Clinical trial results:
A 12 week, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy of Umeclidinium/Vilanterol 62.5/25 mcg in Subjects with COPD

Summary

EudraCT number	2014-000529-19
Trial protocol	HU DE RO BG
Global end of trial date	05 March 2015

Results information

Result version number	v1 (current)
This version publication date	04 June 2016
First version publication date	04 June 2016

Trial information

Trial identification

Sponsor protocol code	201211

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	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	22 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the effect of once-daily UMEC/VI 62.5/25mcg on health-related quality of life as measured using SGRQ total score compared to once-daily placebo in subjects with COPD.

Protection of trial subjects:

To protect trial subjects, subjects were provided with supplemental salbutamol as rescue medication and the concurrent use of inhaled corticosteroids was allowed as maintenance treatment for COPD.

Subjects enrolled in the study had stable disease with no hospitalization for COPD within at least 12 weeks of screening and no use of systemic corticosteroids or antibiotics for a lower respiratory tract infection for at least 6 weeks prior to screening.

Subjects performed an ECG at screening to rule out significant cardiovascular abnormalities, and had a physical examination at the beginning and end of the study to assess health status.

Frequent assessment of adverse events and COPD exacerbations was obtained during the study at clinical visits conducted 1 day following the first dose of study medication and every 4 weeks thereafter to ensure patients safety was closely monitored.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	15 September 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	Bulgaria: 78
Country: Number of subjects enrolled	Germany: 67
Country: Number of subjects enrolled	Hungary: 97
Country: Number of subjects enrolled	Romania: 69
Country: Number of subjects enrolled	Ukraine: 66
Country: Number of subjects enrolled	United States: 159
Country: Number of subjects enrolled	Russian Federation: 91
Worldwide total number of subjects	627
EEA total number of subjects	311

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)	336
From 65 to 84 years	289
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

In this randomized, double-blind, placebo-controlled parallel study, eligible participants received Umeclidinium/Vilanterol(UMEC/VI) 62.5/25 microgram(mcg) once daily(via Dry Powder Inhaler[DPI]) or matching placebo(1:1) for 12 weeks.The study consisted of Run-in Period(7-14 days), treatment period(12 weeks) and follow up period(7+/-2 days).

Pre-assignment

Screening details:

A total of 627 participants who met eligibility criteria were screened; 498 participants were randomized and 496 comprised the Intent to Treat (ITT) population.

Period 1

Period 1 title	12-Week Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants with chronic obstructive pulmonary disease (COPD) received matching placebo via DPI once daily for 12 weeks. In addition, albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the run-in and double-blind treatment periods. Participants were followed up 7 days after the last dose of study medication.

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

Dosage and administration details:

Dry white powder delivered via DPI (2 strips with 30 blisters each, first containing lactose + magnesium stearate per blister and the second containing lactose per blister), administered as one inhalation of placebo, once daily in the morning

Arm title	UMEC/VI 62.5/25 mcg

Arm description:

Participants with COPD received UMEC/VI 62.5/25mcg via DPI once daily for 12 weeks. In addition, albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the run-in and double-blind treatment periods. Participants were followed up 7 days after the last dose of study medication.

Arm type	Experimental
Investigational medicinal product name	Umeclidinium/Vilanterol (UMEC/VI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Dry white powder delivered via dray powder inhaler (DPI; 2 strips with 30 blisters each, first containing UMEC 62.5 mcg + lactose per blister and second containing VI 25 mcg + lactose + magnesium stearate per blister), administered as one inhalation of UMEC/VI 62.5/25 mcg, once daily in the morning

Number of subjects in period 1[1]	Placebo	UMEC/VI 62.5/25 mcg
Started	248	248
Completed	229	230
Not completed	19	18
Adverse event, serious fatal	-	2
Adverse event, non-fatal	6	6
Protocol deviation	1	4
Lost to follow-up	1	-
Withdrew consent	4	2
Lack of efficacy	7	4

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: A total of 627 participants who met eligibility criteria were screened; 498 participants were randomized and 496 comprised the Intent to Treat population.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants with chronic obstructive pulmonary disease (COPD) received matching placebo via DPI once daily for 12 weeks. In addition, albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the run-in and double-blind treatment periods. Participants were followed up 7 days after the last dose of study medication.	
Reporting group title	UMEC/VI 62.5/25 mcg
Reporting group description:	
Participants with COPD received UMEC/VI 62.5/25mcg via DPI once daily for 12 weeks. In addition, albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the run-in and double-blind treatment periods. Participants were followed up 7 days after the last dose of study medication.	

Reporting group values	Placebo	UMEC/VI 62.5/25 mcg	Total
Number of subjects	248	248	496
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62.6	64.1	
standard deviation	± 8.23	± 8.7	-
Gender categorical Units: Subjects			
Female	99	104	203
Male	149	144	293
Race, Customized Units: Subjects			
African American/African Heritage	3	4	7
White - White/Caucasian/European	245	244	489

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants with chronic obstructive pulmonary disease (COPD) received matching placebo via DPI once daily for 12 weeks. In addition, albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the run-in and double-blind treatment periods. Participants were followed up 7 days after the last dose of study medication.

Reporting group title	UMEC/VI 62.5/25 mcg

Reporting group description:

Participants with COPD received UMEC/VI 62.5/25mcg via DPI once daily for 12 weeks. In addition, albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the run-in and double-blind treatment periods. Participants were followed up 7 days after the last dose of study medication.

Primary: Change from Baseline in Mean St.George's Respiratory Questionnaire (SGRQ) total score at Day 84

End point title	Change from Baseline in Mean St.George's Respiratory Questionnaire (SGRQ) total score at Day 84

End point description:

The SGRQ is a disease-specific questionnaire, self-completed by participants(par), to evaluate the effect of UMEC/VI on health-related quality of life as compared to placebo in par with COPD. The SGRQ contains 76 items grouped into three domains (symptoms, activity, impacts) and scores range from 0 (minimum, best possible health status) to 100 (maximum, worst possible health status). Analysis was performed using mixed model repeated measures with covariates of Baseline (scores recorded prior to dosing on Day 1) SGRQ total score, centre group, smoking status, Day, treatment (trt), Day by Baseline interaction and Day by trt interaction, where Day is nominal. Change from Baseline was calculated as the SGRQ total score at a particular visit minus Baseline. Change from Baseline in total score of -4 units or lower is considered as clinically meaningful improvement in quality of life. Intent-to-Treat (ITT) Population included par who received at least one dose of randomized study drug.

End point type	Primary

End point timeframe:

Baseline and Day 84

End point values	Placebo	UMEC/VI 62.5/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	212		
Units: Score on scale				
least squares mean (standard error)	-2.12 (± 0.808)	-6.15 (± 0.803)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Participants represents those with data available at the time point being presented; however, all par. in the ITT population without missing covariate information and with at least one post BL measurement are

included in the analysis.

Comparison groups	UMEC/VI 62.5/25 mcg v Placebo
Number of subjects included in analysis	422
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-4.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.28
upper limit	-1.79

Secondary: Change from Baseline in trough forced expiratory volume in one second (FEV1) at Day 84

End point title	Change from Baseline in trough 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. Trough FEV1 measurements were taken electronically by spirometry on Days 28, 56 and 84. Baseline is defined as the assessment taken pre-dose on Treatment Day 1. Trough FEV1 is defined as the FEV1 value obtained 24 hours after the previous morning's dosing. Change from Baseline at a particular visit was calculated as the trough FEV1 at that visit minus Baseline. Analysis was performed using a repeated measures model with covariates of treatment, Baseline , smoking status, center group, day, and day by Baseline and day by treatment interactions. Intent-to-Treat (ITT) Population included par who received at least one dose of randomized study drug. Par. represents those with data available at the time point being presented; however, all par. in the ITT population without missing covariate information and with at least one post BL measurement are included in analysis

End point type	Secondary

End point timeframe:

Baseline and Day 84

End point values	Placebo	UMEC/VI 62.5/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	227		
Units: Liter				
least squares mean (standard error)	0.03 (± 0.0183)	0.152 (± 0.0181)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	UMEC/VI 62.5/25 mcg v Placebo

Number of subjects included in analysis	451
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	0.122
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.071
upper limit	0.172

Secondary: Change from Baseline (BL) in Mean number of puffs of rescue medication per day used over Weeks 1-12

End point title	Change from Baseline (BL) in Mean number of puffs of rescue medication per day used over Weeks 1-12

End point description:

Albuterol/salbutamol(A/S) was used as rescue medication and was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout treatment periods. The number of puffs of A/S per day over the entire 12 week treatment period was recorded and analyzed. For rescue use, 'day' is referred as the period between one record of rescue use and the next. Total puffs of rescue for each day = number of salbutamol puffs + (2 x number of salbutamol nebules). Analysis performed using mixed model repeated measures with covariates of BL(mean number of total puffs over the duration from First Day; defined as Latest of [7 days before Visit 2 and day after Visit 1] to Last Day[defined as Day before Visit 2]), smoking status, centre group, four-week period, treatment and period by BL interaction. Change from BL used weeks 1-4, 5-8, and 9-12 as covariates in the model and the overall least squares mean change for weeks 1-12 is estimated. ITT population was analyzed.

End point type	Secondary

End point timeframe:

Week 1 to Week 12

End point values	Placebo	UMEC/VI 62.5/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	244		
Units: puffs per day				
least squares mean (standard error)	-0.6 (± 0.13)	-1.4 (± 0.13)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Participants represent all participants in the ITT population without missing covariate information and with at least one post BL measurement.

Comparison groups	UMEC/VI 62.5/25 mcg v Placebo

Number of subjects included in analysis	491
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.4

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 drug until follow-up (Follow-up is defined as up to Day 84 [-4 to +2 days]/Early withdrawal visit plus 7 days [± 2 days]).

Adverse event reporting additional description:

SAEs and non-serious AEs were collected in participants 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	17.1

Reporting groups

Reporting group title	UMEC/VI 62.5/25mcg

Reporting group description:

Participants with COPD received UMEC/VI 62.5/25mcg via DPI once daily for 12 weeks. In addition, albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the run-in and double-blind treatment periods. Participants were followed up 7 days after the last dose of study medication.

Reporting group title	Placebo

Reporting group description:

Participants with chronic obstructive pulmonary disease (COPD) received matching placebo via DPI once daily for 12 weeks. In addition, albuterol/salbutamol was provided to participants to use on an as-needed basis for relief of COPD symptoms throughout the run-in and double-blind treatment periods. Participants were followed up 7 days after the last dose of study medication.

Serious adverse events	UMEC/VI 62.5/25mcg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 248 (6.85%)	13 / 248 (5.24%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Mediastinum neoplasm			
subjects affected / exposed	1 / 248 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Joint injury			

subjects affected / exposed	1 / 248 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 248 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Myocardial ischaemia			
subjects affected / exposed	1 / 248 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 248 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 248 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 248 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 248 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 248 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast			

disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 248 (0.40%)	0 / 248 (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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	8 / 248 (3.23%)	7 / 248 (2.82%)	
occurrences causally related to treatment / all	1 / 11	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Psoriatic arthropathy			
subjects affected / exposed	1 / 248 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 248 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia bacterial			
subjects affected / exposed	0 / 248 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 248 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 248 (1.21%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Dyslipidaemia			
subjects affected / exposed	1 / 248 (0.40%)	0 / 248 (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	UMEC/VI 62.5/25mcg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 248 (11.29%)	30 / 248 (12.10%)	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 248 (6.45%)	16 / 248 (6.45%)	
occurrences (all)	41	36	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 248 (5.24%)	16 / 248 (6.45%)	
occurrences (all)	14	16	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: