Clinical trial results:
A Randomized, Open-Label, 8-Week Cross-Over Study to Compare Umeclidinium/Vilanterol with Tiotropium/Olodaterol Once-Daily in Subjects with Chronic Obstructive Pulmonary Disease (COPD)

Summary

EudraCT number	2016-000585-36
Trial protocol	DE ES
Global end of trial date	27 April 2017

Results information

Result version number	v2 (current)
This version publication date	21 June 2018
First version publication date	19 April 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	204990

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	04 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of UMEC/VI 62.5/25 mcg with TIO/OLO 5/5mcg once daily on lung function in subjects with moderate COPD over 8 weeks of treatment

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 July 2016
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	Germany: 91
Country: Number of subjects enrolled	Spain: 66
Country: Number of subjects enrolled	United Kingdom: 67
Country: Number of subjects enrolled	United States: 219
Worldwide total number of subjects	443
EEA total number of subjects	224

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)	209
From 65 to 84 years	231
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

This is a multicenter, randomized, open label, 2 period crossover complete block design study. Participants (par.) with Chronic Obstructive Pulmonary Disease (COPD) were enrolled across 4 countries: Germany, Spain, the United Kingdom and the United States.

Pre-assignment

Screening details:

Study consisted of a run-in period of approximately 2 weeks followed by two 8-week treatment periods with a washout of approximately 3 weeks. The total duration of the study was approximately 22 weeks including follow-up. A total of 443 par. were screened, of which 236 par. were randomized (207 par. were pre-screen, screen and run-in failures).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Treatment Period 1

Arm description:

In this 2-way crossover study, eligible participants were randomized to receive UMEC/VI inhalation powder 62.5/25 mcg QD administered as 1 inhalation via the ELLIPTA® Inhaler and TIO/OLO 5/5 mcg inhalation spray administered as 2 inhalations via the RESPIMAT® inhaler in 8-week TP1 and TP2 per randomization. This was separated by a 3-week washout period. Albuterol/salbutamol was supplied as an inhalation spray via metered dose inhaler throughout the study for use as-needed

Arm type	Experimental
Investigational medicinal product name	Umeclidinium/Vilanterol 62.5/25 mcg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal powder
Routes of administration	Inhalation use

Dosage and administration details:

UMEC/VI was delivered via ELLIPTA. ELLIPTA dry powder inhaler (DPI) contained a total of 30 doses. Each DPI comprised of two double-foil, laminate blister strips. Each blister of one strip consisted of 62.5 mcg of UMEC blended with lactose and magnesium stearate while each blister of other strip consisted of 25 mcg of VI blended with lactose and magnesium stearate. Each actuation of the DPI delivered the contents of one blister from each strip simultaneously

Investigational medicinal product name	Tiotropium/Olodaterol 5/5 mcg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Inhalation use

Dosage and administration details:

TIO/OLO inhalation spray was supplied as an inhalation spray and was delivered using a RESPIMAT inhaler. Each actuation from the RESPIMAT inhaler delivered 3.124 mcg tiotropium bromide monohydrate (equivalent to 2.5 mcg tiotropium) and 2.736 mcg olodaterol hydrochloride (equivalent to 2.5 mcg olodaterol)

Arm title	Washout Period (3 weeks)

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Treatment Period 2

Arm description:

In this 2-way crossover study, eligible participants were randomized to receive UMEC/VI inhalation powder 62.5/25 mcg QD administered as 1 inhalation via the ELLIPTA® Inhaler and TIO/OLO 5/5 mcg inhalation spray administered as 2 inhalations via the RESPIMAT® inhaler in 8-week TP1 and TP2 per randomization. This was separated by a 3-week washout period. Albuterol/salbutamol was supplied as an inhalation spray via metered dose inhaler throughout the study for use as-needed

Arm type	Experimental
Investigational medicinal product name	Tiotropium/Olodaterol 5/5 mcg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Inhalation use

Dosage and administration details:

TIO/OLO inhalation spray was supplied as an inhalation spray and was delivered using a RESPIMAT inhaler. Each actuation from the RESPIMAT inhaler delivered 3.124 mcg tiotropium bromide monohydrate (equivalent to 2.5 mcg tiotropium) and 2.736 mcg olodaterol hydrochloride (equivalent to 2.5 mcg olodaterol)

Investigational medicinal product name	Umeclidinium/Vilanterol 62.5/25 mcg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal powder
Routes of administration	Inhalation use

Dosage and administration details:

UMEC/VI was delivered via ELLIPTA. ELLIPTA dry powder inhaler (DPI) contained a total of 30 doses. Each DPI comprised of two double-foil, laminate blister strips. Each blister of one strip consisted of 62.5 mcg of UMEC blended with lactose and magnesium stearate while each blister of other strip consisted of 25 mcg of VI blended with lactose and magnesium stearate. Each actuation of the DPI delivered the contents of one blister from each strip simultaneously

Number of subjects in period 1	Treatment Period 1	Washout Period (3 weeks)	Treatment Period 2
Started	236	229	229
Completed	229	229	225
Not completed	7	0	4
Consent withdrawn by subject	5	-	1
Adverse event, non-fatal	-	-	1
Lost to follow-up	2	-	1
Par. reached protocol stopping criteria	-	-	1

Baseline characteristics

Reporting groups[1]	
Reporting group title	Overall Study
Reporting group description:	
Overall Study	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 443 participants were enrolled of which 236 were randomized.

Reporting group values	Overall Study	Total	
Number of subjects	236	236	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 64.4 ± 8.47	 -	
Gender categorical Units: Subjects			
Female	94	94	
Male	142	142	
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	13	13	
White - White/Caucasian/European Heritage	223	223	

End points

End points reporting groups

Reporting group title	Treatment Period 1

Reporting group description:

In this 2-way crossover study, eligible participants were randomized to receive UMEC/VI inhalation powder 62.5/25 mcg QD administered as 1 inhalation via the ELLIPTA® Inhaler and TIO/OLO 5/5 mcg inhalation spray administered as 2 inhalations via the RESPIMAT® inhaler in 8-week TP1 and TP2 per randomization. This was separated by a 3-week washout period. Albuterol/salbutamol was supplied as an inhalation spray via metered dose inhaler throughout the study for use as-needed

Reporting group title	Washout Period (3 weeks)

Reporting group description: -

Reporting group title	Treatment Period 2

Reporting group description:

In this 2-way crossover study, eligible participants were randomized to receive UMEC/VI inhalation powder 62.5/25 mcg QD administered as 1 inhalation via the ELLIPTA® Inhaler and TIO/OLO 5/5 mcg inhalation spray administered as 2 inhalations via the RESPIMAT® inhaler in 8-week TP1 and TP2 per randomization. This was separated by a 3-week washout period. Albuterol/salbutamol was supplied as an inhalation spray via metered dose inhaler throughout the study for use as-needed

Subject analysis set title	Umeclidinium/Vilanterol 62.5/25 mcg
Subject analysis set type	Per protocol

Subject analysis set description:

Eligible par. were administered Umeclidinium/Vilanterol (UMEC/VI) 62.5/25 mcg (as one inhalation) once-daily (QD) via the ELLIPTA Inhaler for 8 weeks followed by a washout period of 3 weeks in period-1 or 2 as per randomization. Albuterol/salbutamol was supplied as an inhalation spray via metered dose inhaler throughout the study for use as-needed

Subject analysis set title	Tiotropium/Olodaterol 5/5 mcg
Subject analysis set type	Per protocol

Subject analysis set description:

Eligible par. were administered Tiotropium/Olodaterol (TIO/OLO) 5/5 mcg inhalation spray as 2 inhalations of 2.5/2.5 mcg each via the RESPIMAT® inhaler for 8 weeks followed by a washout period of 3 weeks in period-1 or 2 as per randomization. Albuterol/salbutamol was supplied as an inhalation spray via metered dose inhaler throughout the study for use as-needed

Primary: Trough forced expiratory volume in one second (FEV1) at Week 8

End point title	Trough forced expiratory volume in one second (FEV1) at Week 8

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 was defined as 23 and 24 hour post-dose FEV1 measurements. All par. in the Intent To Treat (ITT) Population who were not identified as full protocol deviators were included in Per-Protocol (PP) Population. ITT Population, comprised of all randomized subjects, who received at least one dose of study medication.

End point type	Primary

End point timeframe:

Week 8

End point values	Umeclidinium/ Vilanterol 62.5/25 mcg	Tiotropium/Olodaterol 5/5 mcg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	202[1]	192		
Units: Liters				
least squares mean (standard error)				
Liters	1.745 (± 0.0131)	1.692 (± 0.0135)		

Notes:

[1] - Per Protocol Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The correct Number of Subjects Included in Analysis is 236. Due to a system limitation, the value 394 is incorrectly auto-populated.

Comparison groups	Tiotropium/Olodaterol 5/5 mcg v Umeclidinium/Vilanterol 62.5/25 mcg
Number of subjects included in analysis	394
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.026
upper limit	0.08

Notes:

[2] - If the lower bound of the two-sided 95% confidence interval around the (UMEC/VI 62.5/25 mcg versus TIO/OLO 5/5 mcg) treatment difference is above -50 milliliter then UMEC/VI 62.5/25 mcg was to be considered non-inferior to TIO/OLO 5/5 mcg.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-therapy Serious Adverse Events (SAEs) and non-SAEs were collected from the start of study treatment and until follow up visit (Week 22).

Adverse event reporting additional description:

On-therapy SAEs and non-SAEs are reported for ITT Population, comprised of all randomized participants, who received at least one dose of study medication

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Umeclidinium/Vilanterol 62.5/25 mcg

Reporting group description:

Eligible par. were administered Umeclidinium/Vilanterol (UMEC/VI) 62.5/25 mcg (as one inhalation) once-daily (QD) via the ELLIPTA Inhaler for 8 weeks followed by a washout period of 3 weeks in period-1 or 2 as per randomization. Albuterol/salbutamol was supplied as an inhalation spray via metered dose inhaler throughout the study for use as-needed

Reporting group title	Tiotropium/Olodaterol 5/5 mcg

Reporting group description:

Eligible par. were administered Tiotropium/Olodaterol (TIO/OLO) 5/5 mcg inhalation spray as 2 inhalations of 2.5/2.5 mcg each via the RESPIMAT® inhaler for 8 weeks followed by a washout period of 3 weeks in period-1 or 2 as per randomization. Albuterol/salbutamol was supplied as an inhalation spray via metered dose inhaler throughout the study for use as-needed

Serious adverse events	Umeclidinium/Vilanterol 62.5/25 mcg	Tiotropium/Olodaterol 5/5 mcg	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 235 (1.28%)	2 / 230 (0.87%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	1 / 235 (0.43%)	0 / 230 (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			
Rib fracture			
subjects affected / exposed	1 / 235 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 235 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	1 / 235 (0.43%)	0 / 230 (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			
Catheter site haemorrhage			
subjects affected / exposed	0 / 235 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 235 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Umeclidinium/Vilanterol 62.5/25 mcg	Tiotropium/Olodaterol 5/5 mcg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 235 (8.09%)	21 / 230 (9.13%)	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	8 / 235 (3.40%)	7 / 230 (3.04%)	
occurrences (all)	8	7	
Viral upper respiratory tract infection			
subjects affected / exposed	11 / 235 (4.68%)	14 / 230 (6.09%)	
occurrences (all)	11	15	

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