Clinical trial results:
A Randomized, Blinded, Double-dummy, Parallel-group Study to Evaluate the Efficacy and Safety of Umeclidinium (UMEC) 62.5 mcg compared with Tiotropium 18 mcg in Subjects with Chronic Obstructive Pulmonary Disease (COPD)

Summary

EudraCT number	2014-000884-42
Trial protocol	DE IT DK
Global end of trial date	15 June 2015

Results information

Result version number	v1 (current)
This version publication date	27 May 2016
First version publication date	27 May 2016

Trial information

Trial identification

Sponsor protocol code	201316

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	31 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 June 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the efficacy and safety of umeclidinium (UMEC) 62.5 microgram (mcg) with tiotropium 18 mcg in subjects with chronic obstructive pulmonary disease (COPD) over 12 weeks of treatment.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 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	Argentina: 11
Country: Number of subjects enrolled	Canada: 171
Country: Number of subjects enrolled	Chile: 65
Country: Number of subjects enrolled	Denmark: 80
Country: Number of subjects enrolled	France: 48
Country: Number of subjects enrolled	Germany: 123
Country: Number of subjects enrolled	Italy: 50
Country: Number of subjects enrolled	Korea, Republic of: 79
Country: Number of subjects enrolled	Romania: 130
Country: Number of subjects enrolled	Russian Federation: 261
Country: Number of subjects enrolled	South Africa: 79
Country: Number of subjects enrolled	Ukraine: 119
Country: Number of subjects enrolled	United States: 43
Worldwide total number of subjects	1259
EEA total number of subjects	431

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)	640
From 65 to 84 years	612
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

A complete double-blind was not possible since tiotropium inhalation capsules had trade markings that were not present on placebo capsules, although capsules were closely matched in color. Study staff involved with safety and efficacy assessments were not present during dosing in the clinic to limit the possibility of capsule identification.

Pre-assignment

Screening details:

Participants (Par.), with clinical history of chronic obstructive pulmonary disease, who met eligibility criteria at screening were enrolled in a 7 to 14 days run-in period. Eligible par. were randomized (1:1) to receive umeclidinium or tiotropium. A total of 1214 par. were screened; 1017 par. were randomized and entered into the study.

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 62.5 mcg+Placebo QD

Arm description:

Participants received umeclidinium (UMEC) inhalation powder 62.5 microgram (mcg) once-daily (QD) in morning via a novel dry powder inhaler (nDPI) and placebo QD via alternative dry powder inhaler (DPI) for 12 weeks (For participants enrolled in Germany, the duration of treatment was 24 weeks). Participants also received albuterol/salbutamol via metered-dose-inhaler (MDI) or nebules as rescue medication throughout the study for use as needed.

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

Dosage and administration details:

Single dose of umeclidinium (UMEC) 62.5 microgram (mcg) in morning once daily (QD) via novel Dry Powder Inhaler (nDPI) for 12 weeks. For participants enrolled in Germany, the duration of treatment was 24 weeks.

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

Dosage and administration details:

Single dose of matching placebo in morning QD via Handihaler inhaler for 12 weeks. For participants enrolled in Germany, the duration of treatment was 24 weeks.

Arm title	Tiotropium 18 mcg+Placebo QD

Arm description:

Participants received tiotropium (TIO) 18 mcg QD in morning via DPI and placebo QD via nDPI for 12 weeks (For participants enrolled in Germany, the duration of treatment was 24 weeks). Participants also received albuterol/salbutamol via MDI or nebules as rescue medication throughout the study for use as

needed.

Arm type	Active comparator
Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Single dose of Tiotropium 18 mcg in morning QD via Handihaler inhaler for 12 weeks. For participants enrolled in Germany, the duration of treatment was 24 weeks.

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

Dosage and administration details:

Single dose of matching placebo in morning QD via nDPI for 12 weeks. For participants enrolled in Germany, the duration of treatment was 24 weeks.

Number of subjects in period 1[1]	Umeclidinium 62.5 mcg+Placebo QD	Tiotropium 18 mcg+Placebo QD
Started	509	508
Completed	467	474
Not completed	42	34
Adverse event, serious fatal	-	2
Adverse event, non-fatal	10	7
Protocol deviation	5	4
Lost to follow-up	2	2
Withdrew consent	18	14
Lack of efficacy	7	5

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: Participants (Par.), with clinical history of chronic obstructive pulmonary disease, who met eligibility criteria at screening were enrolled in a 7 to 14 days run-in period. Eligible par. were randomized (1:1) to receive umeclidinium and tiotropium. A total of 1214 par. were screened; 1017 par. were randomized and entered into the study.

Baseline characteristics

Reporting groups	
Reporting group title	Umeclidinium 62.5 mcg+Placebo QD
Reporting group description:	
Participants received umeclidinium (UMEC) inhalation powder 62.5 microgram (mcg) once-daily (QD) in morning via a novel dry powder inhaler (nDPI) and placebo QD via alternative dry powder inhaler (DPI) for 12 weeks (For participants enrolled in Germany, the duration of treatment was 24 weeks). Participants also received albuterol/salbutamol via metered-dose-inhaler (MDI) or nebules as rescue medication throughout the study for use as needed.	
Reporting group title	Tiotropium 18 mcg+Placebo QD
Reporting group description:	
Participants received tiotropium (TIO) 18 mcg QD in morning via DPI and placebo QD via nDPI for 12 weeks (For participants enrolled in Germany, the duration of treatment was 24 weeks). Participants also received albuterol/salbutamol via MDI or nebules as rescue medication throughout the study for use as needed.	

Reporting group values	Umeclidinium 62.5 mcg+Placebo QD	Tiotropium 18 mcg+Placebo QD	Total
Number of subjects	509	508	1017
Age categorical Units: Subjects			
Age continuous Units:			
	64.4 ± 8.12	64.1 ± 8.28	-
Gender categorical Units: Subjects			
Female	145	137	282
Male	364	371	735
Race, Customized Units: Subjects			
African American/African Heritage	9	9	18
American Indian or Alaska Native	1	0	1
Central/South Asian Heritage	0	1	1
Japanese/East Asian/South East Asian Heritage	38	37	75
White	458	457	915
African American/African Heritage & White	3	4	7

End points

End points reporting groups

Reporting group title	Umeclidinium 62.5 mcg+Placebo QD

Reporting group description:

Participants received umeclidinium (UMEC) inhalation powder 62.5 microgram (mcg) once-daily (QD) in morning via a novel dry powder inhaler (nDPI) and placebo QD via alternative dry powder inhaler (DPI) for 12 weeks (For participants enrolled in Germany, the duration of treatment was 24 weeks). Participants also received albuterol/salbutamol via metered-dose-inhaler (MDI) or nebules as rescue medication throughout the study for use as needed.

Reporting group title	Tiotropium 18 mcg+Placebo QD

Reporting group description:

Participants received tiotropium (TIO) 18 mcg QD in morning via DPI and placebo QD via nDPI for 12 weeks (For participants enrolled in Germany, the duration of treatment was 24 weeks). Participants also received albuterol/salbutamol via MDI or nebules as rescue medication throughout the study for use as needed.

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

End point title	Change from Baseline in trough forced expiratory volume in one second (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. Trough FEV1 on Day 85 is defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Day 84 (Week 12). Trough FEV1 was measured using spirometry. Baseline trough FEV1 is the mean of the two assessments made -30 and -5 minutes (min) pre-dose on Day 1. Change from baseline was calculated as the trough FEV1 value on Day 85 minus the BL value. Analysis performed using a repeated measures model with covariates of treatment, baseline FEV1, centre group, 24 hour subset flag, Day, Day by baseline and Day by treatment interactions. Per Protocol (PP) Population: Comprised of all participants in the Intent-To-Treat (ITT) population who did not have a full protocol deviation considered to impact efficacy. Only participants with data available at specific time point were analyzed.

End point type	Primary

End point timeframe:

Baseline (BL) and Day 85

End point values	Umeclidinium 62.5 mcg+Placebo QD	Tiotropium 18 mcg+Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	392[1]	416[2]		
Units: Liter				
least squares mean (standard error)	0.154 (± 0.0107)	0.095 (± 0.0106)		

Notes:

[1] - PP population

[2] - PP population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Participants represent those with data available at time point presented; however, all participants in the PP population without missing covariate information and >=1 post Baseline measurement are included in analysis.

Comparison groups	Umeclidinium 62.5 mcg+Placebo QD v Tiotropium 18 mcg+Placebo QD
Number of subjects included in analysis	808
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.029
upper limit	0.088

Notes:

[3] - Alternate hypothesis: the difference between the trt means (umeclidinium minus tiotropium) would be > -50 milliliters (mL). If the lower CI (2.5% 1-sided significance level) of the statistical test should fall above -50 mL, then umeclidinium may be deemed statistically non-inferior to tiotropium. If the lower CI (2.5% 1-sided significance) of the statistical testing exceeded 0 then, umeclidinium may be deemed statistically superior to tiotropium.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment(trt) non-serious adverse events(AEs) and serious AEs are events occurring while par were on trt or events with an onset during follow-up period(up to 13 weeks). AE data for German subjects are only included for the first 12 weeks of trt.

Adverse event reporting additional description:

On-treatment SAEs and non-serious AEs were reported for the ITT Population comprised 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	Tiotropium 18 mcg+Placebo QD

Reporting group description:

Participants received tiotropium (TIO) 18 mcg QD in morning via DPI and placebo QD via nDPI for 12 weeks (For participants enrolled in Germany, the duration of treatment was 24 weeks). Participants also received albuterol/salbutamol via MDI or nebules as rescue medication throughout the study for use as needed.

Reporting group title	Umeclidinium 62.5 mcg+Placebo QD

Reporting group description:

Participants received umeclidinium (UMEC) inhalation powder 62.5 microgram (mcg) once-daily (QD) in morning via a novel dry powder inhaler (nDPI) and placebo QD via alternative dry powder inhaler (DPI) for 12 weeks (For participants enrolled in Germany, the duration of treatment was 24 weeks). Participants also received albuterol/salbutamol via metered-dose-inhaler (MDI) or nebules as rescue medication throughout the study for use as needed.

Serious adverse events	Tiotropium 18 mcg+Placebo QD	Umeclidinium 62.5 mcg+Placebo QD	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 508 (3.15%)	17 / 509 (3.34%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	0 / 508 (0.00%)	1 / 509 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 508 (0.20%)	0 / 509 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung adenocarcinoma metastatic			
subjects affected / exposed	0 / 508 (0.00%)	1 / 509 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	0 / 508 (0.00%)	1 / 509 (0.20%)	
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			
Tibia fracture			
subjects affected / exposed	0 / 508 (0.00%)	1 / 509 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 508 (0.20%)	0 / 509 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 508 (0.00%)	1 / 509 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	1 / 508 (0.20%)	0 / 509 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 508 (0.20%)	1 / 509 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 508 (0.00%)	1 / 509 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Congestive cardiomyopathy			
subjects affected / exposed	0 / 508 (0.00%)	1 / 509 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 508 (0.00%)	1 / 509 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 508 (0.00%)	1 / 509 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 508 (0.20%)	0 / 509 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 508 (0.20%)	0 / 509 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 508 (0.20%)	0 / 509 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 508 (0.00%)	1 / 509 (0.20%)	
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	6 / 508 (1.18%)	2 / 509 (0.39%)	
occurrences causally related to treatment / all	0 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 508 (0.00%)	1 / 509 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 508 (0.00%)	1 / 509 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 508 (0.20%)	1 / 509 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 508 (0.20%)	0 / 509 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 508 (0.00%)	1 / 509 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airway disease			
subjects affected / exposed	1 / 508 (0.20%)	0 / 509 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 508 (0.00%)	1 / 509 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 508 (0.00%)	1 / 509 (0.20%)	
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	Tiotropium 18 mcg+Placebo QD	Umeclidinium 62.5 mcg+Placebo QD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 508 (10.24%)	50 / 509 (9.82%)	
Nervous system disorders			
Headache			
subjects affected / exposed	32 / 508 (6.30%)	30 / 509 (5.89%)	
occurrences (all)	44	49	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	23 / 508 (4.53%)	27 / 509 (5.30%)	
occurrences (all)	26	28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2014	This protocol amendment has been created predominantly to extend the duration of the study from 12 weeks to 24 weeks for subjects enrolled across all study sites in Germany. For these subjects, blinded treatment will continue for a further 12 weeks from the end of the initial 12 week treatment period. The data analysis and statistical considerations section of the protocol (Section 8) has been amended to include a new Intent-To-Treat (ITT) population for Germany and also to revise statistical considerations with regards to the analysis of additional data (St. George's Respiratory Questionnaire [SGRQ], Chronic Obstructive Pulmonary Disease Assessment Test [CAT], rescue medication use and safety) for those subjects enrolled in Germany. Exclusion criterion number 6 has been revised to exclude subjects with both moderate and severe renal impairment (as opposed to severe renal impairment only) unless in the opinion of the investigator, the benefit is likely to outweigh the risk in accordance with the tiotropium label (SmPC; Summary of Product Characteristics). The medical monitor contact information has been revised to include two new medical monitors responsible for specific regions. New text has been included with regards to recent approvals of the UMEC monotherapy 62.5 mcg dose in Canada, USA and in Europe (European Economic Area). Other minor corrections and edits have been made.
26 September 2014	The amendment has been created to clarify that a single dose from the nDPI will consist of 1 inhalation from the nDPI and that a single dose of tiotropium or matching placebo will consist of 2 inhalations of the powder contents of a single capsule with the Handihaler. • Thus the sections, 5.1 (paragraph 7), 5.1.2 (paragraph 1), 5.2 (paragraph 5) have been revised in alignment with the above mentioned text to clarify that a single dose from the nDPI will consist of 1 inhalation from the nDPI and that a single dose of tiotropium or matching placebo will consist of 2 inhalations of the powder contents of a single capsule with the Handihaler. Also, Section 5.2 (paragraph 8) has been revised to clarify that an albuterol/salbutamol new container will be dispensed "as needed after Visit 1". Also, the following revisions are included to revise the medical monitor information, to clarify the calculation of compliance and to include the collection of pneumonia event specific information for pneumonia AEs in a specific Electronic Case Report Form (eCRF). The Disease Related Event (DRE) reporting in section 6.3.14 table was deleted as this is captured separately per explanation in Section 6.3.9: • The Medical Monitor information has been revised to update the global and add the new back-up Medical Monitors. • Section Protocol Summary has been revised for the primary endpoint to include formatting changes, second bullet formatting removed to reflect a single primary endpoint • Section 5.5 has been revised to clarify compliance with the Handihaler is to be determined by counting the number of "unused" capsules remaining • Section 6.3.7 has been added to include collection of pneumonia events specific information occurring after subject randomization in an eCRF. Section 6.3.14 has been revised to include pneumonia events for Prompt Reporting of Serious Adverse Events and Others Events to GlaxoSmithKline.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported