Clinical trial results:
AC4116136: A multicenter, randomized, double-blind, parallelgroup study to evaluate the efficacy and safety of the addition of umeclidinium bromide Inhalation Powder (62.5mcg) once-daily to fluticasone propionate/salmeterol (250/50mcg) twice-daily, umeclidinium bromide Inhalation Powder (125mcg) once-daily to fluticasone propionate/salmeterol (250/50mcg) twice-daily versus placebo to fluticasone propionate/salmeterol (250/50mcg) twice-daily over 12 weeks in subjects with COPD.

Summary

EudraCT number	2012-001871-35
Trial protocol	CZ
Global end of trial date	16 August 2013

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	17 July 2015

Trial information

Trial identification

Sponsor protocol code	AC4116136

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01772147
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 August 2013
Global end of trial reached?	Yes
Global end of trial date	16 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare the efficacy and safety of the addition of UMEC (62.5mcg) once-daily to FSC (250/50mcg) twice-daily, UMEC (125mcg) once-daily to FSC (250/50mcg) twice-daily with placebo to FSC (250/50mcg) twice-daily over 12 weeks for the treatment of subjects with COPD.

Protection of trial subjects:

Several measures were taken to protect trials subjects: these included adverse event monitoring throughout the study, frequent clinic visits (approximately every 4 weeks) to monitor subject status, exclusion of patients with clinically significant and uncontrolled medical conditions and/or ECG findings, and use of treatment arms where all patients received pharmacologic treatment that was appropriate for the disease and disease severity under study (e.g., patients on placebo received appropriate background therapy).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 120
Country: Number of subjects enrolled	Czech Republic: 170
Country: Number of subjects enrolled	Chile: 170
Country: Number of subjects enrolled	Korea, Republic of: 151
Country: Number of subjects enrolled	United States: 261
Worldwide total number of subjects	872
EEA total number of subjects	290

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)	408
From 65 to 84 years	455
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

A total of 606 participants met the eligibility criteria, were randomized, and received open-label fluticasone propionate and salmeterol (FSC) 250/50 micrograms (µg) for up to 12 Weeks during the Treatment Period

Pre-assignment

Screening details:

872 participants were enrolled in the trial and 608 were randomized to treatment. Of these, 606 participants comprised the Intent-to-Treat Population (participants randomized to treatment who received >=1 dose of randomized study medication in the treatment period).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo QD + FSC 250/50 µg BID

Arm description:

Participants received placebo once daily (QD) each morning via a dry powder inhaler (DPI) and FSC 250/50 µg twice daily (BID) (one inhalation each morning and one inhalation each evening) via a DPI for 12 weeks. Placebo was administered as a blinded study drug and FSC was open label.

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

Dosage and administration details:

Once daily via a dry powder inhaler

Arm title	UMEC 62.5 µg QD + FSC 250/50 µg BID

Arm description:

Participants received umeclidinium bromide (UMEC) 62.5 µg QD each morning via a DPI and FSC 250/50 µg BID (one inhalation each morning and one inhalation each evening) via a DPI for 12 weeks. UMEC was administered as a blinded study drug and FSC was open label.

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

Dosage and administration details:

62.5 µg once daily via a dry powder inhaler

Arm title	UMEC 125 µg QD + FSC 250/50 µg BID

Arm description:

Participants received UMEC 125 µg QD each morning via a DPI and FSC 250/50 µg BID (one inhalation

each morning and one inhalation each evening) via a DPI for 12 weeks. UMEC was administered as a blinded study drug and FSC was open label.

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

Dosage and administration details:

125 µg once daily via a dry powder inhaler

Number of subjects in period 1[1]	Placebo QD + FSC 250/50 µg BID	UMEC 62.5 µg QD + FSC 250/50 µg BID	UMEC 125 µg QD + FSC 250/50 µg BID
Started	201	203	202
Completed	170	178	184
Not completed	31	25	18
Adverse event, serious fatal	1	1	-
Consent withdrawn by subject	7	8	4
Adverse event, non-fatal	12	9	6
Lost to follow-up	1	-	1
Protocol deviation	2	1	1
Lack of efficacy	8	6	6

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Although 872 participants were enrolled in the trial worldwide, only 608 were randomized to treatment. Of these, 606 participants comprised the Intent-to-Treat Population (participants randomized to treatment who received >=1 dose of randomized study medication in the treatment period).

Baseline characteristics

Reporting groups	
Reporting group title	Placebo QD + FSC 250/50 µg BID
Reporting group description:	
Participants received placebo once daily (QD) each morning via a dry powder inhaler (DPI) and FSC 250/50 µg twice daily (BID) (one inhalation each morning and one inhalation each evening) via a DPI for 12 weeks. Placebo was administered as a blinded study drug and FSC was open label.	
Reporting group title	UMEC 62.5 µg QD + FSC 250/50 µg BID
Reporting group description:	
Participants received umeclidinium bromide (UMEC) 62.5 µg QD each morning via a DPI and FSC 250/50 µg BID (one inhalation each morning and one inhalation each evening) via a DPI for 12 weeks. UMEC was administered as a blinded study drug and FSC was open label.	
Reporting group title	UMEC 125 µg QD + FSC 250/50 µg BID
Reporting group description:	
Participants received UMEC 125 µg QD each morning via a DPI and FSC 250/50 µg BID (one inhalation each morning and one inhalation each evening) via a DPI for 12 weeks. UMEC was administered as a blinded study drug and FSC was open label.	

Reporting group values	Placebo QD + FSC 250/50 µg BID	UMEC 62.5 µg QD + FSC 250/50 µg BID	UMEC 125 µg QD + FSC 250/50 µg BID
Number of subjects	201	203	202
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	65.7	64.5	65.5
standard deviation	± 7.92	± 8.31	± 7.89
Gender categorical			
Units: Subjects			
Female	78	63	82
Male	123	140	120
Race, Customized			
Units: Subjects			
African American/African Heritage	3	5	4
American Indian or Alaska Native	0	1	0
Japanese/East Asian/South East Asian Heritage	37	33	27
White	161	164	171

Reporting group values	Total		
Number of subjects	606		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical Units: Subjects			
Female	223		
Male	383		
Race, Customized Units: Subjects			
African American/African Heritage	12		
American Indian or Alaska Native	1		
Japanese/East Asian/South East Asian Heritage	97		
White	496		

End points

End points reporting groups

Reporting group title	Placebo QD + FSC 250/50 µg BID

Reporting group description:

Participants received placebo once daily (QD) each morning via a dry powder inhaler (DPI) and FSC 250/50 µg twice daily (BID) (one inhalation each morning and one inhalation each evening) via a DPI for 12 weeks. Placebo was administered as a blinded study drug and FSC was open label.

Reporting group title	UMEC 62.5 µg QD + FSC 250/50 µg BID

Reporting group description:

Participants received umeclidinium bromide (UMEC) 62.5 µg QD each morning via a DPI and FSC 250/50 µg BID (one inhalation each morning and one inhalation each evening) via a DPI for 12 weeks. UMEC was administered as a blinded study drug and FSC was open label.

Reporting group title	UMEC 125 µg QD + FSC 250/50 µg BID

Reporting group description:

Participants received UMEC 125 µg QD each morning via a DPI and FSC 250/50 µg BID (one inhalation each morning and one inhalation each evening) via a DPI for 12 weeks. UMEC was administered as a blinded study drug and FSC was open label.

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

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

End point description:

FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. Trough FEV1 on Treatment Day 85 is defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Treatment Day 84 (i.e., at Week 12). Baseline FEV1 is the mean of the two assessments made at -30 and -5 minutes (min) pre-dose on Treatment Day 1. Change from Baseline was calculated as the Day 85 value minus the Baseline value. Analysis was performed using a repeated measures model with covariates of treatment, Baseline (mean of the two assessments made at -30 and -5 min pre-dose on Treatment Day 1), smoking status, day, day by Baseline, and day by treatment interactions. Intent-to-Treat (ITT) Population: all participants randomized to treatment who received at least one dose of randomized study medication in the Treatment Period.

End point type	Primary

End point timeframe:

Baseline and Day 85

End point values	Placebo QD + FSC 250/50 µg BID	UMEC 62.5 µg QD + FSC 250/50 µg BID	UMEC 125 µg QD + FSC 250/50 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200[1]	203[2]	202[3]	
Units: Liters				
least squares mean (standard error)	-0.001 (± 0.0136)	0.126 (± 0.0133)	0.147 (± 0.0132)	

Notes:

[1] - Analysis included all subjects with at least one post-baseline non-missing trough assessment.

[2] - Analysis included all subjects with at least one post-baseline non-missing trough assessment.

[3] - Analysis included all subjects with at least one post-baseline non-missing trough assessment.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo QD + FSC 250/50 µg BID v UMEC 62.5 µg QD + FSC 250/50 µg BID
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	least squares mean
Point estimate	0.127
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.089
upper limit	0.164

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo QD + FSC 250/50 µg BID v UMEC 125 µg QD + FSC 250/50 µg BID
Number of subjects included in analysis	402
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	least squares mean
Point estimate	0.148
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.111
upper limit	0.185

Secondary: Change from Baseline in 0-6 hour weighted mean FEV1 obtained post-dose at Day 84

End point title	Change from Baseline in 0-6 hour weighted mean FEV1 obtained post-dose at Day 84

End point description:

FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. The weighted mean FEV1 was derived by calculating the area under the curve, and then dividing the value by the relevant time interval. The weighted mean was calculated using the 6-hour serial FEV1 measurements at Day 84, which included pre-dose, and post-dose at 15 min, 30 min, 1 hour, 3 hours, and 6 hours. Baseline FEV1 is the mean of the two assessments made at -30 and -5 min pre-dose on Treatment Day 1. Change from Baseline was calculated as the Day 84 value minus the Baseline value. Analysis was performed using a repeated measures model with covariates of treatment, Baseline (mean of the two assessments made at -30and -5 min pre-dose on Treatment Day 1), smoking status, day, day by Baseline, and day by treatment interactions.

End point type	Secondary

End point timeframe:

Baseline and Day 84

End point values	Placebo QD + FSC 250/50 µg BID	UMEC 62.5 µg QD + FSC 250/50 µg BID	UMEC 125 µg QD + FSC 250/50 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200[4]	203[5]	202[6]	
Units: Liters				
least squares mean (standard error)	0.052 (± 0.0137)	0.196 (± 0.0135)	0.217 (± 0.0133)	

Notes:

[4] - Analysis included all subjects with at least one post-baseline non-missing 0-6 h weighted mean value

[5] - Analysis included all subjects with at least one post-baseline non-missing 0-6 h weighted mean value

[6] - Analysis included all subjects with at least one post-baseline non-missing 0-6 h weighted mean value

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	UMEC 62.5 µg QD + FSC 250/50 µg BID v Placebo QD + FSC 250/50 µg BID
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least squares mean
Point estimate	0.144
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.107
upper limit	0.182

Statistical analysis title	Statistical Analysis 2
Comparison groups	UMEC 125 µg QD + FSC 250/50 µg BID v Placebo QD + FSC 250/50 µg BID
Number of subjects included in analysis	402
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least squares mean
Point estimate	0.165

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.128
upper limit	0.203

Secondary: Change from Baseline in the percentage of rescue-free days over Weeks 1-12

End point title	Change from Baseline in the percentage of rescue-free days over Weeks 1-12

End point description:

A rescue-free day is defined as a day on which no rescue medication was taken. Baseline calculations include a period of the later of 27 days before Visit 2 and the day after Visit 1, up to and including Day 1. The Weeks 1-12 calculations include a period from Study Day 2 up to the earlier of Study Day 85 and the day before Visit 7. Change from Baseline was calculated as the Weeks 1-12 value minus the Baseline value.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1-12

End point values	Placebo QD + FSC 250/50 µg BID	UMEC 62.5 µg QD + FSC 250/50 µg BID	UMEC 125 µg QD + FSC 250/50 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174[7]	191[8]	187[9]	
Units: Percentage of days				
arithmetic mean (standard deviation)	1.9 (± 27.38)	8.4 (± 30.23)	15.2 (± 28.25)	

Notes:

[7] - Only those participants with data available over Weeks 1-12 were summarized.

[8] - Only those participants with data available over Weeks 1-12 were summarized.

[9] - Only those participants with data available over Weeks 1-12 were summarized.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the mean number of puffs per day of rescue albuterol/salbutamol over Weeks 1-12

End point title	Change from Baseline in the mean number of puffs per day of rescue albuterol/salbutamol over Weeks 1-12

End point description:

The number of puffs and nebules per day of rescue albuterol/salbutamol at Baseline and on-treatment was recorded. The total puffs and nebules of rescue albuterol/salbutamol for each day was calculated as: (number of puffs + [2 * number of nebules]). Baseline calculations include a period of the later of 27 days before Visit 2 and the day after Visit 1, up to and including Day 1. The Weeks 1-12 calculations include a period from Study Day 2 up to the earlier of Study Day 85 and the day before Visit 7. Change from Baseline was calculated as the Weeks 1-12 value minus the Baseline value. Analysis was performed using an analysis of covariance (ANCOVA) model with covariates of treatment, Baseline (mean during the 4 weeks prior to Day 1), and smoking status.

End point type	Secondary

End point timeframe:
Baseline and Weeks 1-12

End point values	Placebo QD + FSC 250/50 µg BID	UMEC 62.5 µg QD + FSC 250/50 µg BID	UMEC 125 µg QD + FSC 250/50 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174[10]	191[11]	187[12]	
Units: Puffs				
least squares mean (standard error)	-0.2 (± 0.1)	-0.4 (± 0.1)	-0.7 (± 0.1)	

Notes:
[10] - Only those participants with data available over Weeks 1-12 were analyzed.
[11] - Only those participants with data available over Weeks 1-12 were analyzed.
[12] - Only those participants with data available over Weeks 1-12 were analyzed.

Statistical analyses

Statistical analysis title	Statistical Analysis 3
Comparison groups	Placebo QD + FSC 250/50 µg BID v UMEC 62.5 µg QD + FSC 250/50 µg BID
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.085
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0

Statistical analysis title	Copy of Statistical Analysis 4
Comparison groups	Placebo QD + FSC 250/50 µg BID v UMEC 125 µg QD + FSC 250/50 µg BID
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) are defined as those events occurring while participants were on treatment or those events with an onset during the follow-up period (up to 13 weeks).

Adverse event reporting additional description:

SAEs and non-serious AEs are reported for members of the ITT Population, comprised of all participants randomized to treatment who received at least one dose of randomized study medication in the Treatment Period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Placebo QD + FSC 250/50 µg BID

Reporting group description:

Participants received placebo once daily (QD) each morning via a dry powder inhaler (DPI) and FSC 250/50 µg twice daily (BID) (one inhalation each morning and one inhalation each evening) via a DPI for 12 weeks.

Reporting group title	UMEC 62.5 µg QD + FSC 250/50 µg BID

Reporting group description:

Participants received umeclidinium bromide (UMEC) 62.5 µg QD each morning via a DPI and FSC 250/50 µg BID (one inhalation each morning and one inhalation each evening) via a DPI for 12 weeks.

Reporting group title	UMEC 125 µg QD + FSC 250/50 µg BID

Reporting group description:

Participants received UMEC 125 µg QD each morning via a DPI and FSC 250/50 µg BID (one inhalation each morning and one inhalation each evening) via a DPI for 12 weeks.

Serious adverse events	Placebo QD + FSC 250/50 µg BID	UMEC 62.5 µg QD + FSC 250/50 µg BID	UMEC 125 µg QD + FSC 250/50 µg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 201 (7.46%)	6 / 203 (2.96%)	6 / 202 (2.97%)
number of deaths (all causes)	2	1	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 201 (0.00%)	0 / 203 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoma			

subjects affected / exposed	0 / 201 (0.00%)	1 / 203 (0.49%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metastases to peritoneum			
subjects affected / exposed	0 / 201 (0.00%)	0 / 203 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	1 / 201 (0.50%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 201 (0.50%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery thrombosis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 201 (0.50%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 201 (0.50%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 201 (0.50%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Pericardial effusion			
subjects affected / exposed	1 / 201 (0.50%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 201 (0.50%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 201 (0.50%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 201 (0.50%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	8 / 201 (3.98%)	3 / 203 (1.48%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	1 / 8	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 201 (0.50%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure chronic			
subjects affected / exposed	0 / 201 (0.00%)	1 / 203 (0.49%)	0 / 202 (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
Musculoskeletal and connective tissue disorders			
Dupuytren’s contracture			

subjects affected / exposed	0 / 201 (0.00%)	0 / 203 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	1 / 201 (0.50%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 201 (0.50%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	1 / 201 (0.50%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 201 (0.50%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	2 / 201 (1.00%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 201 (1.99%)	3 / 203 (1.48%)	3 / 202 (1.49%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo QD + FSC 250/50 µg BID	UMEC 62.5 µg QD + FSC 250/50 µg BID	UMEC 125 µg QD + FSC 250/50 µg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 201 (8.96%)	13 / 203 (6.40%)	16 / 202 (7.92%)
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 201 (4.48%)	9 / 203 (4.43%)	6 / 202 (2.97%)
occurrences (all)	32	15	12
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 201 (4.48%)	6 / 203 (2.96%)	10 / 202 (4.95%)
occurrences (all)	13	6	12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2013	The main revisions to the protocol were to clarify the time period for detection of adverse events and serious adverse events, and clarifications to the study procedures and prohibited medications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported