Clinical trial results:
A randomized, parallel group study to evaluate the effect of Umeclidinium (UMEC) added to Inhaled corticosteroid/ long-acting beta-agonist combination therapy in subjects with Chronic Obstructive Pulmonary Disease COPD

Summary

EudraCT number	2014-000611-14
Trial protocol	NL DE GR CZ
Global end of trial date	24 March 2015

Results information

Result version number	v1 (current)
This version publication date	06 March 2016
First version publication date	06 March 2016

Trial information

Trial identification

Sponsor protocol code	201314

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02257372
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Middlesex, Brentford, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, +1 8664357343,
Scientific contact	GSK Response Center, GlaxoSmithKline, +1 8664357343,

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	19 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the efficacy and safety of the addition of UMEC 62.5mcg once-daily to ICS/LABA therapy, compared with placebo once-daily plus ICS/LABA therapy over 12 weeks in subjects with COPD.

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	Netherlands: 42
Country: Number of subjects enrolled	Czech Republic: 74
Country: Number of subjects enrolled	Germany: 101
Country: Number of subjects enrolled	Greece: 49
Worldwide total number of subjects	266
EEA total number of subjects	266

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)	128
From 65 to 84 years	138

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants had used one of the following inhaled corticosteroids (ICS)/long-acting beta2-agonist (LABA) combinations for at least 30 days prior to Screening: Fluticasone Propionate/Salmeterol (FSC) 500/50 microgram (mcg) twice-daily (bid); budesonide/formoterol 200/6 mcg bid or 400/12 mcg bid; ICS/LABA combinations per study procedures manual.

Pre-assignment

Screening details:

Participants who met eligibility criteria at screening completed an approximately one week run-in period and participants who met the randomisation criteria were entered a 12-week treatment period. A total of 266 participants with chronic obstructive pulmonary disease (COPD) were screened; 236 participants 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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo+ICS/LABA

Arm description:

Participants received double-blind placebo via a dry powder inhaler (DPI) once daily and an open-label inhaled corticosteriod (ICS)/Long-acting beta2-agonist(LABA) administered according to the label instructions for 12 weeks. Participants also received albuterol/salbutamol via a metered-dose-inhaler (MDI) or nebules as rescue medication throughout the study for use as needed.

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:

Lactose with magnesium stearate via a DPI once-daily for 12 weeks

Arm title	Umeclidinium 62.5 mcg+ICS/LABA

Arm description:

Participants received Umeclidinium 62.5 microgram(mcg) via a DPI once daily and an open-label ICS/LABA administered according to label instructions for 12 weeks. Participants also received albuterol/salbutamol via a 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:

Umeclidinium 62.5microgram (mcg) via a dry powder inhaler (DPI) once-daily for 12 weeks

Number of subjects in period 1[1]	Placebo+ICS/LABA	Umeclidinium 62.5 mcg+ICS/LABA
Started	117	119
Completed	110	109
Not completed	7	10
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	-
Adverse event, non-fatal	2	7
Lost to follow-up	-	1
Lack of efficacy	2	1
Protocol deviation	1	1

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 266 participants with chronic obstructive pulmonary disease (COPD) were screened; 236 participants randomized and entered into the study.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo+ICS/LABA
Reporting group description:	
Participants received double-blind placebo via a dry powder inhaler (DPI) once daily and an open-label inhaled corticosteriod (ICS)/Long-acting beta2-agonist(LABA) administered according to the label instructions for 12 weeks. Participants also received albuterol/salbutamol via a metered-dose-inhaler (MDI) or nebules as rescue medication throughout the study for use as needed.	
Reporting group title	Umeclidinium 62.5 mcg+ICS/LABA
Reporting group description:	
Participants received Umeclidinium 62.5 microgram(mcg) via a DPI once daily and an open-label ICS/LABA administered according to label instructions for 12 weeks. Participants also received albuterol/salbutamol via a MDI or nebules as rescue medication throughout the study for use as needed.	

Reporting group values	Placebo+ICS/LABA	Umeclidinium 62.5 mcg+ICS/LABA	Total
Number of subjects	117	119	236
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	63.1	65.2	
standard deviation	± 7.86	± 7.46	-
Gender categorical			
Units: Subjects			
Female	42	36	78
Male	75	83	158
Race, Customized			
Units: Subjects			
Asian - Central/South Asian Heritage	1	0	1
White - White/Caucasian/European	116	119	235

End points

End points reporting groups

Reporting group title	Placebo+ICS/LABA

Reporting group description:

Participants received double-blind placebo via a dry powder inhaler (DPI) once daily and an open-label inhaled corticosteriod (ICS)/Long-acting beta2-agonist(LABA) administered according to the label instructions for 12 weeks. Participants also received albuterol/salbutamol via a metered-dose-inhaler (MDI) or nebules as rescue medication throughout the study for use as needed.

Reporting group title	Umeclidinium 62.5 mcg+ICS/LABA

Reporting group description:

Participants received Umeclidinium 62.5 microgram(mcg) via a DPI once daily and an open-label ICS/LABA administered according to label instructions for 12 weeks. Participants also received albuterol/salbutamol via a 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. BL FEV1 is the mean of the two assessments made 30 and 5 minutes (min) pre-dose on Day 1.Change from BL was calculated as the trough FEV1 value on Day 85 minus the BL value. Analysis was performed using mixed model repeated measures with covariates of treatment, BL FEV1 (mean of the values measured at 30 min and 5 min pre-dose on Day 1), type of ICS/LABA, smoking status, Day, Day by BL interaction and Day by treatment interaction, where Day is nominal. Intent-to-treat (ITT) population: all participants randomized to treatment who received at least one dose of randomized study medication in the treatment period. Only participants with data available at specific timepoint were analyzed.

End point type	Primary

End point timeframe:

Baseline (BL) and Day 85

End point values	Placebo+ICS/LABA	Umeclidinium 62.5 mcg+ICS/LABA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110[1]	109[2]		
Units: Liter				
least squares mean (standard error)	-0.033 (± 0.0184)	0.09 (± 0.0183)		

Notes:

[1] - ITT population

[2] - ITT population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

UMEC 62.5+ICS/LABA vs. Placebo+ICS/LABA

Comparison groups	Placebo+ICS/LABA v Umeclidinium 62.5 mcg+ICS/LABA
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed model repeated measures analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.123
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.071
upper limit	0.174

Secondary: Change from Baseline in weighted mean 0-6 hour FEV1 obtained post-dose on Day 84

End point title	Change from Baseline in weighted mean 0-6 hour FEV1 obtained post-dose 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 one second. The weighted mean FEV1 was derived by calculating the area under the curve, and then dividing the value by the relevant time interval. The weighted mean was calculated by performing six-hour serial spirometry from the pre-dose FEV1 and post-dose FEV1 measurements at 15 minutes, 30 minutes, 1 hour, 3 hours and 6 hours. Baseline FEV1 is the mean of the two assessments made 30 and 5 min pre-dose on Treatment Day 1. Change from Baseline was calculated as weighted mean value on Day 84 minus the Baseline value. Analysis was performed using mixed model repeated measures with covariates of treatment, baseline FEV1 (mean of the values measured at 30 min and 5 min pre-dose on Day 1), type of ICS/LABA , smoking status, Day, Day by baseline interaction and Day by treatment interaction, where Day is nominal.

End point type	Secondary

End point timeframe:

Baseline and Day 84

End point values	Placebo+ICS/LABA	Umeclidinium 62.5 mcg+ICS/LABA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110[3]	107[4]		
Units: Liter				
least squares mean (standard error)	0.035 (± 0.0175)	0.184 (± 0.0176)		

Notes:

[3] - ITT population. Only participants with data available at specific timepoint were analyzed.

[4] - ITT population. Only participants with data available at specific timepoint were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

UMEC 62.5+ICS/LABA vs. Placebo+ICS/LABA

Comparison groups	Placebo+ICS/LABA v Umeclidinium 62.5 mcg+ICS/LABA
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed model repeated measures analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.148
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.099
upper limit	0.197

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 treatment and until the follow up contact (13 weeks).

Adverse event reporting additional description:

On-treatment SAEs and non-serious AEs were reported for the ITT Population comprised all subjects 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	Placebo+ICS/LABA

Reporting group description:

Participants received double-blind placebo via a dry powder inhaler (DPI) once daily and an open-label inhaled corticosteriod (ICS)/Long-acting beta2-agonist(LABA) administered according to the label instructions for 12 weeks. Participants also received albuterol/salbutamol via a metered-dose-inhaler (MDI) or nebules as rescue medication throughout the study for use as needed.

Reporting group title	Umeclidinium 62.5 mcg+ICS/LABA

Reporting group description:

Participants received Umeclidinium 62.5 microgram(mcg) via a DPI once daily and an open-label ICS/LABA administered according to label instructions for 12 weeks. Participants also received albuterol/salbutamol via a MDI or nebules as rescue medication throughout the study for use as needed.

Serious adverse events	Placebo+ICS/LABA	Umeclidinium 62.5 mcg+ICS/LABA	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 117 (4.27%)	6 / 119 (5.04%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	1 / 117 (0.85%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Aortic aneurysm rupture			
subjects affected / exposed	0 / 117 (0.00%)	1 / 119 (0.84%)	
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	0 / 117 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Motor neurone disease			
subjects affected / exposed	1 / 117 (0.85%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 117 (0.00%)	1 / 119 (0.84%)	
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 / 117 (2.56%)	3 / 119 (2.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pseudomembranous colitis			
subjects affected / exposed	0 / 117 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 117 (0.00%)	1 / 119 (0.84%)	
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	Placebo+ICS/LABA	Umeclidinium 62.5 mcg+ICS/LABA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 117 (40.17%)	41 / 119 (34.45%)	

Nervous system disorders Headache subjects affected / exposed occurrences (all)	 8 / 117 (6.84%) 12	 4 / 119 (3.36%) 4	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 5 / 117 (4.27%) 6	 2 / 119 (1.68%) 4	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 5 / 117 (4.27%) 7	 2 / 119 (1.68%) 4	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 17 / 117 (14.53%) 23	 16 / 119 (13.45%) 18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2014	Brief description of the changes/reason for the amendment: change inclusion criteria 7 from >=70% to <=70%'. This was an administrative change due to symbols change when protocol was made into a PDF
06 October 2014	Brief description of the changes/reason for amendment: clarified some administrative points
13 October 2014	Clarify the intent of the study protocol is to include patients who are currently taking the dose and frequency of an ICS/LABA combination approved for COPD

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported