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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			
Pneumonia			
subjects affected / exposed	4 / 812 (0.49%)	5 / 809 (0.62%)	4 / 804 (0.50%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 812 (0.25%)	0 / 809 (0.00%)	0 / 804 (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
Appendicitis perforated			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial colitis			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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
Encephalitis			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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
Muscle abscess			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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

Pyelonephritis acute			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Septic shock			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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
Urinary tract infection			
subjects affected / exposed	0 / 812 (0.00%)	0 / 809 (0.00%)	1 / 804 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 812 (0.00%)	1 / 809 (0.12%)	0 / 804 (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
Metabolic acidosis			
subjects affected / exposed	1 / 812 (0.12%)	0 / 809 (0.00%)	0 / 804 (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

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

Non-serious adverse events	UMEC/VI 62.5/25 mcg+ Placebo	Salmeterol 50 mcg+Placebo	UMEC 62.5 mcg + Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 812 (8.37%)	84 / 809 (10.38%)	87 / 804 (10.82%)
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	68 / 812 (8.37%)	84 / 809 (10.38%)	87 / 804 (10.82%)
occurrences (all)	81	94	103

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2017	Amendment 1:: Regulatory Agency Identifying Number(s): A typographical error in the EudraCT no. corrected. IND no. added. Section 4.1and Section 4.4: Typographical errors and inconsistencies corrected. Inconsistencies between Section 4.4, Section 7.3.1.5 and Section 7.1 revised. Section 7.1 Time and Events table: Un-intentional deletion of the ("x") were added to confirm that concomitant medications should be reviewed at every clinic visit was corrected. Increased the visit window. Typographical error and inconsistencies corrected as described in Appendix 9, Section 12.9. Section 7.2.2 Critical procedures performed at Screening (Visit 1): To clarify that height and weight are collected at Visit 1 "Height and weight" added. Section 7.3.2 Spirometry: "At Screening, before the morning dose of usual COPD. medication(s)" added. Section 7.3.7: Physical activity monitor (study subset). Inconsistency between Section 1, Section 4.1 and Section 7.3.7 revised.
21 February 2017	Amendment 2 : This protocol amendment was created to comply with Health Canada guidelines. They require pharmaceutical manufacturers to expeditiously report domestic cases of unusual failure in efficacy (UFIE) for new drugs to the Marketed Health Products Directorate (MHPD) within 15 days of first notification. Changes were made to Section 7.4.1 and Appendix 4.
18 April 2017	Amendment 3: Clarifications concerning study design, stratification, permitted and prohibited COPD medications, stopping criteria, visit windows, chest x-rays performed in the context of the protocol and site professional expertise. Rate of COPD exacerbations from tertiary endpoints to exploratory endpoints. Addition of an inclusion criterion specific to France. Integration of Canadian Amendment 2, Correction of typographical errors and inconsistencies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported