Clinical trial results:
A Randomised, Double Blind, Double Dummy, Parallel Group Study Comparing UMEC/VI (A Fixed Combination Of Umeclidinium and Vilanterol) With Tiotropium In COPD Subjects Who Continue To Have Symptoms on Tiotropium.

Summary

EudraCT number	2012-005007-41
Trial protocol	SE CZ EE NL ES GR
Global end of trial date	22 July 2015

Results information

Result version number	v1 (current)
This version publication date	03 March 2016
First version publication date	03 March 2016

Trial information

Trial identification

Sponsor protocol code	DB2116960

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	30 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare the efficacy of UMEC/VI Inhalation Powder (62.5/25 µg) once-daily with tiotropium (18 µg) once-daily over 12 weeks for the treatment of subjects with COPD who have received tiotropium and continue to have symptoms while on tiotropium.

Protection of trial subjects:

To protect trial subjects only approved standard of care Chronic Obstructive Pulmonary Disease (COPD) medications were evaluated and subjects were not exposed to placebo-only treatment. Additionally study subjects, were provided with supplemental salbuterol as rescue medication.

Subjects enrolled into 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. Additionally, subjects with severe disease requiring long-term oxygen therapy (LTOT) are excluded from participation.

Frequent safety assessments including evaluations of adverse events and vital signs were conducted to ensure patient safety was closely monitored. Subjects were allowed to withdraw from the study at any point without giving a reason, and without affecting their continued medical care.

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	Norway: 31
Country: Number of subjects enrolled	Sweden: 91
Country: Number of subjects enrolled	Estonia: 59
Country: Number of subjects enrolled	Germany: 152
Country: Number of subjects enrolled	Argentina: 122
Country: Number of subjects enrolled	Russian Federation: 94
Country: Number of subjects enrolled	South Africa: 48
Country: Number of subjects enrolled	Ukraine: 118
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	739
EEA total number of subjects	333

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)	351
From 65 to 84 years	384
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Eligible participants (par) completed a 4-week open label tiotropium run-in phase, and were randomized to blinded study medication for 12 weeks. Supplemental albuterol/salbutamol was provided to all par, to be used on an as-needed basis during the run-in phase and up to Day 85.

Pre-assignment

Screening details:

A total of 739 par were enrolled; 496 par randomized and 494 par were included in the Intent-to-Treat (ITT) Population (Pop), comprised of all par randomized to treatment (trt) who received at least 1 dose of randomized study medication in the trt 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

Arms

Are arms mutually exclusive?	Yes
Arm title	Umeclidinium/Vilanterol 62.5/25 µg

Arm description:

Participants self-administered one dose of umeclidinium/vilanterol inhalation powder 62.5/25 micrograms (µg) once daily via an ELLIPTA dry powder inhaler and placebo once daily via a HANDIHALER each morning for 12 weeks. Each inhaler containing placebo was identical in appearance to its corresponding inhaler containing active study medication.

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

Dosage and administration details:

One dose of Umeclidinium/Vilanterol 62.5/25 µg every morning for 12 weeks, via the ELLIPTA dry powder inhaler

Investigational medicinal product name	Placebo matching Umeclidinium/Vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of placebo (lactose blended with magnesium stearate) every morning for 12 weeks, via the ELLIPTA dry powder inhaler

Arm title	Tiotropium bromide 18 µg

Arm description:

Participants self-administered one dose of tiotropium bromide 18 µg once daily via a HANDIHALER and placebo once daily via an ELLIPTA dry powder inhaler each morning for 12 weeks. Each inhaler containing placebo was identical in appearance to its corresponding inhaler containing active study medication.

Arm type	Active comparator

Investigational medicinal product name	Tiotropium bromide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One dose of Tiotropium bromide 18 µg every morning for 12 weeks, via the HANDIHALER

Investigational medicinal product name	Placebo matching Tiotropium bromide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of placebo (lactose) every morning for 12 weeks, via the HANDIHALER

Number of subjects in period 1[1]	Umeclidinium/Vilanterol 62.5/25 µg	Tiotropium bromide 18 µg
Started	247	247
Completed	230	231
Not completed	17	16
Consent withdrawn by subject	9	5
Adverse event, non-fatal	5	4
Lack of efficacy	1	5
Protocol deviation	2	2

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 739 par were enrolled; 496 par randomized and 494 par were included in the Intent-to-Treat (ITT) Population (Pop), comprised of all par randomized to treatment (trt) who received at least 1 dose of randomized study medication in the trt period.

Baseline characteristics

Reporting groups	
Reporting group title	Umeclidinium/Vilanterol 62.5/25 µg
Reporting group description:	
Participants self-administered one dose of umeclidinium/vilanterol inhalation powder 62.5/25 micrograms (µg) once daily via an ELLIPTA dry powder inhaler and placebo once daily via a HANDIHALER each morning for 12 weeks. Each inhaler containing placebo was identical in appearance to its corresponding inhaler containing active study medication.	
Reporting group title	Tiotropium bromide 18 µg
Reporting group description:	
Participants self-administered one dose of tiotropium bromide 18 µg once daily via a HANDIHALER and placebo once daily via an ELLIPTA dry powder inhaler each morning for 12 weeks. Each inhaler containing placebo was identical in appearance to its corresponding inhaler containing active study medication.	

Reporting group values	Umeclidinium/Vilanterol 62.5/25 µg	Tiotropium bromide 18 µg	Total
Number of subjects	247	247	494
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	64.5	64.3	
standard deviation	± 8.71	± 8.74	-
Gender categorical			
Units: Subjects			
Female	84	87	171
Male	163	160	323
Race, Customized			
Units: Subjects			
African American/African Heritage	2	4	6
Asian - Central/South Asian Heritage	1	1	2
White - Arabic/North African Heritage	4	4	8
White - White/Caucasian/European Heritage	239	237	476
White - Mixed Race	1	1	2

End points

End points reporting groups

Reporting group title	Umeclidinium/Vilanterol 62.5/25 µg

Reporting group description:

Participants self-administered one dose of umeclidinium/vilanterol inhalation powder 62.5/25 micrograms (µg) once daily via an ELLIPTA dry powder inhaler and placebo once daily via a HANDIHALER each morning for 12 weeks. Each inhaler containing placebo was identical in appearance to its corresponding inhaler containing active study medication.

Reporting group title	Tiotropium bromide 18 µg

Reporting group description:

Participants self-administered one dose of tiotropium bromide 18 µg once daily via a HANDIHALER and placebo once daily via an ELLIPTA dry powder inhaler each morning for 12 weeks. Each inhaler containing placebo was identical in appearance to its corresponding inhaler containing active study medication.

Primary: Change from Baseline in trough forced expiratory volume in one second (FEV1) on Day 85 (Visit 8)

End point title	Change from Baseline in trough forced expiratory volume in one second (FEV1) on Day 85 (Visit 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 1 second. BL was the mean of the values measured 23 hour and 24 hour after dosing prior to Day 1 (ie. after the last open label [OL] tiotropium dosing and prior to the randomized dose). Change from BL is defined as the post-BL value minus the BL value. Trough FEV1 on Day 85 is defined as the mean of the FEV1 values obtained at 23 and 24 hours after dosing on Day 84 (at Week 12 + 1 day). Analysis performed using a mixed repeated measures model (MMRM) with covariates of treatment, BL, center group, 24 hour subset flag, Day, Day by BL and Day by treatment interactions. ITT Population is defined as participants who received at least one dose of randomized study medication in the treatment period. Only those participants with data available at the specified time point were included in the analysis.

End point type	Primary

End point timeframe:

Baseline (BL) and Day 85

End point values	Umeclidinium/ Vilanterol 62.5/25 µg	Tiotropium bromide 18 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224[1]	225[2]		
Units: Liters				
least squares mean (standard error)	0.074 (± 0.0155)	-0.014 (± 0.0155)		

Notes:

[1] - ITT Population

[2] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Umeclidinium/Vilanterol 62.5/25 µg v Tiotropium bromide 18 µg

Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.088
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.045
upper limit	0.131

Secondary: Change from BL in FEV1 at 3 hours postdose on Day 84

End point title	Change from BL in FEV1 at 3 hours postdose on 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 1 second. FEV1 assessments taken on 0 to 3 hour on Day 84 (pre-dose, 5 minutes (min), 15 min, 30 min, 1 hour, and 3 hour post-dose). Pre-dose was the reading obtained at 24 hours after the previous day's dose (Day 83 dose). BL is defined as mean of the values measured 23 hour and 24 hour after dosing prior to Day 1 (ie. after the last OL tiotropium dosing and prior to the randomized dose). Change from BL is defined as the post-BL value minus the BL value. Analysis performed using mixed model repeated measures with covariates of treatment, BL FEV1, center group, 24 hour subset flag, time, time by treatment interaction and time by BL interaction. Only those participants with data available at the specified time point were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Day 84

End point values	Umeclidinium/ Vilanterol 62.5/25 µg	Tiotropium bromide 18 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225[3]	228[4]		
Units: Liters				
least squares mean (standard error)	0.164 (± 0.0178)	0.091 (± 0.0177)		

Notes:

[3] - ITT Population

[4] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Umeclidinium/Vilanterol 62.5/25 µg v Tiotropium bromide 18 µg

Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.024
upper limit	0.122

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected over a period of a maximum of 94 days starting from Day 1 of treatment until the follow-up contact.

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 medication in the treatment period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Umeclidinium/Vilanterol 62.5/25 µg

Reporting group description:

Participants self-administered one dose of umeclidinium/vilanterol inhalation powder 62.5/25 µg once daily via an ELLIPTA dry powder inhaler and placebo once daily via a HANDIHALER each morning for 12 weeks. Each inhaler containing placebo was identical in appearance to its corresponding inhaler containing active study medication.

Reporting group title	Tiotropium bromide 18 µg

Reporting group description:

Participants self-administered one dose of tiotropium bromide 18 µg once daily via a HANDIHALER and placebo once daily via an ELLIPTA dry powder inhaler each morning for 12 weeks. Each inhaler containing placebo was identical in appearance to its corresponding inhaler containing active study medication.

Serious adverse events	Umeclidinium/Vilanterol 62.5/25 µg	Tiotropium bromide 18 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 247 (2.83%)	6 / 247 (2.43%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	0 / 247 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	0 / 247 (0.00%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 247 (0.00%)	1 / 247 (0.40%)	
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	1 / 247 (0.40%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 247 (0.40%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 247 (0.40%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 247 (0.40%)	1 / 247 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 247 (0.00%)	2 / 247 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 247 (0.40%)	0 / 247 (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			

Pneumonia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 247 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 247 (0.00%)	1 / 247 (0.40%)	
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 µg	Tiotropium bromide 18 µg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 247 (13.77%)	34 / 247 (13.77%)	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 247 (6.48%)	18 / 247 (7.29%)	
occurrences (all)	20	30	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 247 (7.29%)	17 / 247 (6.88%)	
occurrences (all)	19	18	

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