Clinical trial results:
A study to compare the addition of umeclidinium bromide (UMEC) to fluticasone furoate (FF)/vilanterol (VI), with placebo plus FF/VI in subjects with Chronic Obstructive Pulmonary Disease (COPD) -Study 2

Summary

EudraCT number	2013-002239-44
Trial protocol	DE CZ
Global end of trial date	21 April 2014

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	21 June 2015

Trial information

Trial identification

Sponsor protocol code	200110

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02119286
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, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	03 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the efficacy and safety of the addition of UMEC 125 mcg to FF/VI 100/25 mcg once-daily and the addition of UMEC 62.5 mcg to FF/VI 100/25 mcg once-daily, compared with placebo plus FF/VI 100/25 once-daily over 12 weeks in subjects with COPD.

Protection of trial subjects:

Spirometry procedures may cause difficulty breathing, changes in pulse rate/ blood pressure, coughing, wheezing, chest tightness, or fainting. Subjects (sub.) will be monitored during the procedure for these effects, and spirometry will be discontinued if they occur. Skin irritation is rare but could occur during ECG from the ECG electrodes. It may be necessary to have patches of hair on the chest shaved to properly attach electrodes. Sub. will be monitored during the procedure for these effects and should call their study doctor if effects do not resolve. Side effects of albuterol/salbutamol include shakiness, headache, sleeplessness, high blood pressure, heart beating fast/irregular beats, cough, wheezing, shortness of breath, increased fluid in the mouth, nausea, upset stomach, tiredness, anxiety/nervousness, or low blood potassium. Sub. should call their study doctor if they experience any of these symptoms. Sub. with poorly controlled COPD or who experience an exacerbation of COPD during the run-in period will not be randomized. ICS/LABA combination therapy is associated with an increased risk of pneumonia but no other significant side effects in COPD. Sub. with a lower respiratory tract infection that required antibiotics within 6 weeks prior to Visit 1 are excluded from the study in order to ensure safety. LABAs may increase the risk of asthma-related death. Sub. with a current diagnosis of asthma will be excluded from study participation. Cardiovascular (CV) effects such as cardiac arrhythmias, e.g., supraventricular tachycardia and extrasystoles, are also class effects associated with LABAs and LABA-containing therapy. Exclusion criteria have been set for sub. with uncontrolled or severe CV disease according to the PI’s opinion where the potential risk may outweigh the benefit. The Investigator should also determine the clinical significance of abnormal ECG findings at screening and exclude sub. who would be at undue risk by participating in the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 October 2013
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	Czech Republic: 97
Country: Number of subjects enrolled	Germany: 331
Country: Number of subjects enrolled	United States: 221
Country: Number of subjects enrolled	Korea, Republic of: 81
Worldwide total number of subjects	730
EEA total number of subjects	428

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)	405
From 65 to 84 years	321
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Participants ≥ 40 years of age with history of chronic obstructive pulmonary disease (COPD) and a smoking history of ≥ 10 pack-years were enrolled in the study. Participants completed a 4-week run-in period, in which they received fluticasone furoate 100 micrograms(µg)/vilanterol 25 µg, followed by a 12-week treatment period and a 1-week follow-up.

Pre-assignment

Screening details:

A total of 620 participants were randomized to study treatment. However, only 619 of these 620 participants compromised the Intent-to-Treat Population, defined as all participants randomized to treatment who received ≥ 1 dose of randomized study medication in the treatment period.

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	Fluticasone furoate/vilanterol 100/25 µg + placebo

Arm description:

Participants received one inhalation of fluticasone furoate/vilanterol 100/25 µg once-daily (OD) via a dry powder inhaler (DPI), followed by one inhalation of umeclidinium bromide (UMEC) matching placebo, administered via a dry powder inhaler in the morning for 12weeks. In addition, participants were provided supplemental albuterol/salbutamol inhalation aerosol to be used as needed throughout the study, for symptomatic relief from COPD symptoms.

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:

Matching placebo once daily

Investigational medicinal product name	Fluticasone furoate/vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone furoate/vilanterol 100/25 µg once daily

Arm title	Fluticasone furoate/vilanterol 100/25 µg + UMEC 62.5 µg

Arm description:

Participants received one inhalation of fluticasone furoate/vilanterol 100/25 µg once-daily via a dry powder inhaler followed by one inhalation of umeclidinium bromide (UMEC) 62.5 µg administered via a dry powder inhaler in the morning for 12 weeks. In addition, participants were provided supplemental albuterol/salbutamol inhalation aerosol to be used as needed throughout the study, for symptomatic relief from COPD symptoms.

Arm type	Experimental

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

Dosage and administration details:

Umeclidinium bromide 62.5 µg once daily

Investigational medicinal product name	Fluticasone furoate/vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone furoate/vilanterol 100/25 µg once daily

Arm title	Fluticasone furoate/vilanterol 100/25 µg + UMEC 125 µg

Arm description:

Participants received one inhalation of fluticasone furoate/vilanterol 100/25 µg once-daily via a dry powder inhaler followed by one inhalation of umeclidinium bromide 125 µg administered via a dry powder inhaler in the morning for 12 weeks. In addition, participants were provided supplemental albuterol/salbutamol inhalation aerosol to be used as needed throughout the study, for symptomatic relief from COPD symptoms.

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

Dosage and administration details:

Umeclidinium bromide 125 µg once daily

Investigational medicinal product name	Fluticasone furoate/vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone furoate/vilanterol 100/25 µg once daily

Number of subjects in period 1[1]	Fluticasone furoate/vilanterol 100/25 µg + placebo	Fluticasone furoate/vilanterol 100/25 µg + UMEC 62.5 µg	Fluticasone furoate/vilanterol 100/25 µg + UMEC 125 µg
Started	206	206	207
Completed	180	195	200
Not completed	26	11	7
Adverse event, serious fatal	4	4	-
Consent withdrawn by subject	4	1	-
Adverse event, non-fatal	5	3	2
Lost to follow-up	2	-	1
Lack of efficacy	11	3	4

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The baseline period includes only those enrolled participants who were randomized to treatment and received >=1 dose of randomized study medication in the Treatment Period (n=619).

Baseline characteristics

Reporting groups	
Reporting group title	Fluticasone furoate/vilanterol 100/25 µg + placebo
Reporting group description:	
Participants received one inhalation of fluticasone furoate/vilanterol 100/25 µg once-daily (OD) via a dry powder inhaler (DPI), followed by one inhalation of umeclidinium bromide (UMEC) matching placebo, administered via a dry powder inhaler in the morning for 12weeks. In addition, participants were provided supplemental albuterol/salbutamol inhalation aerosol to be used as needed throughout the study, for symptomatic relief from COPD symptoms.	
Reporting group title	Fluticasone furoate/vilanterol 100/25 µg + UMEC 62.5 µg
Reporting group description:	
Participants received one inhalation of fluticasone furoate/vilanterol 100/25 µg once-daily via a dry powder inhaler followed by one inhalation of umeclidinium bromide (UMEC) 62.5 µg administered via a dry powder inhaler in the morning for 12 weeks. In addition, participants were provided supplemental albuterol/salbutamol inhalation aerosol to be used as needed throughout the study, for symptomatic relief from COPD symptoms.	
Reporting group title	Fluticasone furoate/vilanterol 100/25 µg + UMEC 125 µg
Reporting group description:	
Participants received one inhalation of fluticasone furoate/vilanterol 100/25 µg once-daily via a dry powder inhaler followed by one inhalation of umeclidinium bromide 125 µg administered via a dry powder inhaler in the morning for 12 weeks. In addition, participants were provided supplemental albuterol/salbutamol inhalation aerosol to be used as needed throughout the study, for symptomatic relief from COPD symptoms.	

Reporting group values	Fluticasone furoate/vilanterol 100/25 µg + placebo	Fluticasone furoate/vilanterol 100/25 µg + UMEC 62.5 µg	Fluticasone furoate/vilanterol 100/25 µg + UMEC 125 µg
Number of subjects	206	206	207
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	62.6	62.6	63.4
standard deviation	± 9	± 8.12	± 7.49
Gender categorical			
Units: Subjects			
Female	81	71	76
Male	125	135	131
Race, Customized			
Units: Subjects			
African American/African Heritage	6	6	6
Asian - East Asian Heritage	19	25	25
White - White/Caucasian/European	180	174	176
Mixed Race	1	1	0

Reporting group values	Total		
Number of subjects	619		
Age categorical			
Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	228		
Male	391		
Race, Customized Units: Subjects			
African American/African Heritage	18		
Asian - East Asian Heritage	69		
White - White/Caucasian/European	530		
Mixed Race	2		

End points

End points reporting groups

Reporting group title	Fluticasone furoate/vilanterol 100/25 µg + placebo

Reporting group description:

Participants received one inhalation of fluticasone furoate/vilanterol 100/25 µg once-daily (OD) via a dry powder inhaler (DPI), followed by one inhalation of umeclidinium bromide (UMEC) matching placebo, administered via a dry powder inhaler in the morning for 12weeks. In addition, participants were provided supplemental albuterol/salbutamol inhalation aerosol to be used as needed throughout the study, for symptomatic relief from COPD symptoms.

Reporting group title	Fluticasone furoate/vilanterol 100/25 µg + UMEC 62.5 µg

Reporting group description:

Participants received one inhalation of fluticasone furoate/vilanterol 100/25 µg once-daily via a dry powder inhaler followed by one inhalation of umeclidinium bromide (UMEC) 62.5 µg administered via a dry powder inhaler in the morning for 12 weeks. In addition, participants were provided supplemental albuterol/salbutamol inhalation aerosol to be used as needed throughout the study, for symptomatic relief from COPD symptoms.

Reporting group title	Fluticasone furoate/vilanterol 100/25 µg + UMEC 125 µg

Reporting group description:

Participants received one inhalation of fluticasone furoate/vilanterol 100/25 µg once-daily via a dry powder inhaler followed by one inhalation of umeclidinium bromide 125 µg administered via a dry powder inhaler in the morning for 12 weeks. In addition, participants were provided supplemental albuterol/salbutamol inhalation aerosol to be used as needed throughout the study, for symptomatic relief from COPD symptoms.

Primary: Change from Baseline in trough forced expiratory volume in one second (FEV1) at Day 85

End point title	Change from Baseline in trough forced expiratory volume in one second (FEV1) at Day 85

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 on Day 85 is defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Day 84. Analysis was performed using a mixed model repeated measures (MMRM) with covariates of treatment, Baseline FEV1, smoking status, Day, treatment, Day by baseline interaction and Day by treatment interaction, Day being nominal. Baseline FEV1 is the mean of the two assessments made at 30 and 5 minutes (min) pre-dose on Day 1. The change from baseline value is the difference between the on-treatment value and the baseline value. The number of participants presented represent those with data available at the time point being presented; however, all participants in the Intent-to-Treat (ITT) Population without missing covariate information and with at least one post baseline measurement are included in the analysis.

End point type	Primary

End point timeframe:

Day 85

End point values	Fluticasone furoate/vilanterol 100/25 µg + placebo	Fluticasone furoate/vilanterol 100/25 µg + UMEC 62.5 µg	Fluticasone furoate/vilanterol 100/25 µg + UMEC 125 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179[1]	195[2]	199[3]	
Units: Liters				
least squares mean (standard error)	-0.03 (± 0.011)	0.092 (± 0.0107)	0.081 (± 0.0106)	

Notes:

[1] - Note: 205 subjects had analyzable data for one or more timepoints.

[2] - Note: 205 subjects had analyzable data for one or more timepoints.

[3] - Note: 206 subjects had analyzable data for one or more timepoints.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Fluticasone furoate/vilanterol 100/25 µg + UMEC 62.5 µg v Fluticasone furoate/vilanterol 100/25 µg + placebo
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	Mixed Model Repeated Measure
Parameter estimate	Least squared mean difference
Point estimate	0.122
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.091
upper limit	0.152

Notes:

[4] - Restricted maximum likelihood (REM) – based repeated measure approach (MMRM)

Statistical analysis title	Statistical Analysis 2
Comparison groups	Fluticasone furoate/vilanterol 100/25 µg + placebo v Fluticasone furoate/vilanterol 100/25 µg + UMEC 125 µg
Number of subjects included in analysis	378
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001 [6]
Method	Mixed Model Repeated Measure
Parameter estimate	Least squared mean difference
Point estimate	0.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.081
upper limit	0.141

Notes:

[5] - The data presented in this table is showing the comparison of Fluticasone furoate/vilanterol 100/25 µg + UMEC 125 µg v Fluticasone furoate/vilanterol 100/25 µg + placebo

[6] - Restricted maximum likelihood (REM) – based repeated measure approach (MMRM)

Secondary: Change from Baseline in 0-6 hour weighted mean (WM) FEV1 obtained post-dose at Day 84

End point title	Change from Baseline in 0-6 hour weighted mean (WM) FEV1 obtained post-dose at Day 84

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 0-6 hour weighted mean was derived by calculating the area under the FEV1/time curve over the nominal time points of 0 hour (trough value), 15 and 30 min, 1, 3 and 6 hours, using the trapezoidal rule, and then dividing by the actual time between dosing and the 6 hour assessment. Analysis was performed using MMRM with covariates of treatment, Baseline FEV1 (mean of the two assessments made 30 minutes and 5 minutes pre-dose on Day 1), smoking status, Day, and Day by Baseline and Day by treatment interactions. Baseline FEV1 is the mean of the two assessments made at 30 and 5 min pre-dose on Day 1. The change from baseline value is the difference between the on-treatment value and the baseline value. All participants in the ITT Population without missing covariate information and with at least one post baseline measurement are included in the analysis.

End point type	Secondary
End point timeframe:	
Day 84	

End point values	Fluticasone furoate/vilanterol 100/25 µg + placebo	Fluticasone furoate/vilanterol 100/25 µg + UMEC 62.5 µg	Fluticasone furoate/vilanterol 100/25 µg + UMEC 125 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180[7]	195[8]	199[9]	
Units: Liters				
least squares mean (standard error)	0.017 (± 0.0118)	0.164 (± 0.0115)	0.152 (± 0.0114)	

Notes:

[7] - Note: 205 subjects had analyzable data for one or more timepoints.

[8] - Note: 206 subjects had analyzable data for one or more timepoints..

[9] - Note: 206 subjects had analyzable data for one or more timepoints.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Fluticasone furoate/vilanterol 100/25 µg + placebo v Fluticasone furoate/vilanterol 100/25 µg + UMEC 62.5 µg
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	< 0.001 [11]
Method	Mixed Model Repeated Measure
Parameter estimate	Least squared mean difference
Point estimate	0.147
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.114
upper limit	0.179

Notes:

[10] - The data presented in this table is showing the comparison of Fluticasone furoate/vilanterol 100/25 µg + UMEC 62.5 µg v Fluticasone furoate/vilanterol 100/25 µg + placebo

[11] - Restricted maximum likelihood (REM) – based repeated measure approach (MMRM)

Statistical analysis title	Statistical Analysis 2
Comparison groups	Fluticasone furoate/vilanterol 100/25 µg + placebo v Fluticasone furoate/vilanterol 100/25 µg + UMEC 125 µg

Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.001 [13]
Method	Mixed Model Repeated Measure
Parameter estimate	Least squared mean difference
Point estimate	0.135
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.103
upper limit	0.167

Notes:

[12] - The data presented in this table is showing the comparison of Fluticasone furoate/vilanterol 100/25 µg + UMEC 125 µg v Fluticasone furoate/vilanterol 100/25 µg + placebo

[13] - Restricted maximum likelihood (REM) – based repeated measure approach (MMRM)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from start of study medication until follow-up visit (up to 14 weeks)

Adverse event reporting additional description:

On-treatment SAEs and non-serious AEs are reported for members of the ITT Population, comprised of all participants randomized to treatment who received at least one dose of randomized study medication in the treatment period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Fluticasone furoate/vilanterol 100/25 µg + placebo

Reporting group description:

Participants received one inhalation of fluticasone furoate/vilanterol 100/25 µg once-daily (OD) via a dry powder inhaler (DPI), followed by one inhalation of umeclidinium bromide (UMEC) matching placebo, administered via a dry powder inhaler in the morning for 12weeks. In addition, participants were provided supplemental albuterol/salbutamol inhalation aerosol to be used as needed throughout the study, for symptomatic relief from COPD symptoms.

Reporting group title	Fluticasone furoate/vilanterol 100/25 µg + UMEC 62.5 µg

Reporting group description:

Participants received one inhalation of fluticasone furoate/vilanterol 100/25 µg once-daily via a dry powder inhaler followed by one inhalation of umeclidinium bromide (UMEC) 62.5 µg administered via a dry powder inhaler in the morning for 12 weeks. In addition, participants were provided supplemental albuterol/salbutamol inhalation aerosol to be used as needed throughout the study, for symptomatic relief from COPD symptoms.

Reporting group title	Fluticasone furoate/vilanterol 100/25 µg + UMEC 125 µg

Reporting group description:

Participants received one inhalation of fluticasone furoate/vilanterol 100/25 µg once-daily via a dry powder inhaler followed by one inhalation of umeclidinium bromide 125 µg administered via a dry powder inhaler in the morning for 12 weeks. In addition, participants were provided supplemental albuterol/salbutamol inhalation aerosol to be used as needed throughout the study, for symptomatic relief from COPD symptoms.

Serious adverse events	Fluticasone furoate/vilanterol 100/25 µg + placebo	Fluticasone furoate/vilanterol 100/25 µg + UMEC 62.5 µg	Fluticasone furoate/vilanterol 100/25 µg + UMEC 125 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 206 (5.34%)	8 / 206 (3.88%)	3 / 207 (1.45%)
number of deaths (all causes)	4	4	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm			

subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	0 / 207 (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			
Femur fracture			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	0 / 207 (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
Humerus fracture			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 207 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 207 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 207 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial infarction			
subjects affected / exposed	3 / 206 (1.46%)	2 / 206 (0.97%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 0

Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 206 (0.49%)	0 / 206 (0.00%)	0 / 207 (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
Cervicobrachial syndrome			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 206 (1.46%)	3 / 206 (1.46%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	1 / 3	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal aneurysm			
subjects affected / exposed	0 / 206 (0.00%)	0 / 206 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 206 (0.00%)	1 / 206 (0.49%)	0 / 207 (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
Pneumonia			
subjects affected / exposed	1 / 206 (0.49%)	2 / 206 (0.97%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

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

Non-serious adverse events	Fluticasone furoate/vilanterol 100/25 µg + placebo	Fluticasone furoate/vilanterol 100/25 µg + UMEC 62.5 µg	Fluticasone furoate/vilanterol 100/25 µg + UMEC 125 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 206 (13.59%)	23 / 206 (11.17%)	22 / 207 (10.63%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 206 (2.43%)	8 / 206 (3.88%)	4 / 207 (1.93%)
occurrences (all)	6	10	5
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 206 (1.94%)	8 / 206 (3.88%)	2 / 207 (0.97%)
occurrences (all)	7	8	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	22 / 206 (10.68%)	11 / 206 (5.34%)	19 / 207 (9.18%)
occurrences (all)	23	12	19

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported