Clinical trial results:
A Randomised, Double-Blind, Double-Dummy, Multicentre, Parallel Group Study to Assess the Efficacy and Safety of Glycopyrronium/Formoterol Fumarate Fixed-dose Combination Relative to Umeclidinium/Vilanterol Fixed-dose Combination Over 24 Weeks in Patients With Moderate to Very Severe Chronic Obstructive Pulmonary Disease (AERISTO)

Summary

EudraCT number	2016-004655-75
Trial protocol	FR BG
Global end of trial date	04 May 2018

Results information

Result version number	v1 (current)
This version publication date	16 May 2019
First version publication date	16 May 2019

Trial information

Trial identification

Sponsor protocol code	D5970C00002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03162055
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Pepparedsleden 1, Mölndal, Sweden, 43183
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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	04 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of glycopyrronium/formoterol fumarate (GFF) relative to umeclidinium/vilanterol (UV) on lung function as measured by trough forced expiratory volume in 1 second (FEV1) and peak FEV1 in participants with moderate to very severe chronic obstructive pulmonary disease (COPD).

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy:

Participants were provided albuterol/salbutamol metered dose inhaler (MDI) for use as rescue medication for worsening of COPD symptoms during the study. The following maintenance treatments were allowed provided stable dosing prior to Visit 1 and throughout the study:
• In participants who were steroid dependent systemic steroids equivalent of 5 milligrams (mg) prednisone per day or 10 mg every other day.
• Theophylline ≤200 mg twice daily (BD).
• Phosphodiesterase-4 Inhibitors.
• Leukotriene antagonists.
• Cromoglicate.

Evidence for comparator: -

Actual start date of recruitment	25 May 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 164
Country: Number of subjects enrolled	Canada: 93
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Hungary: 178
Country: Number of subjects enrolled	Russian Federation: 303
Country: Number of subjects enrolled	Ukraine: 195
Country: Number of subjects enrolled	United States: 165
Worldwide total number of subjects	1119
EEA total number of subjects	363

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)	570
From 65 to 84 years	543
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 110 centers in 7 countries (Russia, Bulgaria, Ukraine, United States of America, Canada, Hungary and France) between 25 May 2017 and 04 May 2018. Participants with moderate to very severe COPD were recruited in this study.

Pre-assignment

Screening details:

The study had a screening period, followed by a 24-week double-blind and double-dummy treatment period. A total of 1445 participants were screened. Of which, 1119 participants were enrolled and randomized to study 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	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Glycopyrronium/Formoterol Fumarate

Arm description:

Participants were randomized to receive 2 inhalations of glycopyrronium/formoterol fumarate (GFF) fixed-dose combination 7.2/4.8 micrograms (mcg) per actuation administered in the morning and evening by MDI for 24 weeks. Participants also received 1 inhalation of placebo matched to umeclidinium/vilanterol (UV) administered once daily in the morning by dry powder inhaler (DPI) for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Glycopyrronium/Formoterol Fumarate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations of GFF fixed-dose combination 7.2/4.8 mcg per actuation administered by MDI.

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

Dosage and administration details:

1 inhalation of placebo matched to the UV administered by DPI.

Arm title	Umeclidinium/Vilanterol

Arm description:

Participants were randomized to receive 1 inhalation of UV fixed-dose combination 62.5/25 mcg per actuation administered once daily in the morning by DPI for 24 weeks. Participants also received 2 inhalations of placebo matched to the GFF administered twice daily in the morning and evening by MDI for 24 weeks.

Arm type	Active comparator

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations of placebo matched to the GFF administered by MDI.

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

Dosage and administration details:

1 inhalation of UV fixed-dose combination 62.5/25 mcg per actuation administered by DPI.

Number of subjects in period 1	Glycopyrronium/Formoterol Fumarate	Umeclidinium/Vilanterol
Started	559	560
Received treatment	557	560
Safety analysis set	552	552
Full analysis set (FAS)	552	552
Per protocol (PP) analysis set	506	510 [1]
Completed	497	517
Not completed	62	43
Adverse event, serious fatal	3	3
Consent withdrawn by subject	17	2
Adverse event, non-fatal	6	5
Study-specific withdrawal criteria	22	14
Unspecified	8	15
Did not receive treatment	2	-
Lost to follow-up	-	1
Incorrect randomization	4	3

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The PP analysis set is a subset of the FAS, deducting participants with important protocol deviations which may affect efficacy.

Baseline characteristics

Reporting groups

Reporting group title	Glycopyrronium/Formoterol Fumarate

Reporting group description:

Participants were randomized to receive 2 inhalations of glycopyrronium/formoterol fumarate (GFF) fixed-dose combination 7.2/4.8 micrograms (mcg) per actuation administered in the morning and evening by MDI for 24 weeks. Participants also received 1 inhalation of placebo matched to umeclidinium/vilanterol (UV) administered once daily in the morning by dry powder inhaler (DPI) for 24 weeks.

Reporting group title	Umeclidinium/Vilanterol

Reporting group description:

Participants were randomized to receive 1 inhalation of UV fixed-dose combination 62.5/25 mcg per actuation administered once daily in the morning by DPI for 24 weeks. Participants also received 2 inhalations of placebo matched to the GFF administered twice daily in the morning and evening by MDI for 24 weeks.

Reporting group values	Glycopyrronium/Formoterol Fumarate	Umeclidinium/Vilanterol	Total
Number of subjects	559	560	1119
Age, Customized Units: Subjects			
<65 years	276	294	570
65 - 74 years	227	218	445
75 - 84 years	53	45	98
>=85 years	3	3	6
Age Continuous Units: Years			
arithmetic mean	64.3	63.9	
standard deviation	± 7.99	± 8.05	-
Sex: Female, Male Units: Subjects			
Female	145	161	306
Male	414	399	813
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	13	10	23
White	545	550	1095
More than one race	0	0	0
Other	1	0	1

Subject analysis sets

Subject analysis set title	PP Analysis Set: Glycopyrronium/Formoterol Fumarate
Subject analysis set type	Per protocol

Subject analysis set description:

Participants were randomized to receive 2 inhalations of GFF fixed-dose combination 7.2/4.8 mcg per actuation administered in the morning and evening by MDI for 24 weeks. Participants also received 1

inhalation of placebo matched to UV administered once daily in the morning by DPI for 24 weeks. The PP analysis set included the subset of the FAS containing participants with post-randomization data obtained prior to important protocol deviations which may have affected efficacy.

Subject analysis set title	PP Analysis Set: Umeclidinium/Vilanterol
Subject analysis set type	Per protocol

Subject analysis set description:

Participants were randomized to receive 1 inhalation of UV fixed-dose combination 62.5/25 mcg per actuation administered once daily in the morning by DPI for 24 weeks. Participants also received 2 inhalations of placebo matched to the GFF administered twice daily in the morning and evening by MDI for 24 weeks. The PP analysis set included the subset of the FAS containing participants with post-randomization data obtained prior to important protocol deviations which may have affected efficacy.

Reporting group values	PP Analysis Set: Glycopyrronium/Formoterol Fumarate	PP Analysis Set: Umeclidinium/Vilanterol	
Number of subjects	506	510	
Age, Customized Units: Subjects			
<65 years	249	274	
65 - 74 years	205	197	
75 - 84 years	49	36	
>=85 years	3	3	
Age Continuous Units: Years			
arithmetic mean	64.3	63.6	
standard deviation	± 8.0	± 8.0	
Sex: Female, Male Units: Subjects			
Female	126	145	
Male	380	365	
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	11	8	
White	495	502	
More than one race	0	0	
Other	0	0	

End points

End points reporting groups

Reporting group title	Glycopyrronium/Formoterol Fumarate

Reporting group description:

Participants were randomized to receive 2 inhalations of glycopyrronium/formoterol fumarate (GFF) fixed-dose combination 7.2/4.8 micrograms (mcg) per actuation administered in the morning and evening by MDI for 24 weeks. Participants also received 1 inhalation of placebo matched to umeclidinium/vilanterol (UV) administered once daily in the morning by dry powder inhaler (DPI) for 24 weeks.

Reporting group title	Umeclidinium/Vilanterol

Reporting group description:

Participants were randomized to receive 1 inhalation of UV fixed-dose combination 62.5/25 mcg per actuation administered once daily in the morning by DPI for 24 weeks. Participants also received 2 inhalations of placebo matched to the GFF administered twice daily in the morning and evening by MDI for 24 weeks.

Subject analysis set title	PP Analysis Set: Glycopyrronium/Formoterol Fumarate
Subject analysis set type	Per protocol

Subject analysis set description:

Participants were randomized to receive 2 inhalations of GFF fixed-dose combination 7.2/4.8 mcg per actuation administered in the morning and evening by MDI for 24 weeks. Participants also received 1 inhalation of placebo matched to UV administered once daily in the morning by DPI for 24 weeks. The PP analysis set included the subset of the FAS containing participants with post-randomization data obtained prior to important protocol deviations which may have affected efficacy.

Subject analysis set title	PP Analysis Set: Umeclidinium/Vilanterol
Subject analysis set type	Per protocol

Subject analysis set description:

Participants were randomized to receive 1 inhalation of UV fixed-dose combination 62.5/25 mcg per actuation administered once daily in the morning by DPI for 24 weeks. Participants also received 2 inhalations of placebo matched to the GFF administered twice daily in the morning and evening by MDI for 24 weeks. The PP analysis set included the subset of the FAS containing participants with post-randomization data obtained prior to important protocol deviations which may have affected efficacy.

Primary: Mean Change From Baseline in Morning Pre-dose Trough FEV1 Over 24 Weeks

End point title	Mean Change From Baseline in Morning Pre-dose Trough FEV1 Over 24 Weeks

End point description:

To assess the effects of GFF relative to UV on lung function as measured by change from baseline in morning pre-dose trough FEV1 is defined as the average of the -60 and -30 minute pre-dose values at each visit minus baseline using spirometry. Baseline is defined as the mean of the non-missing -60 and -30 minute values obtained prior to dosing at randomization (Day 1). The PP analysis set included the subset of the FAS containing participants with post-randomization data obtained prior to important protocol deviations which may have affected efficacy. Only participants with data available for analysis are presented.

End point type	Primary

End point timeframe:

From Baseline (Day 1) up to 24 weeks

End point values	PP Analysis Set: Glycopyrronium/Formoterol Fumarate	PP Analysis Set: Umeclidinium/ Vilanterol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	474	489		
Units: milliliter (mL)				
least squares mean (standard error)	82.4 (± 11.2)	169.6 (± 11.2)		

Statistical analyses

Statistical analysis title	Treatment difference: Morning pre-dose FEV1

Statistical analysis description:

Estimate of the mean change from baseline over 24 weeks in the GFF treatment group is compared to the UV treatment group using a repeated measures analysis.

Comparison groups	PP Analysis Set: Glycopyrronium/Formoterol Fumarate v PP Analysis Set: Umeclidinium/Vilanterol
Number of subjects included in analysis	963
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.9974 [2]
Method	Repeated measures analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-87.2
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-117
upper limit	-57.4
Variability estimate	Standard error of the mean
Dispersion value	13.3

Notes:

[1] - Change from baseline = Treatment + baseline FEV1 + bronchodilator responsiveness to albuterol/salbutamol MDI + stratification factor (prior treatment) + region + visit + treatment by visit.
[2] - Non-inferiority p-value is calculated corresponding to the non-inferiority margin -50 mL.

Primary: Mean Peak Change From Baseline in FEV1 Within 2 Hours Post-dosing Over 24 Weeks in PP Analysis Set Population

End point title	Mean Peak Change From Baseline in FEV1 Within 2 Hours Post-dosing Over 24 Weeks in PP Analysis Set Population

End point description:

To assess the effects of GFF relative to UV on lung function as measured by peak change from baseline in FEV1 is defined as the maximum of the FEV1 assessments within the 2 hours post-dosing time windows at each visit minus baseline using spirometry. Baseline is defined as the average of the non-missing -60 and -30 minute values obtained prior to dosing at randomization (Day 1). The PP analysis set included the subset of the FAS containing participants with post-randomization data obtained prior to important protocol deviations which may have affected efficacy. Only participants with data available for analysis are presented.

End point type	Primary

End point timeframe:

From Baseline (Day 1) up to 24 weeks

End point values	PP Analysis Set: Glycopyrronium/Formoterol Fumarate	PP Analysis Set: Umeclidinium/ Vilanterol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	506	509		
Units: mL				
least squares mean (standard error)	293.5 (± 10.2)	296.9 (± 10.3)		

Statistical analyses

Statistical analysis title	Treatment difference:FEV1 within 2 hours post-dose

Statistical analysis description:

Estimate of the mean peak change from baseline over 24 weeks in the GFF treatment group is compared to the UV treatment group using a repeated measures analysis.

Comparison groups	PP Analysis Set: Glycopyrronium/Formoterol Fumarate v PP Analysis Set: Umeclidinium/Vilanterol
Number of subjects included in analysis	1015
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.0002 [4]
Method	Repeated measures analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-3.4
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-32.8
upper limit	25.9
Variability estimate	Standard error of the mean
Dispersion value	13.1

Notes:

[3] - Change from baseline = Treatment + baseline FEV1 + bronchodilator responsiveness to albuterol/salbutamol MDI + stratification factor (prior treatment) + region + visit + treatment by visit.
[4] - Non-inferiority p-value is calculated corresponding to the non-inferiority margin -50 mL.

Primary: Mean Peak Change From Baseline in FEV1 Within 2 Hours Post-dosing Over 24 Weeks in FAS Population

End point title	Mean Peak Change From Baseline in FEV1 Within 2 Hours Post-dosing Over 24 Weeks in FAS Population

End point description:

To assess the effects of GFF relative to UV on lung function as measured by peak change from baseline in FEV1 is defined as the maximum of the FEV1 assessments within the 2 hours post-dosing time windows at each visit minus baseline using spirometry. Baseline is defined as the average of the non-missing -60 and -30 minute values obtained prior to dosing at randomization (Day 1). The FAS included all randomized participants who received at least 1 inhalation of IP from the GFF or UV inhaler (active or placebo).

End point type	Primary

End point timeframe:

From Baseline (Day 1) up to 24 weeks

End point values	Glycopyrronium/Formoterol Fumarate	Umeclidinium/Vilanterol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	552	552		
Units: mL				
least squares mean (standard error)	299.1 (± 9.9)	300.8 (± 9.9)		

Statistical analyses

Statistical analysis title	Treatment difference:FEV1 within 2 hours post-dose

Statistical analysis description:

Estimate of the mean peak change from baseline over 24 weeks in the GFF treatment group is compared to the UV treatment group using a repeated measures analysis.

Comparison groups	Glycopyrronium/Formoterol Fumarate v Umeclidinium/Vilanterol
Number of subjects included in analysis	1104
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.5516
Method	Repeated measures analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-1.7
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-30.3
upper limit	27
Variability estimate	Standard error of the mean
Dispersion value	12.8

Notes:

[5] - Change from baseline = Treatment + baseline FEV1 + bronchodilator responsiveness to albuterol/salbutamol MDI + stratification factor (prior treatment) + region + visit + treatment by visit.

Secondary: Percentage of Participants With Increase of FEV1 of >=100 mL From Baseline at 5 Minutes Post-dosing on Day 1

End point title	Percentage of Participants With Increase of FEV1 of >=100 mL From Baseline at 5 Minutes Post-dosing on Day 1

End point description:

The percentage of participants with an increase in FEV1 of >=100 mL from baseline at 5 minutes post-dosing on Day 1 was determined to assess the early onset of action. Baseline is defined as the average of available evaluable -60 and -30 minute pre-dose assessments conducted at randomization (Day 1). Only data assigned to the 5 minute window was used to determine response. Participants with missing data were considered non-responders for the analysis. The FAS analysis set included all randomized participants who received at least 1 inhalation of IP from the GFF or UV inhaler (active or placebo).

End point type	Secondary

End point timeframe:

5 minutes post-dose on Day 1

End point values	Glycopyrronium/Formoterol Fumarate	Umeclidinium/ Vilanterol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	552	552		
Units: Percentage of participants				
number (not applicable)	60.1	40.8		

Statistical analyses

Statistical analysis title	Treatment difference: FEV1 >=100 mL at 5 minutes

Statistical analysis description:

Estimate of the log odds of being a responder in the GFF treatment group compared to the UV treatment group using a logistic regression.

Comparison groups	Glycopyrronium/Formoterol Fumarate v Umeclidinium/Vilanterol
Number of subjects included in analysis	1104
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.79
upper limit	2.95

Notes:

[6] - ln (1/(1-p)) = Treatment + baseline FEV1 + bronchodilator responsiveness to albuterol/salbutamol MDI + stratification factor (prior treatment) + region. p=percentage of participants with increase of >=100 mL.

Secondary: Mean Peak Change From Baseline in Inspiratory Capacity (IC) Within 2 Hours Post-dosing Over 24 Weeks

End point title	Mean Peak Change From Baseline in Inspiratory Capacity (IC) Within 2 Hours Post-dosing Over 24 Weeks

End point description:

Peak change from baseline in IC is defined as the maximum of the IC assessments within the 2 hours post-dosing time windows at each visit minus baseline. Baseline is defined as the average of available evaluable -60 and -30 minute pre-dose assessments conducted at randomization (Day 1). The PP analysis set included the subset of the FAS containing participants with post-randomization data obtained prior to important protocol deviations which may have affected efficacy. Only participants with data available for analysis are presented.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to 24 weeks

End point values	PP Analysis Set: Glycopyrronium/Formoterol Fumarate	PP Analysis Set: Umeclidinium/ Vilanterol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	496	501		
Units: mL				
least squares mean (standard error)	363.1 (± 15.5)	378.3 (± 15.6)		

Statistical analyses

Statistical analysis title	Treatment difference: IC within 2 hours post-dose

Statistical analysis description:

Estimate of the mean peak change from baseline over 24 weeks in the GFF treatment group is compared to the UV treatment group using a repeated measures analysis.

Comparison groups	PP Analysis Set: Glycopyrronium/Formoterol Fumarate v PP Analysis Set: Umeclidinium/Vilanterol
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	= 0.0371 [8]
Method	Repeated measures analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-15.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.4
upper limit	22.9
Variability estimate	Standard error of the mean
Dispersion value	19.4

Notes:

[7] - Change from baseline = Treatment + baseline IC + bronchodilator responsiveness to albuterol/salbutamol MDI + stratification factor (prior treatment) + region + visit + treatment by visit.
[8] - Non-inferiority p-value is calculated corresponding to the non-inferiority margin -50 mL.

Secondary: Mean Transition Dyspnea Index (TDI) Focal Score Over 24 Weeks

End point title	Mean Transition Dyspnea Index (TDI) Focal Score Over 24 Weeks

End point description:

The baseline dyspnea index (BDI) and TDI consist of 3 individual components: functional impairment, magnitude of task, and magnitude of effort. For the BDI, each of these 3 components were rated in 5 grades from 0 (very severe) to 4 (no impairment), and were summed to form a baseline total score from 0 to 12. For the TDI, changes in dyspnea were rated for each component by 7 grades from -3 (major deterioration) to +3 (major improvement), and were added to form a TDI focal score from -9 to +9. Baseline is defined as the latest BDI assessment within 7 days before or at randomization (Day 1). The PP analysis set included the subset of the FAS containing participants with post-randomization data obtained prior to important protocol deviations which may have affected efficacy. Only participants with data available for analysis are presented.

End point type	Secondary

End point timeframe:

From Baseline (Day -7 or 1) up to 24 weeks

End point values	PP Analysis Set: Glycopyrronium/Formoterol Fumarate	PP Analysis Set: Umeclidinium/ Vilanterol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	500	507		
Units: Units on a scale				
least squares mean (standard error)	1.23 (± 0.10)	1.60 (± 0.10)		

Statistical analyses

Statistical analysis title	Treatment difference: TDI score

Statistical analysis description:

Estimate of the mean TDI focal score over 24 weeks in the GFF treatment group is compared to the UV treatment group using a repeated measures analysis.

Comparison groups	PP Analysis Set: Glycopyrronium/Formoterol Fumarate v PP Analysis Set: Umeclidinium/Vilanterol
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
P-value	< 0.0001 [10]
Method	Repeated measures analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[9] - TDI focal score = Treatment + Baseline Dyspnea Index + bronchodilator responsiveness to albuterol/salbutamol MDI + stratification factor (prior treatment) + region + visit + treatment by visit.
[10] - Non-inferiority p-value is calculated corresponding to the non-inferiority margin -1.0 unit.

Secondary: Mean Change From Baseline in Early Morning Symptoms of COPD Instrument (EMSCI) Over 24 Weeks

End point title	Mean Change From Baseline in Early Morning Symptoms of COPD Instrument (EMSCI) Over 24 Weeks

End point description:

Change from baseline in the 6-item EMSCI Symptom Severity Score was derived by averaging the responses from a participant on the 6 item-level symptom scores (scored on a 4-point scale from 1 to 4, whereas 1= mild and 4= very severe). The EMSCI collected data about the frequency and severity of early morning symptoms and the impact of COPD symptoms on early morning activity in participants

with COPD. Participants completed a daily electronic patient-reported outcome (ePRO) questionnaire for their COPD symptoms. Baseline is defined as the average of the non-missing values from the ePRO data collected in the last 7 days before the randomization (Day 1). The PP analysis set included the subset of the FAS containing participants with post-randomization data obtained prior to important protocol deviations which may have affected efficacy. Only participants with data available for analysis are presented.

End point type	Secondary

End point timeframe:

From Baseline (Day -7) up to 24 weeks

End point values	PP Analysis Set: Glycopyrronium/Formoterol Fumarate	PP Analysis Set: Umeclidinium/ Vilanterol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	502	508		
Units: Units on a scale				
least squares mean (standard error)	-0.142 (± 0.018)	-0.176 (± 0.018)		

Statistical analyses

Statistical analysis title	Treatment difference: EMSCI score

Statistical analysis description:

Estimate of the mean change from baseline over 24 weeks in the GFF treatment group is compared to the UV treatment group using a repeated measures analysis.

Comparison groups	PP Analysis Set: Glycopyrronium/Formoterol Fumarate v PP Analysis Set: Umeclidinium/Vilanterol
Number of subjects included in analysis	1010
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	= 0.0017 [12]
Method	Repeated measures analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.034
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.011
upper limit	0.078
Variability estimate	Standard error of the mean
Dispersion value	0.023

Notes:

[11] - Change from baseline = Treatment + baseline EMSCI score + bronchodilator responsiveness to albuterol/salbutamol MDI + stratification factor (prior treatment) + region + time interval + treatment by time interval.

[12] - Non-inferiority p-value is calculated corresponding to the non-inferiority margin 0.1 unit.

Other pre-specified: Mean Change From Baseline in Night-Time Symptoms of COPD Instrument (NiSCI) Over 24 Weeks

End point title	Mean Change From Baseline in Night-Time Symptoms of COPD Instrument (NiSCI) Over 24 Weeks

End point description:

Change from baseline in the 6-item NiSCI Symptom Severity Score was derived by averaging the responses from a participant on the 6 item-level symptom scores (scored on a 4-point scale from 1 to 4, whereas 1= mild and 4= very severe). The NiSCI collected data about the frequency and severity of night-time symptoms and the impact of COPD symptoms on night-time awakenings in participants with COPD. Participants completed a daily ePRO questionnaire for their COPD symptoms. Baseline is defined as the average of the non-missing values from the ePRO data collected in the last 7 days before the randomization (Day 1). The PP analysis set included the subset of the FAS containing participants with post-randomization data obtained prior to important protocol deviations which may have affected efficacy. Only participants with data available for analysis are presented.

End point type	Other pre-specified

End point timeframe:

From Baseline (Day -7) up to 24 weeks

End point values	PP Analysis Set: Glycopyrronium/Formoterol Fumarate	PP Analysis Set: Umeclidinium/ Vilanterol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	502	508		
Units: Units on a scale				
least squares mean (standard error)	-0.165 (± 0.019)	-0.207 (± 0.019)		

Statistical analyses

Statistical analysis title	Treatment difference: NiSCI score

Statistical analysis description:

Estimate of the mean change from baseline over 24 weeks in the GFF treatment group is compared to the UV treatment group using a repeated measures analysis.

Comparison groups	PP Analysis Set: Glycopyrronium/Formoterol Fumarate v PP Analysis Set: Umeclidinium/Vilanterol
Number of subjects included in analysis	1010
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
P-value	= 0.0088 [14]
Method	Repeated measures analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.024

Notes:

[13] - Change from baseline = Treatment + baseline NiSCI score + bronchodilator responsiveness to albuterol/salbutamol MDI + stratification factor (prior treatment) + region + time interval + treatment by time interval.

[14] - Non-inferiority p-value is calculated corresponding to the non-inferiority margin 0.1 unit.

Other pre-specified: Mean Change From Baseline in Daily Rescue (albuterol/salbutamol MDI) Use Over 24 Weeks

End point title	Mean Change From Baseline in Daily Rescue (albuterol/salbutamol MDI) Use Over 24 Weeks

End point description:

The number of inhalations of rescue albuterol/salbutamol MDI was recorded in the participant ePRO in the morning and evening. Baseline is defined as the average of the non-missing values from the ePRO data collected in the last 7 days before the randomization (Day 1). The rescue medication user analysis set included all participants in the FAS with average baseline rescue albuterol/salbutamol MDI use of >=1 inhalation/day. Only participants with data available for analysis are presented.

End point type	Other pre-specified

End point timeframe:

From Baseline (Day -7) up to 24 weeks

End point values	Glycopyrronium/Formoterol Fumarate	Umeclidinium/ Vilanterol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	450	450		
Units: Puffs/day				
least squares mean (standard error)	-1.70 (± 0.16)	-2.35 (± 0.16)		

Statistical analyses

Statistical analysis title	Treatment difference: Daily rescue use

Statistical analysis description:

Estimate of the mean change from baseline over 24 weeks in the GFF treatment group is compared to the UV treatment group using a repeated measures analysis.

Comparison groups	Glycopyrronium/Formoterol Fumarate v Umeclidinium/Vilanterol
Number of subjects included in analysis	900
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.9995
Method	Repeated measures analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	1.04
Variability estimate	Standard error of the mean
Dispersion value	0.2

Notes:

[15] - Change from baseline =Treatment + baseline rescue albuterol/salbutamol MDI use + bronchodilator responsiveness to albuterol/salbutamol MDI + stratification factor (prior treatment) + region + time interval + treatment by time interval.

Other pre-specified: Mean Change From Baseline in CAT Score Over 24 Weeks

End point title	Mean Change From Baseline in CAT Score Over 24 Weeks

End point description:

The CAT is used to quantify the impact of COPD symptoms on health status. The CAT has a scoring range of 0-40, and it is calculated as the sum of the responses given for each of the 8 items (scored on a 6-point scale from 0 to 5), with higher scores indicating a higher impact of COPD symptoms on health status. If the response to 1 of the 8 items is missing, the missing item was considered equal to the average of the 7 non-missing items for that participant. If more than 1 item is missing the score was considered missing. Baseline is defined as the latest assessment within 7 days before or at randomization (Day 1). The PP analysis set included the subset of the FAS containing participants with post-randomization data obtained prior to important protocol deviations which may have affected efficacy. Only participants with data available for analysis are presented.

End point type	Other pre-specified

End point timeframe:

From Baseline (Day -7 or 1) up to 24 weeks

End point values	PP Analysis Set: Glycopyrronium/Formoterol Fumarate	PP Analysis Set: Umeclidinium/ Vilanterol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	500	506		
Units: Units on a scale				
least squares mean (standard error)	-2.97 (± 0.21)	-3.56 (± 0.22)		

Statistical analyses

Statistical analysis title	Treatment difference: CAT score

Statistical analysis description:

Estimate of the mean change from baseline over 24 weeks in the GFF treatment group is compared to the UV treatment group using a repeated measures analysis.

Comparison groups	PP Analysis Set: Glycopyrronium/Formoterol Fumarate v PP Analysis Set: Umeclidinium/Vilanterol
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	non-inferiority[16]
P-value	< 0.0001 [17]
Method	Repeated measures analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	1.11

Variability estimate	Standard error of the mean
Dispersion value	0.27

Notes:

[16] - Change from baseline = Treatment + baseline CAT score + bronchodilator responsiveness to albuterol/salbutamol MDI + stratification factor (prior treatment) + region + visit + treatment by visit.
[17] - Non-inferiority p-value is calculated corresponding to the non-inferiority margin 2.0 unit.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline (Day 1) up to 14 days after last IP dose, approximately 26 weeks.

Adverse event reporting additional description:

The safety analysis set included all participants who received at least 1 inhalation of the randomized active IP that they were assigned.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Glycopyrronium/Formoterol Fumarate

Reporting group description:

Participants were randomized to receive 2 inhalations of GFF fixed-dose combination 7.2/4.8 mcg per actuation administered in the morning and evening by MDI for 24 weeks. Participants also received 1 inhalation of placebo matched to UV administered once daily in the morning by DPI for 24 weeks.

Reporting group title	Umeclidinium/Vilanterol

Reporting group description:

Participants were randomized to receive 1 inhalation of UV fixed-dose combination 62.5/25 mcg per actuation administered once daily in the morning by DPI for 24 weeks. Participants also received 2 inhalations of placebo matched to the GFF administered twice daily in the morning and evening by MDI for 24 weeks.

Serious adverse events	Glycopyrronium/Formoterol Fumarate	Umeclidinium/Vilanterol	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 552 (5.80%)	40 / 552 (7.25%)	
number of deaths (all causes)	3	3	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	1 / 552 (0.18%)	0 / 552 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian fibroma			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			

subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
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	1 / 552 (0.18%)	0 / 552 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Essential hypertension			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 552 (0.18%)	0 / 552 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
subjects affected / exposed	1 / 552 (0.18%)	0 / 552 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post thrombotic syndrome			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
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			
Death			
subjects affected / exposed	1 / 552 (0.18%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	

Incarcerated hernia			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 552 (0.18%)	0 / 552 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
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	16 / 552 (2.90%)	10 / 552 (1.81%)	
occurrences causally related to treatment / all	0 / 17	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 552 (0.18%)	0 / 552 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 552 (0.00%)	2 / 552 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Contusion			

subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 552 (0.18%)	0 / 552 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
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 / 552 (0.18%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 552 (0.18%)	2 / 552 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 552 (0.18%)	0 / 552 (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 / 552 (0.18%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 552 (0.00%)	2 / 552 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Myocardial infarction			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 552 (0.18%)	0 / 552 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 552 (0.18%)	0 / 552 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric artery thrombosis			

subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 552 (0.00%)	2 / 552 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 552 (0.18%)	2 / 552 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 552 (0.54%)	3 / 552 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia bacterial			
subjects affected / exposed	1 / 552 (0.18%)	2 / 552 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	1 / 552 (0.18%)	0 / 552 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 552 (0.18%)	0 / 552 (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			
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 552 (0.00%)	1 / 552 (0.18%)	
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: 1 %

Non-serious adverse events	Glycopyrronium/Formoterol Fumarate	Umeclidinium/Vilanterol	
Total subjects affected by non-serious adverse events subjects affected / exposed	129 / 552 (23.37%)	153 / 552 (27.72%)	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	13 / 552 (2.36%) 16	7 / 552 (1.27%) 8	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	34 / 552 (6.16%) 52	41 / 552 (7.43%) 55	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	5 / 552 (0.91%) 6	6 / 552 (1.09%) 6	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	4 / 552 (0.72%) 4	7 / 552 (1.27%) 8	
Constipation subjects affected / exposed occurrences (all)	1 / 552 (0.18%) 1	7 / 552 (1.27%) 7	
Diarrhoea subjects affected / exposed occurrences (all)	7 / 552 (1.27%) 8	13 / 552 (2.36%) 15	
Dry mouth subjects affected / exposed occurrences (all)	2 / 552 (0.36%) 2	6 / 552 (1.09%) 6	
Toothache subjects affected / exposed occurrences (all)	1 / 552 (0.18%) 1	6 / 552 (1.09%) 6	
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	20 / 552 (3.62%) 22	20 / 552 (3.62%) 22	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 552 (0.18%)	6 / 552 (1.09%)	
occurrences (all)	1	7	
Back pain			
subjects affected / exposed	12 / 552 (2.17%)	9 / 552 (1.63%)	
occurrences (all)	13	9	
Pain in extremity			
subjects affected / exposed	1 / 552 (0.18%)	7 / 552 (1.27%)	
occurrences (all)	1	7	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	30 / 552 (5.43%)	36 / 552 (6.52%)	
occurrences (all)	32	42	
Sinusitis			
subjects affected / exposed	4 / 552 (0.72%)	6 / 552 (1.09%)	
occurrences (all)	4	8	
Upper respiratory tract infection			
subjects affected / exposed	10 / 552 (1.81%)	10 / 552 (1.81%)	
occurrences (all)	13	13	
Viral upper respiratory tract infection			
subjects affected / exposed	17 / 552 (3.08%)	26 / 552 (4.71%)	
occurrences (all)	18	27	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 July 2017	Primary and secondary objective tables updated by moving the peak change from baseline in FEV1 within 2 hours post-dosing over 24 weeks from secondary endpoint to become a primary endpoint, and statistical methods, including hierarchical testing procedures, updated accordingly. Section 1.3 (benefit/risk and ethical assessment) updated to add clarification on the chest x-ray. Inclusion criterion 9 updated with clarification on chest x-ray requirements. Exclusion criteria 2, 3 and 10 updated with clarifications and to correct an omission. Requirements for screening/enrolment and treatment period visits clarified in Section 4. Section 5.1.1 updated to clarify timing and acceptable manoeuvres for spirometry assessments. Section 5.1.2 updated to clarify when certain assessments should not be done. Table 8 on prohibited COPD medications: use of the ICS/LABA combination clarified and triple therapy removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported