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

Summary

EudraCT number	2012-000524-18
Trial protocol	CZ ES HU DE DK NL
Global end of trial date	07 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	DB2116134

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01822899
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	26 November 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 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 (62.5/25 µg once daily) with fluticasone propionate/salmeterol (500/50 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 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	04 April 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	Netherlands: 62
Country: Number of subjects enrolled	Poland: 87
Country: Number of subjects enrolled	Spain: 60
Country: Number of subjects enrolled	Czech Republic: 87
Country: Number of subjects enrolled	Denmark: 42
Country: Number of subjects enrolled	Germany: 224
Country: Number of subjects enrolled	Hungary: 178
Country: Number of subjects enrolled	Russian Federation: 269
Worldwide total number of subjects	1009
EEA total number of subjects	740

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)	625
From 65 to 84 years	381
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Participants who met the eligibility criteria at Screening (Visit 1) completed a 7- to 14-day Run-in Period, followed by a 12-week Treatment Period.

Pre-assignment

Screening details:

A total of 717 participants, representing the enrolled participants, were randomized to study treatment. Of these, 716 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	Umeclidinium bromide/vilanterol 62.5/25 µg

Arm description:

Participants received umeclidinium bromide (UMEC) 62.5 micrograms (µg)/vilanterol (VI) 25 µg once daily (QD) each morning via a dry powder inhaler (DPI) and placebo twice daily (BID) (once in the morning and once in the evening) via a 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	Fluticasone propionate/salmeterol 500/50 µg

Arm description:

Participants received fluticasone propionate/salmeterol (FSC) 500 µg/50 µg BID (once in the morning and once in the evening) via a DPI and placebo administered QD via a DPI for 12 weeks.

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:

500/50 µg twice-daily via dry powder inhaler

Number of subjects in period 1[1]	Umeclidinium bromide/vilanterol 62.5/25 µg	Fluticasone propionate/salmeterol 500/50 µg
Started	358	358
Completed	334	340
Not completed	24	18
Consent withdrawn by subject	5	7
Adverse event, non-fatal	6	5
Lost to follow-up	1	-
Lack of efficacy	6	3
Protocol deviation	6	3

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 1009 participants were enrolled in the trial, only 717 were randomized to treatment. Of these, 716 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	Umeclidinium bromide/vilanterol 62.5/25 µg
Reporting group description:	
Participants received umeclidinium bromide (UMEC) 62.5 micrograms (µg)/vilanterol (VI) 25 µg once daily (QD) each morning via a dry powder inhaler (DPI) and placebo twice daily (BID) (once in the morning and once in the evening) via a DPI for 12 weeks.	
Reporting group title	Fluticasone propionate/salmeterol 500/50 µg
Reporting group description:	
Participants received fluticasone propionate/salmeterol (FSC) 500 µg/50 µg BID (once in the morning and once in the evening) via a DPI and placebo administered QD via a DPI for 12 weeks.	

Reporting group values	Umeclidinium bromide/vilanterol 62.5/25 µg	Fluticasone propionate/salmeterol 500/50 µg	Total
Number of subjects	358	358	716
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	61.8	61.4	
standard deviation	± 7.94	± 8.06	-
Gender categorical Units: Subjects			
Female	97	104	201
Male	261	254	515
Race Units: Subjects			
White - White/Caucasian/European Heritage	358	358	716

End points

End points reporting groups

Reporting group title	Umeclidinium bromide/vilanterol 62.5/25 µg
Reporting group description:	
Participants received umeclidinium bromide (UMEC) 62.5 micrograms (µg)/vilanterol (VI) 25 µg once daily (QD) each morning via a dry powder inhaler (DPI) and placebo twice daily (BID) (once in the morning and once in the evening) via a DPI for 12 weeks.	
Reporting group title	Fluticasone propionate/salmeterol 500/50 µg
Reporting group description:	
Participants received fluticasone propionate/salmeterol (FSC) 500 µg/50 µg BID (once in the morning and once in the evening) via a DPI and placebo administered QD via a DPI for 12 weeks.	

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

End point title	Change from Baseline (BL) in 0 to 24 hour weighted mean serial forced expiratory volume in one 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 (pre-evening dose), 13, 15, 18, 23, and 24 hours after the morning dose. Analysis was performed using an analysis of covariance (ANCOVA) model with covariates of treatment, Baseline FEV1 (mean of the two assessments made 30 minutes and 5 minutes pre-dose on Day 1), and smoking status.	
End point type	Primary
End point timeframe:	
Baseline and Day 84	

End point values	Umeclidinium bromide/vilanterol 62.5/25 µg	Fluticasone propionate/salmeterol 500/50 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332[1]	337[2]		
Units: Liters				
least squares mean (standard error)	0.166 (± 0.0122)	0.087 (± 0.0121)		

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 µg v Fluticasone propionate/salmeterol 500/50 µg

Number of subjects included in analysis	669
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.046
upper limit	0.113

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	Umeclidinium bromide/vilanterol 62.5/25 µg	Fluticasone propionate/salmeterol 500/50 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	333[3]	338[4]		
Units: Liters				
least squares mean (standard error)	0.151 (± 0.0126)	0.062 (± 0.0125)		

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 µg v Fluticasone propionate/salmeterol 500/50 µg

Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Repeated measures
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.055
upper limit	0.125

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 are 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

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Umeclidinium bromide/vilanterol 62.5/25 µg

Reporting group description:

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

Reporting group title	Fluticasone propionate/salmeterol 500/50 µg

Reporting group description:

Participants received fluticasone propionate/salmeterol (FSC) 500 µg/50 µg BID (once in the morning and once in the evening) via a DPI and placebo administered QD via a DPI for 12 weeks.

Serious adverse events	Umeclidinium bromide/vilanterol 62.5/25 µg	Fluticasone propionate/salmeterol 500/50 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 358 (1.96%)	2 / 358 (0.56%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 358 (0.28%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden cardiac death			
subjects affected / exposed	1 / 358 (0.28%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			

Inguinal hernia			
subjects affected / exposed	0 / 358 (0.00%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 358 (0.84%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin burning sensation			
subjects affected / exposed	1 / 358 (0.28%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 358 (0.28%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	0 / 358 (0.00%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	1 / 358 (0.28%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 358 (0.28%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Umeclidinium bromide/vilanterol 62.5/25 µg	Fluticasone propionate/salmeterol 500/50 µg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 358 (10.89%)	32 / 358 (8.94%)	
Nervous system disorders			
Headache			
subjects affected / exposed	33 / 358 (9.22%)	25 / 358 (6.98%)	
occurrences (all)	48	61	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 358 (2.79%)	11 / 358 (3.07%)	
occurrences (all)	10	11	

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