Clinical trial results:
Study DB2116961, A Multicentre, Randomised, Blinded, Parallel Group Study to Compare UMEC/VI (Umeclidinium/Vilanterol) in a Fixed Dose Combination With Indacaterol Plus Tiotropium in Symptomatic Subjects With Moderate to Very Severe COPD

Summary

EudraCT number	2013-001827-38
Trial protocol	DE IT RO HU SK PL EE
Global end of trial date	04 May 2015

Results information

Result version number	v1 (current)
This version publication date	06 April 2016
First version publication date	06 April 2016

Trial information

Trial identification

Sponsor protocol code	116961

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
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	29 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to demonstrate that Umeclidinium/Vilanterol (UMEC/VI), when used in symptomatic moderate to very severe chronic obstructive pulmonary disorder (COPD) subjects, is non-inferior to the combination of indacaterol plus tiotropium, as measured by trough forced expiratory volume in 1 second (FEV1) on treatment day 85 (Visit 8).

Protection of trial subjects:

To protect trial subjects only approved standard of care COPD medications were evaluated and subjects were not exposed to placebo-only treatment. Additionally, study subjects were provided with supplemental salbuterol as rescue medication and the use of inhaled corticosteroids was allowed as a concurrent medication.

Subjects enrolled into the study had stable disease with no hospitalization for COPD within at least 12 weeks of screening and no use of systemic corticosteroids or antibiotics for a lower respiratory tract infection for at least 6 weeks prior to screening.

Frequent assessment of adverse events and COPD exacerbations was obtained during the study at clinic visits conducted 1 day following the first dose of study medication and every 2 to 4 weeks thereafter to ensure patient safety was closely monitored. Vital signs were monitored prior to study enrollment and at the study conclusion. Subjects were allowed to withdraw from the study at any point without giving a reason, and without affecting their continued medical care.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 October 2014
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: 109
Country: Number of subjects enrolled	Chile: 74
Country: Number of subjects enrolled	Estonia: 39
Country: Number of subjects enrolled	France: 54
Country: Number of subjects enrolled	Germany: 200
Country: Number of subjects enrolled	Hungary: 121
Country: Number of subjects enrolled	Italy: 43
Country: Number of subjects enrolled	Peru: 80
Country: Number of subjects enrolled	Poland: 100
Country: Number of subjects enrolled	Romania: 108
Country: Number of subjects enrolled	Russian Federation: 203

Country: Number of subjects enrolled	Slovakia: 59
Worldwide total number of subjects	1190
EEA total number of subjects	724

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)	606
From 65 to 84 years	580
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Eligible participants (par) completed a 5-7 day run-in period, and were randomized to blinded study medication for 12 weeks. Supplemental albuterol/salbutamol was provided to all par, to be used on an as-needed basis during run-in and up to Day 85.

Pre-assignment

Screening details:

A total of 1190 par were screened; 967 par randomized and 961 par comprised the Intent-to-Treat (ITT) Population (Pop), comprised of all par randomized to treatment (trt) who received at least 1 dose of randomized study medication in the trt 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

Arms

Are arms mutually exclusive?	Yes
Arm title	Umeclidinium/Vilanterol 62.5/25 µg

Arm description:

Participants self-administered one dose each morning from each of the following three inhalers for 12 weeks: ELLIPTA dry powder inhaler containing umeclidinium/vilanterol inhalation powder 62.5/25 micrograms (µg), BREEZHALER containing placebo, and HANDIHALER containing placebo. Each inhaler containing placebo was identical in appearance to its corresponding inhaler containing active study medication.

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

Dosage and administration details:

One dose of Umeclidinium/Vilanterol 62.5/25 mcg every morning for 12 weeks, via the ELLIPTA dry powder inhaler

Investigational medicinal product name	Placebo matching Umeclidinium/Vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of placebo (lactose blended with magnesium stearate) every morning for 12 weeks, via the ELLIPTA dry powder inhaler

Arm title	Indacaterol 150 µg + Tiotropium bromide 18 µg

Arm description:

Participants self-administered one dose each morning from each of the following three inhalers for 12 weeks: ELLIPTA dry powder inhaler containing placebo, BREEZHALER containing indacaterol 150 µg, and HANDIHALER containing tiotropium bromide 18 µg. The inhaler containing placebo was identical in appearance to its corresponding inhaler containing active study medication.

Arm type	Active comparator

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

Dosage and administration details:

One dose of Indacaterol 150 mcg every morning for 12 weeks, via the BREEZHALER

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

Dosage and administration details:

One dose of Tiotropium bromide 18 mcg every morning for 12 weeks, via the HANDIHALER

Investigational medicinal product name	Placebo matching Indacaterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of placebo (lactose) every morning for 12 weeks, via the BREEZHALER

Investigational medicinal product name	Placebo matching Tiotropium bromide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of placebo (lactose) every morning for 12 weeks, via the HANDIHALER

Number of subjects in period 1[1]	Umeclidinium/Vilanterol 62.5/25 µg	Indacaterol 150 µg + Tiotropium bromide 18 µg
Started	482	479
Completed	460	457
Not completed	22	22
Adverse event, serious fatal	4	1
Consent withdrawn by subject	4	4
Adverse event, non-fatal	8	7
Lost to follow-up	-	1
Lack of efficacy	1	2
Protocol deviation	5	7

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: A total of 1190 par were screened; 967 par randomized and 961 par comprised the Intent-to-Treat (ITT) Population (Pop), comprised of all par randomized to treatment (trt) who received at least 1 dose of randomized study medication in the trt period.

Baseline characteristics

Reporting groups	
Reporting group title	Umeclidinium/Vilanterol 62.5/25 µg
Reporting group description:	
Participants self-administered one dose each morning from each of the following three inhalers for 12 weeks: ELLIPTA dry powder inhaler containing umeclidinium/vilanterol inhalation powder 62.5/25 micrograms (µg), BREEZHALER containing placebo, and HANDIHALER containing placebo. Each inhaler containing placebo was identical in appearance to its corresponding inhaler containing active study medication.	
Reporting group title	Indacaterol 150 µg + Tiotropium bromide 18 µg
Reporting group description:	
Participants self-administered one dose each morning from each of the following three inhalers for 12 weeks: ELLIPTA dry powder inhaler containing placebo, BREEZHALER containing indacaterol 150 µg, and HANDIHALER containing tiotropium bromide 18 µg. The inhaler containing placebo was identical in appearance to its corresponding inhaler containing active study medication.	

Reporting group values	Umeclidinium/Vilanterol 62.5/25 µg	Indacaterol 150 µg + Tiotropium bromide 18 µg	Total
Number of subjects	482	479	961
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	64.4	64	
standard deviation	± 7.75	± 8.44	-
Gender categorical Units: Subjects			
Female	127	138	265
Male	355	341	696
Race Units: Subjects			
American Indian or Alaska Native	24	27	51
Asian - Central/South Asian Heritage	1	0	1
Asian - East Asian Heritage	0	1	1
Asian - Japanese Heritage	4	1	5
White - Arabic/North African Heritage	0	1	1
White -White/Caucasian/European Heritage	453	449	902

End points

End points reporting groups

Reporting group title	Umeclidinium/Vilanterol 62.5/25 µg

Reporting group description:

Participants self-administered one dose each morning from each of the following three inhalers for 12 weeks: ELLIPTA dry powder inhaler containing umeclidinium/vilanterol inhalation powder 62.5/25 micrograms (µg), BREEZHALER containing placebo, and HANDIHALER containing placebo. Each inhaler containing placebo was identical in appearance to its corresponding inhaler containing active study medication.

Reporting group title	Indacaterol 150 µg + Tiotropium bromide 18 µg

Reporting group description:

Participants self-administered one dose each morning from each of the following three inhalers for 12 weeks: ELLIPTA dry powder inhaler containing placebo, BREEZHALER containing indacaterol 150 µg, and HANDIHALER containing tiotropium bromide 18 µg. The inhaler containing placebo was identical in appearance to its corresponding inhaler containing active study medication.

Primary: Change from Baseline in trough forced expiratory volume in one second (FEV1) on Treatment Day 85 (Visit 8)

End point title	Change from Baseline in trough forced expiratory volume in one second (FEV1) on Treatment Day 85 (Visit 8)

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 1 second. BL was the mean of the 2 assessments made 30 and 5 minutes (min) pre-dose (PD) on Day 1. Trough FEV1 measurements were taken electronically by spirometry on Days 2, 28, 56, 84 and 85. Trough FEV1 on Day 85 is defined as the mean of the FEV1 values obtained at 23 and 24 hours (hr) after dosing on Day 84 (at Week 12 + 1 day). Analysis was performed using mixed model repeated measures (RM) with covariates of trt, BL FEV1 (mean of values measured at 30 and 5 min PD on Day 1), center group, day, day by BL interaction and day by trt interaction, where day was nominal. Per Protocol (PP) Pop: all ITT Pop par who were not full protocol deviators considered to impact efficacy. Only par with data available at the specified time points (TP) were analyzed but all par without (w/o) missing covariate information and with >= 1 post BL measurement were included in the analysis.

End point type	Primary

End point timeframe:

Baseline (BL) and Day 85

End point values	Umeclidinium/ Vilanterol 62.5/25 µg	Indacaterol 150 µg + Tiotropium bromide 18 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	392[1]	392[2]		
Units: Liters				
least squares mean (standard error)	0.172 (± 0.0107)	0.171 (± 0.0108)		

Notes:

[1] - PP Population

[2] - PP Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Umeclidinium/Vilanterol 62.5/25 µg v Indacaterol 150 µg + Tiotropium bromide 18 µg
Number of subjects included in analysis	784
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.964
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.029
upper limit	0.03

Notes:

[3] - Alternate hypothesis:the difference between the trt means (umeclidinium/vilanterol minus indacaterol + tiotropium bromide) would be > -50 milliliters (mL). If the lower CI (2.5% 1-sided significance level) of the statistical test should fall above -50 mL, then umeclidinium/vilanterol may be deemed statistically non-inferior to indacaterol plus tiotropium. If the lower CI (2.5% 1-sided significance) of the statistical testing exceeded 0 then, statistical superiority would have been established.

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

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

End point description:

BL FEV1 was the mean of the 2 assessments made 30 and 5 min PD on Day 1. WM FEV1 derived by calculating the area under the FEV1/time curve (AUC) using the trapezoidal rule, and then dividing the value by the time interval over which the AUC was calculated. The WM was calculated at Days 1 and 84 using the 0-6 hr post-dose FEV1 measurements collected on that day, which included PD FEV1 (taken 30 and 5 min prior to dosing on Day 1 and the 30 and 5 min reading prior to dosing on Day 84) and post-dose FEV1 measurements at 1, 3 and 6 hr post-dose.WM change from BL was the WM at at the visit minus the BL value. Analysis was performed using a RM model with covariates of trt, BL FEV1 (mean of values measured at 30 and 5 min PD on Day 1) center group, day, day by BL and day by trt interaction, where day was nominal. Only par with data available at the specified TP were analyzed but all par w/o missing covariate information and with >=1 post-BL measurement were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Day 84

End point values	Umeclidinium/ Vilanterol 62.5/25 µg	Indacaterol 150 µg + Tiotropium bromide 18 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	455[4]	452[5]		
Units: Liters				
least squares mean (standard error)	0.235 (± 0.0111)	0.258 (± 0.0111)		

Notes:
[4] - ITT Population
[5] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 2
Comparison groups	Umeclidinium/Vilanterol 62.5/25 µg v Indacaterol 150 µg + Tiotropium bromide 18 µg
Number of subjects included in analysis	907
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.145
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.023
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.054
upper limit	0.008

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected over a period of a maximum of 96 days starting from Day 1 of treatment until the follow-up contact.

Adverse event reporting additional description:

On-treatment SAEs and non-serious AEs were 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	18

Reporting groups

Reporting group title	Indacaterol 150 µg + Tiotropium bromide 18 µg

Reporting group description:

Participants self-administered one dose each morning from each of the following three inhalers for 12 weeks: ELLIPTA dry powder inhaler containing placebo, BREEZHALER containing indacaterol 150 µg, and HANDIHALER containing tiotropium bromide 18 µg. The inhaler containing placebo was identical in appearance to its corresponding inhaler containing active study medication.

Reporting group title	Umeclidinium/Vilanterol 62.5/25 µg

Reporting group description:

Participants self-administered one dose each morning from each of the following three inhalers for 12 weeks: ELLIPTA dry powder inhaler containing umeclidinium/vilanterol inhalation powder 62.5/25 micrograms (µg), BREEZHALER containing placebo, and HANDIHALER containing placebo. Each inhaler containing placebo was identical in appearance to its corresponding inhaler containing active study medication.

Serious adverse events	Indacaterol 150 µg + Tiotropium bromide 18 µg	Umeclidinium/Vilanterol 62.5/25 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 479 (3.34%)	21 / 482 (4.36%)	
number of deaths (all causes)	4	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer			
subjects affected / exposed	0 / 479 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 479 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the oral cavity			
subjects affected / exposed	0 / 479 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 479 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 479 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral artery thrombosis			

subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 479 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
alternative dictionary used: Angina pectoris Angina pe			
subjects affected / exposed	0 / 479 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 479 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 479 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac failure			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Coronary artery disease			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 479 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	0 / 479 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 479 (0.63%)	6 / 482 (1.24%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 479 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	0 / 479 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 479 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 479 (0.42%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Gastroenteritis			

subjects affected / exposed	0 / 479 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 479 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Indacaterol 150 µg + Tiotropium bromide 18 µg	Umeclidinium/Vilanterol 62.5/25 µg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 479 (13.57%)	76 / 482 (15.77%)	
Nervous system disorders			
Headache			
subjects affected / exposed	28 / 479 (5.85%)	36 / 482 (7.47%)	
occurrences (all)	60	56	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 479 (3.55%)	16 / 482 (3.32%)	
occurrences (all)	18	18	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	27 / 479 (5.64%)	32 / 482 (6.64%)	
occurrences (all)	31	34	

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