Clinical trial results:
A Phase IV, 12 week, randomised, double-blind, double-dummy study to compare single inhaler triple therapy, fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI), with tiotropium monotherapy based on lung function and symptoms in participants with chronic obstructive pulmonary disease

Summary

EudraCT number	2017-001190-16
Trial protocol	PL
Global end of trial date	17 July 2019

Results information

Result version number	v1 (current)
This version publication date	22 April 2020
First version publication date	22 April 2020

Trial information

Trial identification

Sponsor protocol code	207626

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	30 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of single inhaler triple therapy (FF/UMEC/VI) compared to Tiotropium after 12 weeks of treatment on lung function

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 March 2018
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	Poland: 400
Country: Number of subjects enrolled	Russian Federation: 198
Country: Number of subjects enrolled	United States: 202
Worldwide total number of subjects	800
EEA total number of subjects	400

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)	321
From 65 to 84 years	473
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

This was a randomized, multicenter, parallel group study where participants with chronic obstructive pulmonary disease (COPD) were randomized to receive either fluticasone furoate/umeclidinium/vilanterol or tiotropium in a 1:1 ratio. The study was conducted across 68 centers in 3 countries.

Pre-assignment

Screening details:

A total of 1049 participants were screened, of which 179 failed screening. Total of 870 participants entered in run-in period, of which 70 were run-in failures. Total of 800 participants were enrolled and randomized.

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	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg

Arm description:

Participants received fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100/62.5/25 microgram (mcg) via the ELLIPTA (once daily in the morning) plus placebo to match tiotropium (TIO) via HandiHaler (once daily in the morning) for 84 days. Participants received albuterol/salbutamol as rescue medication via metered dose inhaler (MDI) during conduct of the study, if required.

Arm type	Experimental
Investigational medicinal product name	Fluticasone furoate/Umeclidinium/Vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone furoate/Umeclidinium/Vilanterol (100/62.5/25 mcg) was available as dry white powder to be administered via ELLIPTA once daily in the morning.

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

Dosage and administration details:

Placebo matching tiotropium was available as hard gelatin capsule containing lactose. Participants received placebo matching tiotropium once daily in the morning via HandiHaler device.

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 short acting Albuterol/Salbutamol as rescue medication during the study period, if required.

Arm title	Tiotropium 18 mcg

Arm description:

Participants received tiotropium 18 mcg via HandiHaler (once daily in the morning) plus placebo to match fluticasone furoate/umeclidinium/vilanterol via the ELLIPTA (once daily in the morning) for 84 days. Participants received albuterol/salbutamol as rescue medication via MDI during conduct of the study, if required.

Arm type	Active comparator
Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium was available as a hard gelatin capsule containing 18 mcg of tiotropium bromide blended with lactose. Participants received tiotropium (18 mcg) once daily in the morning via HandiHaler device.

Investigational medicinal product name	Placebo to match Fluticasone furoate/Umeclidinium/Vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Placebo matching Fluticasone furoate/Umeclidinium/Vilanterol was available as dry white powder to be administered 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 short acting Albuterol/Salbutamol as rescue medication during the study period, if required.

Number of subjects in period 1	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg	Tiotropium 18 mcg
Started	400	400
Received study treatment	400	399
Completed	383	387
Not completed	17	13
Adverse event, serious fatal	1	1
Physician decision	3	2
Consent withdrawn by subject	5	7
Investigator site closed	1	-
Adverse event, non-fatal	5	2
Lost to follow-up	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg
Reporting group description:	
Participants received fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100/62.5/25 microgram (mcg) via the ELLIPTA (once daily in the morning) plus placebo to match tiotropium (TIO) via HandiHaler (once daily in the morning) for 84 days. Participants received albuterol/salbutamol as rescue medication via metered dose inhaler (MDI) during conduct of the study, if required.	
Reporting group title	Tiotropium 18 mcg
Reporting group description:	
Participants received tiotropium 18 mcg via HandiHaler (once daily in the morning) plus placebo to match fluticasone furoate/umeclidinium/vilanterol via the ELLIPTA (once daily in the morning) for 84 days. Participants received albuterol/salbutamol as rescue medication via MDI during conduct of the study, if required.	

Reporting group values	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg	Tiotropium 18 mcg	Total
Number of subjects	400	400	800
Age categorical Units: Subjects			
Total participants	400	400	800
Age Continuous Units: Years			
arithmetic mean	66.2	66.1	
standard deviation	± 8.08	± 7.78	-
Sex: Female, Male Units: Participants			
Female	126	131	257
Male	274	269	543
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	10	12	22
White - White/Caucasian/European Heritage	390	388	778

End points

End points reporting groups

Reporting group title	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg

Reporting group description:

Participants received fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100/62.5/25 microgram (mcg) via the ELLIPTA (once daily in the morning) plus placebo to match tiotropium (TIO) via HandiHaler (once daily in the morning) for 84 days. Participants received albuterol/salbutamol as rescue medication via metered dose inhaler (MDI) during conduct of the study, if required.

Reporting group title	Tiotropium 18 mcg

Reporting group description:

Participants received tiotropium 18 mcg via HandiHaler (once daily in the morning) plus placebo to match fluticasone furoate/umeclidinium/vilanterol via the ELLIPTA (once daily in the morning) for 84 days. Participants received albuterol/salbutamol as rescue medication via MDI during conduct of the study, if required.

Primary: Change from Baseline in trough forced expiratory volume in 1 second (FEV1) on Day 85

End point title	Change from Baseline in trough forced expiratory volume in 1 second (FEV1) on 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 was defined as the mean of the two planned spirometry FEV1 measurements. Change from Baseline in trough FEV1 on Day 85 was calculated by subtracting Baseline FEV1 value from the trough FEV1 value on Day 85. Baseline FEV1 was defined as the mean of the two assessments made at 30 and 5 minutes pre-dose on Day 1. Intent-To-Treat (ITT) Population comprised of all randomized participants, excluding those who were randomized in error. Only those participants with data available at the specified time point were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1 [Pre-dose at 30 minutes and 5 minutes]) and Day 85

End point values	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg	Tiotropium 18 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362[1]	375[2]		
Units: Liters				
least squares mean (standard error)	0.115 (± 0.0119)	0.020 (± 0.0117)		

Notes:

[1] - ITT Population

[2] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg v Tiotropium 18 mcg

Number of subjects included in analysis	737
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (net)
Point estimate	0.095
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.062
upper limit	0.128
Variability estimate	Standard error of the mean
Dispersion value	0.0167

Notes:

[3] - The MMRM model included Baseline FEV1, visit, geographical region, and treatment as covariates and visit-by-Baseline FEV1 and visit-by-treatment interaction terms.

Secondary: Change from Baseline in trough FEV1 on Day 28

End point title	Change from Baseline in trough FEV1 on Day 28

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 28 was defined as the average of the two pre-dose FEV1 measurements recorded before the morning dose of randomized study medication on Day 28. Change from Baseline in trough FEV1 on Day 28 was calculated by subtracting Baseline FEV1 value from the trough FEV1 value on Day 28. Baseline FEV1 was defined as the mean of the two assessments made at 30 and 5 minutes pre-dose on Day 1. Only those participants with data available at the specified time point were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1 [Pre-dose at 30 minutes and 5 minutes]) and Day 28

End point values	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg	Tiotropium 18 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	385[4]	390[5]		
Units: Liters				
least squares mean (standard error)	0.115 (± 0.0102)	-0.007 (± 0.0101)		

Notes:

[4] - ITT Population

[5] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg v Tiotropium 18 mcg

Number of subjects included in analysis	775
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (net)
Point estimate	0.122
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.094
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	0.0144

Notes:

[6] - The MMRM model included Baseline FEV1, visit, geographical region, and treatment as covariates and visit-by-Baseline FEV1 and visit-by-treatment interaction terms.

Secondary: Change from Baseline in trough FEV1 on Day 84

End point title	Change from Baseline in trough FEV1 on 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. Trough FEV1 on Day 84 was defined as the average of the two pre-dose FEV1 measurements recorded before the morning dose of randomized study medication on Day 84. Change from Baseline in trough FEV1 on Day 84 was calculated by subtracting Baseline FEV1 value from the trough FEV1 value on Day 84. Baseline FEV1 was defined as the mean of the two assessments made at 30 and 5 minutes pre-dose on Day 1. Only those participants with data available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1 [Pre-dose at 30 minutes and 5 minutes]) and Day 84

End point values	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg	Tiotropium 18 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376[7]	386[8]		
Units: Liters				
least squares mean (standard error)	0.105 (± 0.0113)	0.018 (± 0.0111)		

Notes:

[7] - ITT Population

[8] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg v Tiotropium 18 mcg

Number of subjects included in analysis	762
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (net)
Point estimate	0.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.056
upper limit	0.118
Variability estimate	Standard error of the mean
Dispersion value	0.0159

Notes:

[9] - The MMRM model included Baseline FEV1, visit, geographical region, and treatment as covariates and visit-by-Baseline FEV1 and visit-by-treatment interaction terms.

Secondary: Number of participants with non-serious adverse events (non-SAEs) and serious adverse events (SAEs)

End point title	Number of participants with non-serious adverse events (non-SAEs) and serious adverse events (SAEs)

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. Any untoward event resulting in death, life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, congenital anomaly/birth defect or any other important medical event according to medical or scientific judgement was categorized as SAE. Non-SAEs and SAEs were presented for all randomized participants excluding one participant in ITT population who was randomized correctly to "Tiotropium 18 mcg" arm but did not take any randomized study treatment due to withdrawal of consent.

End point type	Secondary

End point timeframe:

Up to Day 95

End point values	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg	Tiotropium 18 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	400[10]	399[11]		
Units: Participants				
Non-SAEs	31	29		
SAEs	13	11		

Notes:

[10] - ITT Population

[11] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP)

End point title	Change from Baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP)

End point description:

SBP and DBP were assessed in the sitting position after approximately 5 minutes rest. Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-first-dose assessment with a non-missing value, including those from unscheduled visits. Only those participants with data available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1, Pre-dose) and Day 84

End point values	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg	Tiotropium 18 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387[12]	392[13]		
Units: Millimeters of mercury				
arithmetic mean (standard deviation)				
SBP	-0.3 (± 12.53)	-0.1 (± 11.02)		
DBP	-0.3 (± 8.17)	-0.7 (± 7.88)		

Notes:

[12] - ITT Population

[13] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in pulse rate

End point title	Change from Baseline in pulse rate

End point description:

Pulse rate was assessed in the sitting position after approximately 5 minutes rest. Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value. Baseline was defined as the latest pre-first-dose assessment with a non-missing value, including those from unscheduled visits. Only those participants with data available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1, Pre-dose) and Day 84

End point values	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg	Tiotropium 18 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387[14]	392[15]		
Units: Beats per minute				
arithmetic mean (standard deviation)	0.2 (± 8.55)	0.8 (± 8.51)		

Notes:

[14] - ITT Population

[15] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Non-SAEs and SAEs were reported from start of study treatment and up to 95 days

Adverse event reporting additional description:

Non-SAEs and SAEs were presented for all randomized participants excluding one randomized participant who withdrew consent and never received study treatment in "Tiotropium 18 mcg" arm. Adverse events were presented treatment-wise.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg

Reporting group description:

Participants received fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100/62.5/25 microgram (mcg) via the ELLIPTA (once daily in the morning) plus placebo to match tiotropium (TIO) via HandiHaler (once daily in the morning) for 84 days. Participants received albuterol/salbutamol as rescue medication via metered dose inhaler (MDI) during conduct of the study, if required.

Reporting group title	Tiotropium 18 mcg

Reporting group description:

Participants received tiotropium 18 mcg via HandiHaler (once daily in the morning) plus placebo to match fluticasone furoate/umeclidinium/vilanterol via the ELLIPTA (once daily in the morning) for 84 days. Participants received albuterol/salbutamol as rescue medication via MDI during conduct of the study, if required.

Serious adverse events	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg	Tiotropium 18 mcg	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 400 (3.25%)	11 / 399 (2.76%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events			
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 400 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 400 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			

subjects affected / exposed	1 / 400 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Haemorrhagic stroke			
subjects affected / exposed	0 / 400 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic stroke			
subjects affected / exposed	0 / 400 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 400 (0.25%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 400 (0.25%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 400 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 400 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	1 / 400 (0.25%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	5 / 400 (1.25%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 400 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 400 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 400 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 400 (0.25%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 400 (0.25%)	0 / 399 (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			
Diabetes mellitus inadequate control			

subjects affected / exposed	0 / 400 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg	Tiotropium 18 mcg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 400 (7.75%)	29 / 399 (7.27%)	
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 400 (4.50%)	22 / 399 (5.51%)	
occurrences (all)	30	69	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 400 (4.00%)	8 / 399 (2.01%)	
occurrences (all)	17	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2018	This amendment was required to update the QT interval corrected for heart rate (QTc) stopping criteria to that which was used in the Phase III Trelegy registration studies. In addition, a section describing Smoking Cessation Counselling has been added as does a corresponding assessment at the end of study (Visit 4). Clarified that run-in treatment should be collected at Visit 2, study treatment at Visit 3, and albuterol/salbutamol at Visit 5. Also, wording regarding suggested order for assessments and procedures has been added to the end of the Schedule of Activities section. Removed reference to Fridericia formula in calculation of QTc. Clarification regarding collecting the COPD Assessment Test (CAT) assessment questionnaire prior to the St. George's Respiratory Questionnaire for COPD participants (SGRQ-C) has also been provided along with clarification that vital signs should be collected before the electrocardiogram (ECG) and prior to spirometry. Also added clarification that CAT and SGRQ-C should be collected at Visit 3 to mirror the Schedule of Activities (SoA). Corrected reporting time regarding pregnancy. Finally, added wording to Genetics Appendix regarding withdraw process and sample destruction process.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported