



## Clinical trial results:

**DB2114930: A randomized, multi-center, double-blind, double-dummy, parallel group study to evaluate the efficacy and safety of umecclidinium/vilanterol compared with fluticasone propionate/salmeterol over 12 weeks in subjects with COPD.**

### Summary

EudraCT number	2012-000525-45
Trial protocol	GR
Global end of trial date	25 October 2013

### 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	DB2114930
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01817764
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	14 January 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 October 2013
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 (62.5/25mcg oncedaily) with fluticasone propionate/salmeterol (250/50mcg 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 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.

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 patients were on active treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 March 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	Argentina: 126
Country: Number of subjects enrolled	Chile: 124
Country: Number of subjects enrolled	Greece: 69
Country: Number of subjects enrolled	Peru: 16
Country: Number of subjects enrolled	Romania: 192
Country: Number of subjects enrolled	Ukraine: 210
Country: Number of subjects enrolled	United States: 184
Worldwide total number of subjects	921
EEA total number of subjects	261

Notes:

<b>Subjects enrolled per age group</b>	
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)	531
From 65 to 84 years	385
85 years and over	5

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 707 participants, representing the enrolled participants, were randomized to study treatment. Of these, 706 comprised the Intent-to-Treat Population (participants randomized to treatment who received  $\geq 1$  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
<b>Arm title</b>	Umeclidinium bromide/vilanterol 62.5/25 mcg

Arm description:

Participants were randomized to umeclidinium bromide/vilanterol (UMEC/VI) 62.5/25 micrograms ( $\mu\text{g}$ ) once-daily (QD) treatment in the morning via a dry powder inhaler (DPI) and placebo in the morning and evening via a separate DPI.

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 mcg once-daily via dry powder inhaler

<b>Arm title</b>	Fluticasone propionate/salmeterol 250/50 mcg
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Arm description:

Participants were randomized to fluticasone propionate/salmeterol (FSC) 250/50  $\mu\text{g}$  twice-daily (BID) treatment in the morning and evening via a DPI and placebo in the morning via a separate DPI.

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

Dosage and administration details:

250/50 mcg twice-daily via dry powder inhaler

<b>Number of subjects in period 1<sup>[1]</sup></b>	Umeclidinium bromide/vilanterol 62.5/25 mcg	Fluticasone propionate/salmeterol 250/50 mcg
Started	353	353
Completed	319	315
Not completed	34	38
Consent withdrawn by subject	10	12
Adverse event, non-fatal	7	10
Lost to follow-up	1	4
Lack of efficacy	9	7
Protocol deviation	7	5

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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 921 participants were enrolled in the trial worldwide, only 707 were randomized to treatment. Of these, 706 participants comprised the Intent-to-Treat Population (participants randomized to treatment who received  $\geq 1$  dose of randomized study medication in the treatment period).

## Baseline characteristics

### Reporting groups

Reporting group title	Umeclidinium bromide/vilanterol 62.5/25 mcg
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Reporting group description:

Participants were randomized to umeclidinium bromide/vilanterol (UMEC/VI) 62.5/25 micrograms (µg) once-daily (QD) treatment in the morning via a dry powder inhaler (DPI) and placebo in the morning and evening via a separate DPI.

Reporting group title	Fluticasone propionate/salmeterol 250/50 mcg
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Reporting group description:

Participants were randomized to fluticasone propionate/salmeterol (FSC) 250/50 µg twice-daily (BID) treatment in the morning and evening via a DPI and placebo in the morning via a separate DPI.

Reporting group values	Umeclidinium bromide/vilanterol 62.5/25 mcg	Fluticasone propionate/salmeterol 250/50 mcg	Total
Number of subjects	353	353	706
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	62.5 ± 9.05	63 ± 8.91	-
Gender categorical Units: Subjects			
Female	100	109	209
Male	253	244	497
Race Units: Subjects			
African American/African Heritage	4	3	7
American Indian or Alaska Native	5	5	10
Asian - East Asian Heritage	1	1	2
Asian - Japanese Heritage	2	1	3
White - Arabic/North African Heritage	0	1	1
White - White/Caucasian/European	341	342	683

## End points

### End points reporting groups

Reporting group title	Umeclidinium bromide/vilanterol 62.5/25 mcg
Reporting group description: Participants were randomized to umeclidinium bromide/vilanterol (UMEC/VI) 62.5/25 micrograms (µg) once-daily (QD) treatment in the morning via a dry powder inhaler (DPI) and placebo in the morning and evening via a separate DPI.	
Reporting group title	Fluticasone propionate/salmeterol 250/50 mcg
Reporting group description: Participants were randomized to fluticasone propionate/salmeterol (FSC) 250/50 µg twice-daily (BID) treatment in the morning and evening via a DPI and placebo in the morning via a separate DPI.	

### Primary: Change from Baseline in 24-hour weighted-mean serial FEV1 on Treatment Day 84

End point title	Change from Baseline in 24-hour weighted-mean serial FEV1 on Treatment 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. Weighted mean is calculated from the pre-dose FEV1 and post-dose FEV1 measurements at 5 and 15 minutes and 1, 3, 6, 9, 12 (pre-evening dose), 13, 15, 18, 23, and 24 hours after the morning dose. Change from Baseline was calculated as the value at Day 84 minus the value at Baseline. Analysis was performed using an analysis of covariance of treatment, Baseline (mean of the two assessments made 30 minutes and 5 minutes pre-dose on Day 1), and smoking status. par.=participants.	
End point type	Primary
End point timeframe: Baseline and Day 84	

End point values	Umeclidinium bromide/vilanterol 62.5/25 mcg	Fluticasone propionate/salmeterol 250/50 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315 <sup>[1]</sup>	310 <sup>[2]</sup>		
Units: Liters				
least squares mean (standard error)	0.165 (± 0.013)	0.091 (± 0.0131)		

Notes:

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

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

### Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Umeclidinium bromide/vilanterol 62.5/25 mcg v Fluticasone propionate/salmeterol 250/50 mcg

Number of subjects included in analysis	625
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.074
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.038
upper limit	0.11

## Secondary: Change from Baseline in trough FEV1 on Day 85

End point title	Change from Baseline in trough 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. 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	Umeclidinium bromide/vilanterol 62.5/25 mcg	Fluticasone propionate/salmeterol 250/50 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317 <sup>[3]</sup>	312 <sup>[4]</sup>		
Units: Liters				
least squares mean (standard error)	0.154 (± 0.0133)	0.072 (± 0.0134)		

Notes:

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

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

## Statistical analyses

Statistical analysis title	Analysis 2
Comparison groups	Umeclidinium bromide/vilanterol 62.5/25 mcg v Fluticasone propionate/salmeterol 250/50 mcg



Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Repeated measures
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.045
upper limit	0.119

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of study medication until the follow-up contact (up to 13 weeks).

Adverse event reporting additional description:

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

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

### Reporting groups

Reporting group title	Umeclidinium bromide/vilanterol 62.5/25 mcg
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Reporting group description:

Participants were randomized to umeclidinium bromide/vilanterol (UMEC/VI) 62.5/25 micrograms (µg) once-daily (QD) treatment in the morning via a dry powder inhaler (DPI) and placebo in the morning and evening via a separate DPI.

Reporting group title	Fluticasone propionate/salmeterol 250/50 mcg
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Reporting group description:

Participants were randomized to fluticasone propionate/salmeterol (FSC) 250/50 µg twice-daily (BID) treatment in the morning and evening via a DPI and placebo in the morning via a separate DPI.

Serious adverse events	Umeclidinium bromide/vilanterol 62.5/25 mcg	Fluticasone propionate/salmeterol 250/50 mcg	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 353 (1.70%)	10 / 353 (2.83%)	
number of deaths (all causes)	0	3	
number of deaths resulting from adverse events	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 353 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	0 / 353 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			

subjects affected / exposed	1 / 353 (0.28%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 353 (0.28%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 353 (0.28%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 353 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 353 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 353 (0.00%)	2 / 353 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 353 (0.28%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Obstructive airways disorder			

subjects affected / exposed	1 / 353 (0.28%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 353 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 353 (0.28%)	3 / 353 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burn infection			
subjects affected / exposed	0 / 353 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 353 (0.28%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 353 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 353 (0.00%)	3 / 353 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

<b>Non-serious adverse events</b>	Umeclidinium bromide/vilanterol 62.5/25 mcg	Fluticasone propionate/salmeterol 250/50 mcg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 353 (10.76%)	25 / 353 (7.08%)	
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 353 (6.52%)	17 / 353 (4.82%)	
occurrences (all)	36	29	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 353 (4.53%)	8 / 353 (2.27%)	
occurrences (all)	18	9	

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported