Clinical trial results:
A randomized, multi-center, double-blind, doubledummy, parallel group study to evaluate the efficacy and safety of umeclidinium/vilanterol compared with fluticasone propionate/salmeterol over 12 weeks in subjects with COPD.

Summary

EudraCT number	2012-002156-16
Trial protocol	RO
Global end of trial date	09 January 2014

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	01 May 2015

Trial information

Trial identification

Sponsor protocol code	DB2114951

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01879410
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	13 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Compare the efficacy and safety of UMEC/VI Inhalation Powder (62.5/25 µg oncedaily) with fluticasone propionate/salmeterol (250/50 µg twice-daily) over 12 weeks in subjects with COPD who have a history of infrequent COPD exacerbations

Protection of trial subjects:

Several measures were taken to protect trials participants: these included adverse event monitoring throughout the study, frequent clinic visits (approximately every 4 weeks) to monitor participant status, exclusion of participants with clinically significant and uncontrolled medical conditions and/or ECG findings, and use of treatment arms where all participants received pharmacologic treatment that was appropriate for the disease and disease severity under study.
Fluticasone propionate/salmeterol combination inhalation powder is a marketed product and was administered according to the local label. Fluticasone propionate/salmeterol has an acceptable safety profile for use. This conclusion is supported by the results of previously performed clinical studies and post-marketing experience (see local label).
All participants were on active treatment.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	13 June 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	Chile: 100
Country: Number of subjects enrolled	Mexico: 50
Country: Number of subjects enrolled	Russian Federation: 269
Country: Number of subjects enrolled	South Africa: 110
Country: Number of subjects enrolled	United States: 232
Country: Number of subjects enrolled	Norway: 70
Country: Number of subjects enrolled	Romania: 135
Worldwide total number of subjects	966
EEA total number of subjects	205

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)	518
From 65 to 84 years	438
85 years and over	10

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 700 participants (par.) representing the enrolled participants, were randomized to study treatment. Of these, 697 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	UMEC/VI 62.5/25 µg

Arm description:

Participants received umeclidinium bromide/vilanterol (UMEC/VI) 62.5/25 micrograms (µg) once daily (QD) in the morning via a dry powder inhaler (DPI) and placebo in the morning and evening via a separate DPI for 12 weeks.

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

Dosage and administration details:

62.5/25 µg once-daily via dry powder inhaler

Arm title	FSC 250/50 µg

Arm description:

Participants received fluticasone propionate/salmeterol (FSC) 250/50 µg twice daily (BID) in the morning and evening via a DPI and placebo in the morning via a separate DPI for 12 weeks.

Arm type	Active comparator
Investigational medicinal product name	fluticasone propionate/salmeterol Inhalation Powder
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Respiratory use

Dosage and administration details:

250/50 µg twice-daily via dry powder inhaler

Number of subjects in period 1[1]	UMEC/VI 62.5/25 µg	FSC 250/50 µg
Started	349	348
Completed	326	312
Not completed	23	36
Adverse event, serious fatal	2	3
Consent withdrawn by subject	7	8
Adverse event, non-fatal	7	11
Lost to follow-up	2	1
Lack of efficacy	4	6
Protocol deviation	1	7

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 966 participants were enrolled in the trial worldwide, only 700 were randomized to treatment. Of these, 697 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	UMEC/VI 62.5/25 µg
Reporting group description:	
Participants received umeclidinium bromide/vilanterol (UMEC/VI) 62.5/25 micrograms (µg) once daily (QD) in the morning via a dry powder inhaler (DPI) and placebo in the morning and evening via a separate DPI for 12 weeks.	
Reporting group title	FSC 250/50 µg
Reporting group description:	
Participants received fluticasone propionate/salmeterol (FSC) 250/50 µg twice daily (BID) in the morning and evening via a DPI and placebo in the morning via a separate DPI for 12 weeks.	

Reporting group values	UMEC/VI 62.5/25 µg	FSC 250/50 µg	Total
Number of subjects	349	348	697
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	63.2	64	
standard deviation	± 8.57	± 8.53	-
Gender categorical			
Units: Subjects			
Female	85	84	169
Male	264	264	528
Race			
Units: Subjects			
African American/African Heritage	18	13	31
American Indian or Alaska Native	7	2	9
Asian	4	2	6
Native Hawaiian or other Pacific Islander	0	0	0
White	317	326	643
American Indian or Alaska Native & White	3	5	8

End points

End points reporting groups

Reporting group title	UMEC/VI 62.5/25 µg

Reporting group description:

Participants received umeclidinium bromide/vilanterol (UMEC/VI) 62.5/25 micrograms (µg) once daily (QD) in the morning via a dry powder inhaler (DPI) and placebo in the morning and evening via a separate DPI for 12 weeks.

Reporting group title	FSC 250/50 µg

Reporting group description:

Participants received fluticasone propionate/salmeterol (FSC) 250/50 µg twice daily (BID) in the morning and evening via a DPI and placebo in the morning via a separate DPI for 12 weeks.

Primary: Change from Baseline (BL) in 0 to 24 hour weighted mean forced expiratory volume over 1 second (FEV1) at Day 84

End point title	Change from Baseline (BL) in 0 to 24 hour weighted mean forced expiratory volume over 1 second (FEV1) 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 was calculated from the pre-dose FEV1 and post-dose FEV1 measurements at 5 and 15 minutes and 1, 3, 6, 9, 12 hours (pre-evening dose), 13, 15, 18, 23, and 24 hours after the morning dose. Baseline is defined as the mean of the assessments made 30 and 5 minutes (min) pre-dose on treatment Day 1. Analysis was performed using an analysis of covariance model with covariates of baseline FEV1 (mean of the two assessments made 30 mins and 5 mins pre-dose on Day 1), smoking status, and treatment. Change from baseline was calculated as the value at Day 84 minus the value at Baseline. Participants analyzed were those with data available at the presented time point; but, all participants without missing covariate information and with >= post BL measurement were included in the analysis.

End point type	Primary

End point timeframe:

Baseline and Day 84

End point values	UMEC/VI 62.5/25 µg	FSC 250/50 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	322[1]	311[2]		
Units: Liters				
least squares mean (standard error)	0.213 (± 0.0137)	0.112 (± 0.0139)		

Notes:

[1] - Intent-to-Treat (ITT) Population

[2] - ITT Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	UMEC/VI 62.5/25 µg v FSC 250/50 µg

Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.101
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.063
upper limit	0.139

Notes:

[3] - Least squares mean difference=UMEC/VI 62.5/25 µg minus FSC 250/50 µg.

Secondary: Change from Baseline(BL) in trough forced expiratory volume in one second (FEV1) at Day 85

End point title	Change from Baseline(BL) in trough forced expiratory volume in one second (FEV1) at 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. BL is defined as the mean of the assessments made 30 and 5 min pre-dose on treatment (trt) Day 1. Trough FEV1 on Day 85 is defined as the mean of the FEV1 values obtained 23 and 24 hours after morning dosing on Day 84. Analysis was performed using a repeated measures model with covariates of trt, BL (mean of the 2 assessments made 30 and 5 min pre-dose on Day 1), smoking status, day, day by BL and day by trt interactions. The model used all available trough FEV1 values recorded on Days 28, 56, 84, and 85. Missing data were not directly imputed in this analysis; however, all non-missing data for a par. were used to estimate the trt effect for trough FEV1 at Day 85. Change from BL=value at Day 84 minus value at BL. Par. analyzed were those with data available at the time point; but, all par. without missing covariate information were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Day 85

End point values	UMEC/VI 62.5/25 µg	FSC 250/50 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323[4]	311[5]		
Units: Liters				
least squares mean (standard error)	0.185 (± 0.0138)	0.087 (± 0.014)		

Notes:

[4] - ITT Population

[5] - ITT Population

Statistical analyses

Statistical analysis title	Analysis 2
Comparison groups	UMEC/VI 62.5/25 µg v FSC 250/50 µg

Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Repeated measures
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.059
upper limit	0.137

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious adverse events (AEs) collected from the start of study treatment up to the Follow-up Visit or premature withdrawal (up to Day 94)

Adverse event reporting additional description:

SAEs and non-serious AEs are reported for members of the ITT Population, comprised of all randomized participants who received at least 1 dose of randomized study drug in the treatment period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	UMEC/VI 62.5/25 µg

Reporting group description:

Participants received UMEC/VI 62.5/25 µg QD in the morning via a DPI and placebo in the morning and evening via a separate DPI for 12 weeks

Reporting group title	FSC 250/50 µg

Reporting group description:

Participants received FSC 250/50 µg BID in the morning and evening via a DPI and placebo in the morning via a separate DPI for 12 weeks.

Serious adverse events	UMEC/VI 62.5/25 µg	FSC 250/50 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 349 (3.15%)	13 / 348 (3.74%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 349 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 349 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			

subjects affected / exposed	0 / 349 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Peripheral artery thrombosis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 349 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 349 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 349 (0.29%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Pleurisy			
subjects affected / exposed	0 / 349 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	0 / 349 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 349 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	4 / 349 (1.15%)	4 / 348 (1.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	1 / 349 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 349 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 349 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 349 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 349 (0.29%)	4 / 348 (1.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	

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

Non-serious adverse events	UMEC/VI 62.5/25 µg	FSC 250/50 µg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 349 (10.32%)	28 / 348 (8.05%)	
Nervous system disorders			
Headache			
subjects affected / exposed	24 / 349 (6.88%)	23 / 348 (6.61%)	
occurrences (all)	52	41	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 349 (4.01%)	6 / 348 (1.72%)	
occurrences (all)	17	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported