Clinical trial results:
A Clinical Study to Evaluate Four Doses of Umeclidinium Bromide in Combination with Fluticasone Furoate in COPD Subjects with an Asthmatic Component

Summary

EudraCT number	2014-000883-16
Trial protocol	DE RO PL
Global end of trial date	18 July 2015

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	01 April 2016

Trial information

Trial identification

Sponsor protocol code	200699

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	Clinical Trials HelpDesk, GlaxoSmithKline Research & Development Ltd, +44 208990 4466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials HelpDesk, GlaxoSmithKline Research & Development Ltd, +44 208990 4466, 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	02 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the dose-response of once-daily UMEC in combination with FF (100/15.6, 100/62.5, 100/125, and 100/250 mcg) compared to FF 100 mcg monotherapy over a 4-week treatment period in COPD subjects with an asthmatic component.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 13
Country: Number of subjects enrolled	Russian Federation: 60
Country: Number of subjects enrolled	Ukraine: 96
Country: Number of subjects enrolled	United States: 37
Country: Number of subjects enrolled	Poland: 42
Country: Number of subjects enrolled	Romania: 61
Country: Number of subjects enrolled	Germany: 29
Worldwide total number of subjects	338
EEA total number of subjects	132

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)	251
From 65 to 84 years	87
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants (par.) with sufficient signs and symptoms to diagnose as having chronic obstructive pulmonary disease (COPD) and evidence of an asthmatic component as demonstrated by spirometry, reversibility and current therapy at the point of screening were eligible for participation in the study.

Pre-assignment

Screening details:

Participants on inhaled corticosteroid therapy over the previous 12 weeks, including a stable dose during the 4 weeks prior to Visit 0, entered the 4-week run-in period on open-label fluticasone propionate 250 microgram (µg) and salmeterol 50 µg combination. Eligible par. were stratified by smoking status, age and randomized to Treatment Phase A.

Period 1

Period 1 title	Treatment Phase A (4 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	FF 100 µg

Arm description:

Participants received fluticasone furoate (FF) 100 µg once daily in the morning by inhalation using a dry powder inhaler (DPI) for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via metered-dose inhaler (MDI) to be used on an as-needed basis (rescue medication) throughout the study.

Arm type	Active comparator
Investigational medicinal product name	Fluticasone Furoate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone furoate is available as fluticasone furoate inhalation powder (100 mcg per blister) once daily in the morning

Arm title	FF/UMEC 100/15.6 µg

Arm description:

Participants received FF 100 µg in combination with umeclidinium bromide (UMEC) 15.6 µg once daily in the morning by inhalation using a DPI for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

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

Dosage and administration details:

A combination of fluticasone furoate/umeclidinium bromide inhalation powder (fluticasone furoate: 100 mcg per blister, umeclidinium bromide: 15.6, 62.5, 125, or 250 mcg per blister) once daily in the morning

Arm title	FF/UMEC 100/62.5 µg

Arm description:

Participants received FF 100 µg in combination with UMEC 62.5 µg once daily in the morning by inhalation using a DPI for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

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

Dosage and administration details:

A combination of fluticasone furoate/umeclidinium bromide inhalation powder (fluticasone furoate: 100 mcg per blister, umeclidinium bromide: 15.6, 62.5, 125, or 250 mcg per blister) once daily in the morning

Arm title	FF/UMEC 100/125 µg

Arm description:

Participants received FF 100 µg in combination with UMEC 125 µg once daily in the morning by inhalation using a DPI for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

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

Dosage and administration details:

A combination of fluticasone furoate/umeclidinium bromide inhalation powder (fluticasone furoate: 100 mcg per blister, umeclidinium bromide: 15.6, 62.5, 125, or 250 mcg per blister) once daily in the morning

Arm title	FF/UMEC 100/250 µg

Arm description:

Participants received FF 100 µg in combination with UMEC 250 µg once daily in the morning by inhalation using a DPI for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

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

Dosage and administration details:

A combination of fluticasone furoate/umeclidinium bromide inhalation powder (fluticasone furoate: 100 mcg per blister, umeclidinium bromide: 15.6, 62.5, 125, or 250 mcg per blister) once daily in the morning

Arm title	FF/VI 100/25 µg

Arm description:

Participants received FF 100 µg in combination with vilanterol trifenatate (VI) 25 µg once daily in the morning by inhalation using a DPI for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Arm type	Active comparator

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

Dosage and administration details:

Combination of fluticasone furoate/vilanterol inhalation powder (fluticasone furoate: 100 mcg per blister, vilanterol: 25 mcg per blister) once daily in the morning

Number of subjects in period 1	FF 100 µg	FF/UMEC 100/15.6 µg	FF/UMEC 100/62.5 µg
Started	41	42	40
Completed	39	42	39
Not completed	2	0	1
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	-	-	1
Protocol defined stopping criteria	1	-	-
Lack of efficacy	-	-	-

Number of subjects in period 1	FF/UMEC 100/125 µg	FF/UMEC 100/250 µg	FF/VI 100/25 µg
Started	46	85	84
Completed	44	82	83
Not completed	2	3	1
Consent withdrawn by subject	-	2	-
Adverse event, non-fatal	1	-	-
Protocol defined stopping criteria	1	-	1
Lack of efficacy	-	1	-

Period 2

Period 2 title	Treatment Phase B (1 Week)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes

Arm title	FF/UMEC 100/250 µg

Arm description:

Participants received FF 100 µg in combination with umeclidinium bromide (UMEC) 250 µg and placebo once daily in the morning by inhalation using two separate DPIs for 1 week. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

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

Dosage and administration details:

A combination of fluticasone furoate/umeclidinium bromide inhalation powder (fluticasone furoate: 100 mcg per blister, umeclidinium bromide: 15.6, 62.5, 125, or 250 mcg per blister) once daily in the morning

Arm title	FF/UMEC/VI 100/250/25 µg

Arm description:

Participants received FF 100 µg in combination with umeclidinium bromide (UMEC) 250 µg and VI 25 µg once daily in the morning by inhalation using two separate DPIs (FF/UMEC 100/250 & VI 25) for 1 week. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

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

Dosage and administration details:

Combination of fluticasone furoate/umeclidinium bromide/vilanterol inhalation powder (fluticasone furoate: 100 mcg per blister, umeclidinium bromide: 250 mcg per blister, vilanterol: 25 mcg per blister) once daily in the morning (as two separate inhalers: FF/UMEC 100/250 & VI 25)

Number of subjects in period 2	FF/UMEC 100/250 µg	FF/UMEC/VI 100/250/25 µg
Started	166	163
Completed	163	162
Not completed	3	1
Physician decision	-	1
Adverse event, non-fatal	2	-
Protocol defined stopping criteria	1	-

Period 3

Period 3 title	Treatment Phase C (1 Week)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	FF 100 µg

Arm description:

Participants on inhaled FF/UMEC 100/250 µg once daily in the morning during Treatment Phase B, received inhaled FF 100 µg and placebo once daily in the morning using two separate DPIs for 1 week. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Arm type	Active comparator
Investigational medicinal product name	Fluticasone Furoate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone furoate is available as fluticasone furoate inhalation powder (100 mcg per blister) once daily in the morning

Arm title	FF/UMEC 100/250 µg

Arm description:

Participants on inhaled FF/UMEC 100/250 µg once daily in the morning during Treatment Phase B, received inhaled FF/UMEC 100/250 µg and placebo once daily in the morning using two separate DPIs for 1 week. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

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

Dosage and administration details:

A combination of fluticasone furoate/umeclidinium bromide inhalation powder (fluticasone furoate: 100 mcg per blister, umeclidinium bromide: 15.6, 62.5, 125, or 250 mcg per blister) once daily in the morning

Arm title	FF/VI 100/25 µg

Arm description:

Participants on inhaled FF/UMEC/VI 100/250/25 µg once daily in the morning during Treatment Phase B, received inhaled FF/VI 100/25 µg and placebo once daily in the morning using two separate DPIs for 1 week. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Arm type	Active comparator
Investigational medicinal product name	Fluticasone Furoate/Vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Combination of fluticasone furoate/vilanterol inhalation powder (fluticasone furoate: 100 mcg per blister, vilanterol: 25 mcg per blister) once daily in the morning

Arm title	FF/UMEC/VI 100/250/25 µg

Arm description:

Participants on inhaled FF/UMEC/VI 100/250/25 µg once daily in the morning during Treatment Phase B, received inhaled FF/UMEC/VI 100 /250 /25 µg (as two separate inhalers: FF/UMEC 100/250 and VI 25) once daily in the morning using two separate DPIs for 1 week. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

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

Dosage and administration details:

Combination of fluticasone furoate/umeclidinium bromide/vilanterol inhalation powder (fluticasone furoate: 100 mcg per blister, umeclidinium bromide: 250 mcg per blister, vilanterol: 25 mcg per blister) once daily in the morning (as two separate inhalers: FF/UMEC 100/250 & VI 25)

Number of subjects in period 3	FF 100 µg	FF/UMEC 100/250 µg	FF/VI 100/25 µg
Started	79	84	82
Completed	78	84	82
Not completed	1	0	0
Consent withdrawn by subject	1	-	-
Physician decision	-	-	-
Adverse event, non-fatal	-	-	-

Number of subjects in period 3	FF/UMEC/VI 100/250/25 µg
Started	80
Completed	78
Not completed	2
Consent withdrawn by subject	-
Physician decision	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	FF 100 µg
Reporting group description:	
Participants received fluticasone furoate (FF) 100 µg once daily in the morning by inhalation using a dry powder inhaler (DPI) for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via metered-dose inhaler (MDI) to be used on an as-needed basis (rescue medication) throughout the study.	
Reporting group title	FF/UMEC 100/15.6 µg
Reporting group description:	
Participants received FF 100 µg in combination with umeclidinium bromide (UMEC) 15.6 µg once daily in the morning by inhalation using a DPI for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.	
Reporting group title	FF/UMEC 100/62.5 µg
Reporting group description:	
Participants received FF 100 µg in combination with UMEC 62.5 µg once daily in the morning by inhalation using a DPI for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.	
Reporting group title	FF/UMEC 100/125 µg
Reporting group description:	
Participants received FF 100 µg in combination with UMEC 125 µg once daily in the morning by inhalation using a DPI for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.	
Reporting group title	FF/UMEC 100/250 µg
Reporting group description:	
Participants received FF 100 µg in combination with UMEC 250 µg once daily in the morning by inhalation using a DPI for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.	
Reporting group title	FF/VI 100/25 µg
Reporting group description:	
Participants received FF 100 µg in combination with vilanterol trifenatate (VI) 25 µg once daily in the morning by inhalation using a DPI for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.	

Reporting group values	FF 100 µg	FF/UMEC 100/15.6 µg	FF/UMEC 100/62.5 µg
Number of subjects	41	42	40
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.4	55.5	56.7
standard deviation	± 8.59	± 11.33	± 10.14
Gender categorical Units: Subjects			
Female	21	23	19
Male	20	19	21

Race, Customized Units: Subjects			
African American/African Heritage	1	0	1
White- Arabic/ North African Heritage	0	0	0
White- White/Caucasian/European Heritage	40	42	39
Mixed Race	0	0	0

Reporting group values	FF/UMEC 100/125 µg	FF/UMEC 100/250 µg	FF/VI 100/25 µg
Number of subjects	46	85	84
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.2	57.8	57.6
standard deviation	± 10.47	± 11.03	± 10.95
Gender categorical Units: Subjects			
Female	18	38	41
Male	28	47	43
Race, Customized Units: Subjects			
African American/African Heritage	1	3	1
White- Arabic/ North African Heritage	1	0	0
White- White/Caucasian/European Heritage	44	81	83
Mixed Race	0	1	0

Reporting group values	Total		
Number of subjects	338		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	160		
Male	178		
Race, Customized Units: Subjects			
African American/African Heritage	7		
White- Arabic/ North African Heritage	1		
White- White/Caucasian/European Heritage	329		
Mixed Race	1		

End points

End points reporting groups

Reporting group title	FF 100 µg

Reporting group description:

Participants received fluticasone furoate (FF) 100 µg once daily in the morning by inhalation using a dry powder inhaler (DPI) for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via metered-dose inhaler (MDI) to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF/UMEC 100/15.6 µg

Reporting group description:

Participants received FF 100 µg in combination with umeclidinium bromide (UMEC) 15.6 µg once daily in the morning by inhalation using a DPI for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF/UMEC 100/62.5 µg

Reporting group description:

Participants received FF 100 µg in combination with UMEC 62.5 µg once daily in the morning by inhalation using a DPI for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF/UMEC 100/125 µg

Reporting group description:

Participants received FF 100 µg in combination with UMEC 125 µg once daily in the morning by inhalation using a DPI for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF/UMEC 100/250 µg

Reporting group description:

Participants received FF 100 µg in combination with UMEC 250 µg once daily in the morning by inhalation using a DPI for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF/VI 100/25 µg

Reporting group description:

Participants received FF 100 µg in combination with vilanterol trifenatate (VI) 25 µg once daily in the morning by inhalation using a DPI for 4 weeks. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF/UMEC 100/250 µg

Reporting group description:

Participants received FF 100 µg in combination with umeclidinium bromide (UMEC) 250 µg and placebo once daily in the morning by inhalation using two separate DPIs for 1 week. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF/UMEC/VI 100/250/25 µg

Reporting group description:

Participants received FF 100 µg in combination with umeclidinium bromide (UMEC) 250 µg and VI 25 µg once daily in the morning by inhalation using two separate DPIs (FF/UMEC 100/250 & VI 25) for 1 week. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF 100 µg

Reporting group description:

Participants on inhaled FF/UMEC 100/250 µg once daily in the morning during Treatment Phase B, received inhaled FF 100 µg and placebo once daily in the morning using two separate DPIs for 1 week. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF/UMEC 100/250 µg

Reporting group description:

Participants on inhaled FF/UMEC 100/250 µg once daily in the morning during Treatment Phase B, received inhaled FF/UMEC 100/250 µg and placebo once daily in the morning using two separate DPIs for 1 week. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF/VI 100/25 µg

Reporting group description:

Participants on inhaled FF/UMEC/VI 100/250/25 µg once daily in the morning during Treatment Phase B, received inhaled FF/VI 100/25 µg and placebo once daily in the morning using two separate DPIs for 1 week. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF/UMEC/VI 100/250/25 µg

Reporting group description:

Participants on inhaled FF/UMEC/VI 100/250/25 µg once daily in the morning during Treatment Phase B, received inhaled FF/UMEC/VI 100 /250 /25 µg (as two separate inhalers: FF/UMEC 100/250 and VI 25) once daily in the morning using two separate DPIs for 1 week. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Primary: Change from Baseline in clinic trough forced expiratory volume in one second (FEV1) at the end of Treatment Phase A (Visit 6/Day 29)

End point title	Change from Baseline in clinic trough forced expiratory volume in one second (FEV1) at the end of Treatment Phase A (Visit 6/Day 29)

End point description:

FEV1 is defined as forced expiratory volume in one second and measured in the morning at Visits 1 through 8 between 6:00 and 11:00 electronically by spirometry. Change from Baseline in trough FEV1 is defined as the difference in the value obtained at Visit 6 (24 hours post-dose on Visit 5) and the last acceptable/borderline acceptable value obtained prior to randomization (from Visit 2 pre-bronchodilator or Visit 3 pre-dose). Trough FEV1 is defined as the acceptable/borderline acceptable FEV1 value obtained at Visit 6, approximately 24 hours after morning dosing on Visit 5. ITT population is comprised of all participants randomized to treatment who received at least one dose of randomized study medication in the treatment period. All comparisons for statistical purposes are with the FF 100 µg arm.

End point type	Primary

End point timeframe:

Baseline and Day 29

End point values	FF 100 µg	FF/UMEC 100/15.6 µg	FF/UMEC 100/62.5 µg	FF/UMEC 100/125 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[1]	42[2]	39[3]	44[4]
Units: Liters				
arithmetic mean (standard deviation)	0.047 (± 0.3002)	0.146 (± 0.233)	0.193 (± 0.2192)	0.175 (± 0.2478)

Notes:

[1] - ITT Population. Only those participants available at the specified time point were analyzed.

[2] - ITT Population. Only those participants available at the specified time point were analyzed.

[3] - ITT Population. Only those participants available at the specified time point were analyzed.

[4] - ITT Population. Only those participants available at the specified time point were analyzed.

End point values	FF/UMEC 100/250 µg	FF/VI 100/25 µg		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81[5]	83[6]		
Units: Liters				
arithmetic mean (standard deviation)	0.143 (± 0.315)	0.121 (± 0.2779)		

Notes:

[5] - ITT Population. Only those participants available at the specified time point were analyzed.

[6] - ITT Population. Only those participants available at the specified time point were analyzed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	FF 100 µg v FF/UMEC 100/15.6 µg
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	Final step dose response model
Parameter estimate	Mean difference (net)
Point estimate	0.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.014
upper limit	0.193

Statistical analysis title	Statistical Analysis 2
Comparison groups	FF 100 µg v FF/UMEC 100/62.5 µg
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	Final step dose response model
Parameter estimate	Mean difference (net)
Point estimate	0.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.014
upper limit	0.193

Statistical analysis title	Statistical Analysis 3
Comparison groups	FF 100 µg v FF/UMEC 100/125 µg

Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	Final step dose response model
Parameter estimate	Mean difference (net)
Point estimate	0.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.014
upper limit	0.193

Statistical analysis title	Statistical Analysis 4
Comparison groups	FF 100 µg v FF/UMEC 100/250 µg
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	Final step dose response model
Parameter estimate	Mean difference (net)
Point estimate	0.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.014
upper limit	0.193

Statistical analysis title	Statistical Analysis 5
Comparison groups	FF 100 µg v FF/VI 100/25 µg
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.152
Method	Final step dose response model
Parameter estimate	Mean difference (net)
Point estimate	0.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.027
upper limit	0.172

Secondary: Mean change from Baseline in rescue medication use at the end of

Treatment Phase A

End point title	Mean change from Baseline in rescue medication use at the end of Treatment Phase A

End point description:

All participants (par) received the albuterol/salbutamol via MDI as a rescue medication on an as-needed basis. Total daily rescue medication (RM) use for a given day is defined as the sum of daytime albuterol/salbutamol use recorded in PM and nighttime albuterol/salbutamol use recorded in AM the next day.The number of puffs of albuterol (salbutamol) MDI used in the last 12 hours for relief of symptoms were recorded morning and evening in the eDiary by the par. End of Treatment Phase A is defined as the last 7 days of Treatment Phase A.Change from Baseline at the end of Treatment Phase is the difference between the end of Treatment Phase value and the appropriate baseline week.Analysis performed using analysis of covariance with covariates of treatment, age, sex, baseline RM use, pack years smoked per randomization stratification and age when first treated with an inhaler per randomization stratification.Baseline is the last 7 days of run-in period of randomization.

End point type	Secondary

End point timeframe:

Baseline and End of Treatment Phase A (All comparisons for statistical purposes are with the FF 100 µg arm).

End point values	FF 100 µg	FF/UMEC 100/15.6 µg	FF/UMEC 100/62.5 µg	FF/UMEC 100/125 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41[7]	42[8]	40[9]	46[10]
Units: Puffs				
least squares mean (standard error)				
Daily rescue medication, n=39,42,39,43,80,82	0.6 (± 0.29)	-0.4 (± 0.29)	-0.5 (± 0.29)	0 (± 0.27)

Notes:

[7] - ITT Population. Only those participants available at the specified time point were analyzed.

[8] - ITT Population. Only those participants available at the specified time point were analyzed.

[9] - ITT Population. Only those participants available at the specified time point were analyzed.

[10] - ITT Population. Only those participants available at the specified time point were analyzed.

End point values	FF/UMEC 100/250 µg	FF/VI 100/25 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85[11]	84[12]		
Units: Puffs				
least squares mean (standard error)				
Daily rescue medication, n=39,42,39,43,80,82	-0.2 (± 0.21)	-0.1 (± 0.21)		

Notes:

[11] - ITT Population. Only those participants available at the specified time point were analyzed.

[12] - ITT Population. Only those participants available at the specified time point were analyzed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	FF 100 µg v FF/UMEC 100/15.6 µg

Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	-0.2

Statistical analysis title	Statistical Analysis 2
Comparison groups	FF 100 µg v FF/UMEC 100/62.5 µg
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	-0.4

Statistical analysis title	Statistical Analysis 3
Comparison groups	FF 100 µg v FF/UMEC 100/125 µg
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.083
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0.1

Statistical analysis title	Statistical Analysis 4

Comparison groups	FF 100 µg v FF/UMEC 100/250 µg
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	-0.2

Statistical analysis title	Statistical Analysis 5
Comparison groups	FF 100 µg v FF/VI 100/25 µg
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-0.1

Secondary: Mean change from Baseline in E-RS total scores at the end of Treatment Phase A

End point title	Mean change from Baseline in E-RS total scores at the end of Treatment Phase A

End point description:

A daily symptoms score for exacerbations of chronic pulmonary disease tool - Respiratory Symptoms (E-RS) is derived by summing the 11 item-level E-RS scores. E-RS is intended to capture information related to the respiratory symptoms of COPD. The Baseline E-RS score is defined as the mean within-subject daily score over 7 days prior to randomization, with data present for a minimum of 4 of the 7 days. End of Treatment Phase A is defined as the last 7 days of Treatment Phase A. Change from Baseline at the end of Treatment Phase is the difference between the end of Treatment Phase value and the appropriate Baseline week. Analysis performed using analysis of covariance with covariates of treatment, age, sex, baseline score, pack years smoked per randomization stratification and age when first treated with an inhaler per randomization stratification. Baseline is the last 7 days of the run-in period prior to randomization. All comparisons for statistical purposes are with the FF 100 µg arm

End point type	Secondary

End point timeframe:

Baseline and End of Treatment Phase A

End point values	FF 100 µg	FF/UMEC 100/15.6 µg	FF/UMEC 100/62.5 µg	FF/UMEC 100/125 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[13]	42[14]	39[15]	43[16]
Units: Score on scale				
least squares mean (standard error)	0.5 (± 0.54)	-2.6 (± 0.55)	-2.5 (± 0.56)	-1.5 (± 0.52)

Notes:

[13] - ITT Population. Only those participants available at the specified time point were analyzed.

[14] - ITT Population. Only those participants available at the specified time point were analyzed.

[15] - ITT Population. Only those participants available at the specified time point were analyzed.

[16] - ITT Population. Only those participants available at the specified time point were analyzed.

End point values	FF/UMEC 100/250 µg	FF/VI 100/25 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81[17]	83[18]		
Units: Score on scale				
least squares mean (standard error)	-1.5 (± 0.4)	-1.1 (± 0.41)		

Notes:

[17] - ITT Population. Only those participants available at the specified time point were analyzed.

[18] - ITT Population. Only those participants available at the specified time point were analyzed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	FF 100 µg v FF/UMEC 100/15.6 µg
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	-1.7

Statistical analysis title	Statistical Analysis 2
Comparison groups	FF 100 µg v FF/UMEC 100/62.5 µg

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	-1.6

Statistical analysis title	Statistical Analysis 3
Comparison groups	FF 100 µg v FF/UMEC 100/125 µg
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	-0.6

Statistical analysis title	Statistical Analysis 4
Comparison groups	FF 100 µg v FF/UMEC 100/250 µg
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	-0.7

Statistical analysis title	Statistical Analysis 5

Comparison groups	FF 100 µg v FF/VI 100/25 µg
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	-0.4

Secondary: Change from Baseline in daily morning (AM) PEF (pre-dose and pre-rescue bronchodilator) measured at home and averaged over the last 21 days of Treatment Phase A

End point title	Change from Baseline in daily morning (AM) PEF (pre-dose and pre-rescue bronchodilator) measured at home and averaged over the last 21 days of Treatment Phase A

End point description:

Peak expiratory flow (PEF) stability limit was calculated from AM PEF measurements on the 7days preceding Visit 3 as mean AM PEF from the available 7days preceding Visit 3x80%.The PEF stability limit serves as a benchmark of the participants run-in COPD status and used for comparison during the treatment phase to assess subject safety.Change from Baseline over the last 21days of Treatment Phase A is the difference between the last 21days of Treatment Phase Aand the appropriate Baseline week.The last 21days of Treatment Phase A include the AM assessments on the date of Visit 6.For the AM assessments, these include the date of Visit 6 and the 20 consecutive days preceding the date of Visit Analysis performed using analysis of covariance with covariates of treatment, age, sex, Baseline AM PEF, pack years smoked per randomization stratification and age when first treated with an inhaler per randomization stratification.Baseline is the last 7days of the run-in period prior to randomization

End point type	Secondary

End point timeframe:

Baseline and from Day 8 through Day 29 (All comparisons for statistical purposes are with the FF 100 µg arm)

End point values	FF 100 µg	FF/UMEC 100/15.6 µg	FF/UMEC 100/62.5 µg	FF/UMEC 100/125 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[19]	42[20]	39[21]	43[22]
Units: Liters per minute (L/min)				
least squares mean (standard error)	-14.2 (± 4.62)	3.9 (± 4.7)	7.6 (± 4.76)	5.5 (± 4.4)

Notes:

[19] - ITT Population. Only those participants available at the specified time point were analyzed.

[20] - ITT Population. Only those participants available at the specified time point were analyzed.

[21] - ITT Population. Only those participants available at the specified time point were analyzed.

[22] - ITT Population. Only those participants available at the specified time point were analyzed.

End point values	FF/UMEC 100/250 µg	FF/VI 100/25 µg		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81[23]	83[24]		
Units: Liters per minute (L/min)				
least squares mean (standard error)	10.5 (± 3.37)	4.3 (± 3.47)		

Notes:

[23] - ITT Population. Only those participants available at the specified time point were analyzed.

[24] - ITT Population. Only those participants available at the specified time point were analyzed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	FF 100 µg v FF/UMEC 100/15.6 µg
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	18.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.9
upper limit	30.3

Statistical analysis title	Statistical Analysis 2
Comparison groups	FF 100 µg v FF/UMEC 100/62.5 µg
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	21.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.4
upper limit	34.1

Statistical analysis title	Statistical Analysis 3
Comparison groups	FF 100 µg v FF/UMEC 100/125 µg

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	19.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.7
upper limit	31.7

Statistical analysis title	Statistical Analysis 4
Comparison groups	FF 100 µg v FF/UMEC 100/250 µg
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	24.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.1
upper limit	35.4

Statistical analysis title	Statistical Analysis 5
Comparison groups	FF 100 µg v FF/VI 100/25 µg
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	18.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	8
upper limit	29.1

Secondary: Change from trough in clinic FEV1 at 3 hours post-study Treatment at

Visit 5/Day 28

End point title	Change from trough in clinic FEV1 at 3 hours post-study Treatment at Visit 5/Day 28

End point description:

FEV1 is defined as forced expiratory volume in one second and measured in the morning between 6:00 and 11:00 electronically by spirometry.At Visit 5, after trough FEV1 is measured the subject received investigational product.3 hours post-dose, spirometry was repeated and subject then receiving 2 puffs of albuterol/salbutamol.After 30 minutes elapsed, the subject repeated the spirometry assessment again.Change from Baseline in clinic trough (pre-dose) FEV1 is defined as the difference in the trough value at 3 hours post-dose peak FEV1 and the Baseline value.If either the trough value or the Baseline was missing, then change from Baseline was considered as missing.Baseline value of clinic FEV1 is the last acceptable/borderline acceptable (pre-dose) FEV1 value obtained prior to randomization (either from Visit 3 pre-dose or from Visit 2 pre-bronchodilator).

End point type	Secondary

End point timeframe:

Baseline and Day 28

End point values	FF 100 µg	FF/UMEC 100/15.6 µg	FF/UMEC 100/62.5 µg	FF/UMEC 100/125 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38[25]	42[26]	39[27]	45[28]
Units: Liters (L)				
least squares mean (standard error)	0.048 (± 0.0307)	0.093 (± 0.0305)	0.088 (± 0.0309)	0.072 (± 0.0279)

Notes:

[25] - ITT Population. Only those participants available at the specified time point were analyzed.

[26] - ITT Population. Only those participants available at the specified time point were analyzed.

[27] - ITT Population. Only those participants available at the specified time point were analyzed.

[28] - ITT Population. Only those participants available at the specified time point were analyzed.

End point values	FF/UMEC 100/250 µg	FF/VI 100/25 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81[29]	82[30]		
Units: Liters (L)				
least squares mean (standard error)	0.052 (± 0.022)	0.124 (± 0.0227)		

Notes:

[29] - ITT Population. Only those participants available at the specified time point were analyzed.

[30] - ITT Population. Only those participants available at the specified time point were analyzed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	FF 100 µg v FF/UMEC 100/15.6 µg
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.264
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.045

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.034
upper limit	0.125

Statistical analysis title	Statistical Analysis 2
Comparison groups	FF 100 µg v FF/UMEC 100/62.5 µg
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.328
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.041
upper limit	0.121

Statistical analysis title	Statistical Analysis 3
Comparison groups	FF 100 µg v FF/UMEC 100/125 µg
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.534
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.025
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.054
upper limit	0.103

Statistical analysis title	Statistical Analysis 4
Comparison groups	FF 100 µg v FF/UMEC 100/250 µg

Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.895
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.065
upper limit	0.075

Statistical analysis title	Statistical Analysis 5
Comparison groups	FF 100 µg v FF/VI 100/25 µg
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.007
upper limit	0.146

Secondary: Change in clinic FEV1 following 2 puffs of albuterol/salbutamol given 3 hours post-study treatment dose at Visit 5/Day 28

End point title	Change in clinic FEV1 following 2 puffs of albuterol/salbutamol given 3 hours post-study treatment dose at Visit 5/Day 28

End point description:

FEV1 is defined as forced expiratory volume in one second and measured in the morning electronically by spirometry. At Visit 5 trough FEV1 is measured and subject received investigational product. 3 hours post-dose, spirometry was repeated and subject then received 2 puffs of albuterol/salbutamol. After 30 minutes elapsed, subject repeated spirometry assessment. Change from Baseline in clinic trough (pre-dose) FEV1 is defined as the difference in trough value at 3 hours post-dose peak FEV1 and Baseline. If either trough or Baseline value was missing, change from Baseline was considered missing. Baseline clinic FEV1 is the last acceptable/borderline acceptable (pre-dose) FEV1 prior to randomization. Analysis performed using analysis of covariance with covariates of treatment, age, sex, baseline clinic trough FEV1, pre-dose trough FEV1 at Visit 5, pack years smoked per randomization stratification and age when first treated with an inhaler per randomization stratification.

End point type	Secondary

End point timeframe:

Baseline and Day 28

End point values	FF 100 µg	FF/UMEC 100/15.6 µg	FF/UMEC 100/62.5 µg	FF/UMEC 100/125 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37[31]	40[32]	38[33]	42[34]
Units: Liters				
least squares mean (standard error)	0.249 (± 0.0287)	0.161 (± 0.0284)	0.159 (± 0.0284)	0.16 (± 0.0262)

Notes:

[31] - ITT Population. Only those participants available at the specified time point were analyzed.

[32] - ITT Population. Only those participants available at the specified time point were analyzed.

[33] - ITT Population. Only those participants available at the specified time point were analyzed.

[34] - ITT Population. Only those participants available at the specified time point were analyzed.

End point values	FF/UMEC 100/250 µg	FF/VI 100/25 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80[35]	80[36]		
Units: Liters				
least squares mean (standard error)	0.189 (± 0.0202)	0.087 (± 0.0209)		

Notes:

[35] - ITT Population. Only those participants available at the specified time point were analyzed.

[36] - ITT Population. Only those participants available at the specified time point were analyzed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	FF 100 µg v FF/UMEC 100/15.6 µg
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.088
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.162
upper limit	-0.014

Statistical analysis title	Statistical Analysis 2
Comparison groups	FF 100 µg v FF/UMEC 100/62.5 µg

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.165
upper limit	-0.016

Statistical analysis title	Statistical Analysis 3
Comparison groups	FF 100 µg v FF/UMEC 100/125 µg
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.089
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.162
upper limit	-0.016

Statistical analysis title	Statistical Analysis 4
Comparison groups	FF 100 µg v FF/UMEC 100/250 µg
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.066
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.124
upper limit	0.004

Statistical analysis title	Statistical Analysis 5

Comparison groups	FF 100 µg v FF/VI 100/25 µg
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.163
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.227
upper limit	-0.099

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AE) and serious adverse events (SAE) were collected from start of the run-in period until follow-up. SAEs related to participation or GSK concomitant medication were recorded from time of consent up to and including any follow up contact.

Adverse event reporting additional description:

AEs and SAEs were collected for the ITT population, comprised of all participants randomized to treatment who received at least one dose of randomized study medication in the treatment period. Assessed as related to participation might include; study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	FF 100 µg

Reporting group description:

Participants received fluticasone furoate (FF) 100 µg once daily in the morning by inhalation using a dry powder inhaler (DPI) for 4 weeks during Treatment Phase A and 1 week during Treatment Phase C. In addition, all participants received supplemental albuterol/salbutamol via metered-dose inhaler (MDI) to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF/UMEC 100/15.6 µg

Reporting group description:

Participants received FF 100 µg in combination with umeclidinium bromide (UMEC) 15.6 µg once daily in the morning by inhalation using a DPI for 4 weeks during Treatment Phase A. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF/UMEC 100/62.5 µg

Reporting group description:

Participants received FF 100 µg in combination with UMEC 62.5 µg once daily in the morning by inhalation using a DPI for 4 weeks during Treatment Phase A. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF/UMEC 100/125 µg

Reporting group description:

Participants received FF 100 µg in combination with UMEC 125 µg once daily in the morning by inhalation using a DPI for 4 weeks during Treatment Phase A. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF/UMEC 100/250 µg

Reporting group description:

Participants received FF 100 µg in combination with UMEC 250 µg once daily in the morning by inhalation using a DPI for 4 weeks during Treatment Phase A and 1 week during Treatment Phase B and C. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF/VI 100/25 µg

Reporting group description:

Participants received FF 100 µg in combination with vilanterol trifenatate (VI) 25 µg once daily in the morning by inhalation using a DPI for 4 weeks during Treatment Phase A and 1 week during Treatment Phase C. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Reporting group title	FF/UMEC/VI 100/250/25 µg

Reporting group description:

Participants received FF 100 µg in combination with umeclidinium bromide (UMEC) 250 µg and VI 25 µg once daily in the morning by inhalation using two separate DPIs (FF/UMEC 100/250 & VI 25)

for 1 week during Treatment Phase B and C. In addition, all participants received supplemental albuterol/salbutamol via MDI to be used on an as-needed basis (rescue medication) throughout the study.

Serious adverse events	FF 100 µg	FF/UMEC 100/15.6 µg	FF/UMEC 100/62.5 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 111 (0.00%)	0 / 42 (0.00%)	0 / 40 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypertensive crisis	Additional description: One subject had a non-fatal SAE of pneumonia 2 days after withdrawal, which resolved. This subject also had 2 fatal SAEs; TIA and PE, onset 14 and 17 days after last dose, respectively. The investigator considered pneumonia and PE treatment-related.		
subjects affected / exposed	0 / 111 (0.00%)	0 / 42 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	FF/UMEC 100/125 µg	FF/UMEC 100/250 µg	FF/VI 100/25 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 46 (0.00%)	1 / 210 (0.48%)	0 / 146 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypertensive crisis	Additional description: One subject had a non-fatal SAE of pneumonia 2 days after withdrawal, which resolved. This subject also had 2 fatal SAEs; TIA and PE, onset 14 and 17 days after last dose, respectively. The investigator considered pneumonia and PE treatment-related.		
subjects affected / exposed	0 / 46 (0.00%)	1 / 210 (0.48%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	FF/UMEC/VI 100/250/25 µg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 163 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertensive crisis	Additional description: One subject had a non-fatal SAE of pneumonia 2 days after withdrawal, which resolved. This subject also had 2 fatal SAEs; TIA and PE, onset 14 and 17 days after last dose, respectively. The investigator considered pneumonia and PE treatment-related.		

subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	FF 100 µg	FF/UMEC 100/15.6 µg	FF/UMEC 100/62.5 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 111 (5.41%)	5 / 42 (11.90%)	4 / 40 (10.00%)
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	0 / 111 (0.00%)	3 / 42 (7.14%)	1 / 40 (2.50%)
occurrences (all)	0	3	1
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 42 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 111 (5.41%)	3 / 42 (7.14%)	2 / 40 (5.00%)
occurrences (all)	6	3	3

Non-serious adverse events	FF/UMEC 100/125 µg	FF/UMEC 100/250 µg	FF/VI 100/25 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 46 (8.70%)	5 / 210 (2.38%)	4 / 146 (2.74%)
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	0 / 46 (0.00%)	1 / 210 (0.48%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	3 / 46 (6.52%)	0 / 210 (0.00%)	0 / 146 (0.00%)
occurrences (all)	3	0	0
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	2 / 46 (4.35%)	4 / 210 (1.90%)	4 / 146 (2.74%)
occurrences (all)	2	4	4

Non-serious adverse events	FF/UMEC/VI 100/250/25 µg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 163 (0.00%)		
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 August 2014	This amendment was implemented in order to modify the treatment duration of Phase B and visit windows of Phase B and Phase C. Updates were also made to clarify procedures, update inclusion/exclusion criteria, ensure consistency in the definition of severe exacerbation, and ensure the EXACT endpoint definition was consistent with the EXACT manual. Minor adjustments in wording were made to exploratory endpoints and statistical testing methods.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported