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

Summary

EudraCT number	2017-001149-28
Trial protocol	DE CZ NL
Global end of trial date	14 March 2019

Results information

Result version number	v1 (current)
This version publication date	01 February 2020
First version publication date	01 February 2020

Trial information

Trial identification

Sponsor protocol code	207608

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	31 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on lung function

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 June 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	Germany: 71
Country: Number of subjects enrolled	Czech Republic: 85
Country: Number of subjects enrolled	Netherlands: 24
Country: Number of subjects enrolled	United States: 548
Worldwide total number of subjects	728
EEA total number of subjects	180

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)	330
From 65 to 84 years	397

85 years and over	1

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 budesonide/formoterol plus tiotropium in a 1:1 ratio. The study was conducted across 65 centers in 4 countries.

Pre-assignment

Screening details:

A total of 1036 participants were screened in the study, of which 215 failed during screening. Of the 821 participants who entered the run-in period, 92 were run-in failures. A total of 729 participants were randomized in the study, of which one participant was randomized in error. A total of 728 participants received randomized treatment.

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, Monitor, Carer, Data analyst, Subject, Assessor

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 budesonide/formoterol (BUD/FOR) via metered dose inhaler (MDI) (two inhalations twice daily) plus placebo to match tiotropium (TIO) via HandiHaler (once daily in the morning) for 84 days. Participants received albuterol/salbutamol as rescue medication 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 Budesonide/Formoterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

Participants received two inhalations of placebo matching Budesonide/Formoterol via MDI twice daily.

Investigational medicinal product name	Placebo matching Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
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	Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg

Arm description:

Participants received two inhalations of budesonide/formoterol 160/4.5 mcg via MDI in the morning and two inhalations in the evening (total dose of 320/9 mcg twice daily) plus 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 during conduct of the study, if required.

Arm type	Active comparator
Investigational medicinal product name	Budesonide/Formoterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

Budesonide/Formoterol was available as suspension for inhalation. Participants received two inhalations of Budesonide/Formoterol (320/9 mcg) via MDI twice daily.

Investigational medicinal product name	Placebo matching 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	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
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	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	Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg
Started	363	365
Completed	350	347
Not completed	13	18
Physician decision	1	3
Consent withdrawn by subject	7	7
Adverse event, non-fatal	5	3
Lost to follow-up	-	5

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 budesonide/formoterol (BUD/FOR) via metered dose inhaler (MDI) (two inhalations twice daily) plus placebo to match tiotropium (TIO) via HandiHaler (once daily in the morning) for 84 days. Participants received albuterol/salbutamol as rescue medication during conduct of the study, if required.

Reporting group title	Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg

Reporting group description:

Participants received two inhalations of budesonide/formoterol 160/4.5 mcg via MDI in the morning and two inhalations in the evening (total dose of 320/9 mcg twice daily) plus 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 during conduct of the study, if required.

Reporting group values	Fluticasone furoate/Umeclidinium/Vilanterol 100/62.5/25 mcg	Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg	Total
Number of subjects	363	365	728
Age categorical Units: Subjects			
Total participants	363	365	728
Age Continuous Units: Years			
arithmetic mean	65.4	64.9	
standard deviation	± 7.90	± 8.06	-
Sex: Female, Male Units: Participants			
Female	180	164	344
Male	183	201	384
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	34	33	67
American Indian Or Alaska Native	0	1	1
Asian - Central/South Asian Heritage	1	0	1
Asian - South East Asian Heritage	0	1	1
White - Arabic/North African Heritage	0	2	2
White - White/Caucasian/European	327	328	655
Multiple	1	0	1

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 budesonide/formoterol (BUD/FOR) via metered dose inhaler (MDI) (two inhalations twice daily) plus placebo to match tiotropium (TIO) via HandiHaler (once daily in the morning) for 84 days. Participants received albuterol/salbutamol as rescue medication during conduct of the study, if required.

Reporting group title	Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg

Reporting group description:

Participants received two inhalations of budesonide/formoterol 160/4.5 mcg via MDI in the morning and two inhalations in the evening (total dose of 320/9 mcg twice daily) plus 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 during conduct of the study, if required.

Primary: Weighted mean change from Baseline in forced expiratory volume in 1 second (FEV1) over 0-24 hours at Week 12 for modified per protocol (mPP) population

End point title	Weighted mean change from Baseline in forced expiratory volume in 1 second (FEV1) over 0-24 hours at Week 12 for modified per protocol (mPP) population

End point description:

FEV1 is the maximum amount of air that can be forced out in 1 second after taking a deep breath. Serial FEV1 assessments were performed at multiple time points (-30, -5 minutes[m] pre-dose and 5m, 15m, 30m, 1 hour[h], 3h, 6h, 12h, 15h, 21h, 23h and 24h post-dose) at Week 12. The weighted mean was derived by calculating the area under the FEV1 time curve (AUC) over the actual time of assessment relative to the time of dosing using the trapezoidal rule, and then dividing the value by the time interval over which the AUC was calculated. Baseline FEV1 is average of the two FEV1 measurements made at 30m and 5m pre-dose on Day 1. Weighted mean change from Baseline was calculated by subtracting post-dose weighted mean FEV1 from Baseline FEV1. mPP Population included participants in Intent-to-Treat (ITT) population who do not have protocol deviation of not meeting eligibility or randomization criteria. Only those participants with data available at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline and Week 12

End point values	Fluticasone furoate/Umeclidinium/Vilanterol 100/62.5/25 mcg	Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282[1]	272[2]		
Units: Liters				
least squares mean (standard error)	0.045 (± 0.0101)	0.030 (± 0.0101)		

Notes:

[1] - mPP Population

[2] - mPP Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The primary treatment effect estimated (hypothetical effect) excluded data following intercurrent events: discontinuation of treatment, taking wrong treatment, taking prohibited medication, unblinding, noncompliance, COPD exacerbation or pneumonia.

Comparison groups	Fluticasone furoate/Umeclidinium/Vilanterol 100/62.5/25 mcg v Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg
Number of subjects included in analysis	554
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Mean difference (net)
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.013
upper limit	0.043
Variability estimate	Standard error of the mean
Dispersion value	0.0143

Notes:

[3] - Non-inferiority was to be demonstrated, if the lower bound of the two-sided 95 percentage (%) confidence interval around the (FF/UMEC/VI versus BUD/FOR+TIO) treatment difference was above -50 milliliter.

Primary: Weighted mean change from Baseline in FEV1 over 0-24 hours at Week 12 for ITT population

End point title	Weighted mean change from Baseline in FEV1 over 0-24 hours at Week 12 for ITT population

End point description:

FEV1 is the maximum amount of air that can be forced out in 1 second after taking a deep breath. Serial FEV1 assessments were performed at multiple time points (-30 and -5m pre-dose, and 5m, 15m, 30m, 1h, 3h, 6h, 12h, 15h, 21h, 23h and 24h post dose) over 24h period at Week 12. The weighted mean was derived by calculating the area under the FEV1 time curve (AUC) over the actual time of assessment relative to the time of dosing using the trapezoidal rule, and then dividing the value by the time interval over which the AUC was calculated. Baseline FEV1 is the average of the two FEV1 measurements made at 30m and 5m pre-dose on Day 1. Weighted mean change from Baseline at week 12 was calculated by subtracting weighted mean FEV1 at week 12 from Baseline FEV1. ITT Population included all randomized participants, excluding those who were randomized in error. Only those participants with data available at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline and Week 12

End point values	Fluticasone furoate/Umeclidinium/Vilanterol 100/62.5/25 mcg	Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	336[4]	332[5]		
Units: Liters				
least squares mean (standard error)	0.046 (± 0.0097)	0.032 (± 0.0098)		

Notes:

[4] - ITT Population

[5] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The treatment effect to be estimated was hypothetical effect if all participants stayed on their randomized study treatment. Only on treatment data was included in analysis.

Comparison groups	Fluticasone furoate/Umeclidinium/Vilanterol 100/62.5/25 mcg v Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg
Number of subjects included in analysis	668
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.335 [6]
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.014
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.0138

Notes:

[6] - The analysis was performed using mixed model repeated measures analysis, which included covariates of Baseline FEV1, geographical region, treatment, visit, visit by treatment and visit by Baseline interaction.

Secondary: Change from Baseline in trough FEV1 on Day 2, Day 28, Day 84 and Day 85

End point title	Change from Baseline in trough FEV1 on Day 2, Day 28, Day 84 and Day 85

End point description:

FEV1 is an important measure of pulmonary function and is the maximum amount of air that can be forced out in one second after taking a deep breath. FEV1 was measured using spirometry. For Day 2 and Day 85, trough FEV1 was defined as the mean of the 23-hour and 24-hour serial spirometry FEV1 measurements. For Day 28 and Day 84, trough FEV1 was defined as the average of the pre-dose FEV1 measurements recorded before the morning dose of randomized study treatment. Change from Baseline in trough FEV1 was calculated by subtracting post-dose trough FEV1 value from Baseline FEV1, where Baseline FEV1 is the average of the two FEV1 measurements made at 30 minutes and 5 minutes pre-dose on Day 1. The treatment effect to be estimated for trough FEV1 was hypothetical effect if all participants stayed on their randomized study treatment. Only those participants with data available at the specified time points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline, Days 2, 28, 84 and 85

End point values	Fluticasone furoate/Umeclidinium/Vilanterol 100/62.5/25 mcg	Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358[7]	359[8]		
Units: Liters				
least squares mean (standard error)				
Day 2, n=358,359	0.008 (± 0.0098)	0.018 (± 0.0098)		
Day 28, n=355,353	0.046 (± 0.0088)	-0.015 (± 0.0088)		
Day 84, n=344,340	0.040 (± 0.0094)	-0.018 (± 0.0094)		
Day 85, n=341,337	0.026 (± 0.0099)	-0.012 (± 0.0099)		

Notes:

[7] - ITT Population

[8] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Day 2	
Comparison groups	Fluticasone furoate/Umeclidinium/Vilanterol 100/62.5/25 mcg v Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg
Number of subjects included in analysis	717
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.481 [9]
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.037
upper limit	0.018
Variability estimate	Standard error of the mean
Dispersion value	0.0139

Notes:

[9] - Only if superiority is achieved on the primary study endpoint, then inferences can be made on change from Baseline in trough FEV1 on Day 2 using p-values.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Day 28	
Comparison groups	Fluticasone furoate/Umeclidinium/Vilanterol 100/62.5/25 mcg v Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg

Number of subjects included in analysis	717
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [10]
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.086
Variability estimate	Standard error of the mean
Dispersion value	0.0124

Notes:

[10] - Only if superiority is achieved on the primary study endpoint, then inferences can be made on change from Baseline in trough FEV1 on Day 28 using p-values.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Day 84

Comparison groups	Fluticasone furoate/Umeclidinium/Vilanterol 100/62.5/25 mcg v Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg
Number of subjects included in analysis	717
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [11]
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.032
upper limit	0.084
Variability estimate	Standard error of the mean
Dispersion value	0.0133

Notes:

[11] - Only if superiority is achieved on the primary study endpoint, then inferences can be made on change from Baseline in trough FEV1 on Day 84 using p-values.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Day 85

Comparison groups	Fluticasone furoate/Umeclidinium/Vilanterol 100/62.5/25 mcg v Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg
Number of subjects included in analysis	717
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 [12]
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.038

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.066
Variability estimate	Standard error of the mean
Dispersion value	0.014

Notes:

[12] - Only if superiority is achieved on the primary study endpoint, then inferences can be made on change from Baseline in trough FEV1 on Day 85 using p-values.

Secondary: Weighted mean change from Baseline in FEV1 over 0-24 hours on Day 1

End point title	Weighted mean change from Baseline in FEV1 over 0-24 hours on Day 1

End point description:

FEV1 is the maximum amount of air that can be forced out in 1 second after taking a deep breath. FEV1 was measured using spirometry. Serial FEV1 assessments were performed at multiple time points (-30 and -5 minutes pre-dose, and 5 minutes, 15 minutes, 30 minutes, 1 hour, 3 hours, 6 hours, 12 hours, 15 hours, 21 hours, 23 hours and 24 hours post dose) over 24-hour period on Day 1. The weighted mean was derived by calculating the area under the FEV1 time curve (AUC) over the actual time of assessment relative to the time of dosing using the trapezoidal rule, and then dividing the value by the time interval over which the AUC was calculated. Baseline FEV1 is the average of the two FEV1 measurements made at 30 minutes and 5 minutes pre-dose on Day 1. Weighted mean change from Baseline on Day 1 was calculated by subtracting weighted mean FEV1 on Day 1 from Baseline FEV1. Only those participants with data available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Day 1

End point values	Fluticasone furoate/Umeclidinium/Vilanterol 100/62.5/25 mcg	Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354[13]	355[14]		
Units: Liters				
least squares mean (standard error)	0.054 (± 0.0078)	0.063 (± 0.0077)		

Notes:

[13] - ITT Population

[14] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The treatment effect to be estimated was hypothetical effect if all participants stayed on their randomized study treatment. Only on treatment data was included in analysis.

Comparison groups	Fluticasone furoate/Umeclidinium/Vilanterol 100/62.5/25 mcg v Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg

Number of subjects included in analysis	709
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.415 [15]
Method	Mixed model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.013
Variability estimate	Standard error of the mean
Dispersion value	0.011

Notes:

[15] - Only if superiority is achieved on the primary study endpoint, then inferences can be made on weighted mean change from Baseline in FEV1 over 0-24 hours on Day 1 using p-values.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-SAEs were reported from start of study treatment and up to Week 13

Adverse event reporting additional description:

Non-SAEs and SAEs were reported for ITT Population. 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 budesonide/formoterol (BUD/FOR) via metered dose inhaler (MDI) (two inhalations twice daily) plus placebo to match tiotropium (TIO) via HandiHaler (once daily in the morning) for 84 days. Participants received albuterol/salbutamol as rescue medication during conduct of the study, if required.

Reporting group title	Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg

Reporting group description:

Participants received two inhalations of budesonide/formoterol 160/4.5 mcg via MDI in the morning and two inhalations in the evening (total dose of 320/9 mcg twice daily) plus 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 during conduct of the study, if required.

Serious adverse events	Fluticasone furoate/Umeclidinium/Vilanterol 100/62.5/25 mcg	Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 363 (7.99%)	16 / 365 (4.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 363 (0.28%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			

subjects affected / exposed	1 / 363 (0.28%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 363 (0.28%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 363 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	0 / 363 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 363 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 363 (0.00%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 363 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 363 (0.28%)	0 / 365 (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 / 363 (0.28%)	0 / 365 (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 / 363 (0.28%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 363 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 363 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 363 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 363 (0.28%)	0 / 365 (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	2 / 363 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	15 / 363 (4.13%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	4 / 19	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 363 (0.28%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 363 (0.00%)	1 / 365 (0.27%)	
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	0 / 363 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 363 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 363 (0.28%)	0 / 365 (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			
Arthralgia			
subjects affected / exposed	0 / 363 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	2 / 363 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Influenza			
subjects affected / exposed	1 / 363 (0.28%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 363 (1.10%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 363 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoas abscess			
subjects affected / exposed	0 / 363 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 363 (0.55%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 2	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	Budesonide/Formoterol 320/9 mcg plus Tiotropium 18 mcg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 363 (4.96%)	12 / 365 (3.29%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 363 (4.96%)	12 / 365 (3.29%)	
occurrences (all)	20	12	

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 it is preferable to have the participants stay at the clinic or approved facility during the serial spirometry assessments. The physical form of Symbicort and matching placebo was reported as a solution for inhalation, which is incorrect, and should be corrected to a suspension for inhalation. An additional footnote has been added to the Schedule of Activities (SoA), to provide clarity on the collection of trough forced expiratory volume in 1 second (FEV1) spirometry on Day 28. Clarified that run-in treatment will be collected at Visit 2. Correction made (reference section) regarding prohibited medications within a specified time interval during pre-screening and prior to Visit 1. Also, wording regarding suggested order for assessments and procedures had been added to the end of the Schedule of Activities section. Removed reference to Fridericia formula in calculation of QTc. Clarification regarding collecting the Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT) assessment questionnaire prior to the Saint George's Respiratory Questionnaire for COPD participants (SGRQ-C) had also been provided along with clarification that vital signs should be collected before the electrocardiogram (ECG) and prior to spirometry. Corrected reporting time regarding pregnancy. Routine urinalysis assessment has been deleted as this will not be collected during the study. 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