



Clinical trial results:

A Randomized, Parallel-group, Open-label Study to Evaluate the Efficacy and Safety of Umeclidinium (UMEC) 62.5 mcg compared with Glycopyrronium 44 mcg in Subjects with Chronic Obstructive Pulmonary Disease (COPD)

Summary

EudraCT number	2014-000885-23
Trial protocol	SE DE ES HU CZ
Global end of trial date	02 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	201315
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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	23 July 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to compare the efficacy and safety of umeclidinium (UMEC) 62.5 micrograms (mcg) with glycopyrronium (GLYCO) 44 mcg in subjects with COPD over 12 weeks of treatment.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 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: 103
Country: Number of subjects enrolled	Chile: 174
Country: Number of subjects enrolled	Czech Republic: 131
Country: Number of subjects enrolled	Germany: 185
Country: Number of subjects enrolled	Hungary: 104
Country: Number of subjects enrolled	Norway: 93
Country: Number of subjects enrolled	Romania: 97
Country: Number of subjects enrolled	Russian Federation: 309
Country: Number of subjects enrolled	Spain: 57
Country: Number of subjects enrolled	Sweden: 99
Worldwide total number of subjects	1352
EEA total number of subjects	766

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)	668
From 65 to 84 years	673
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

A total of 1290 par. were screened; 1037 par. were randomized and 1034 were in the ITT population which comprised of all participants randomized to treatment who received at least one dose of randomized study medication in the treatment period. Two par. were randomized in error and one par. was randomized, but did not take any study medication.

Pre-assignment

Screening details:

Participants (par.), with clinical history of chronic obstructive pulmonary disease, who meet the eligibility criteria at screening were enrolled in a 7 to 14 day run-in period. Par. meeting continuation criteria, during run-in period, were randomized (1:1) to receive umeclidinium or glycopyrronium.

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?	Yes
Arm title	UMEC 62.5 mcg 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) for 12 weeks. Participants also received albuterol/salbutamol via metered-dose-inhaler (MDI) or nebulas as needed throughout the study.

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 via dry powder inhaler for 12 weeks

Arm title	GLYCO 44 mcg QD
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Arm description:

Participants received glycopyrronium bromide (GLYCO) inhalation capsules 44 mcg QD in morning via an alternative dry powder inhaler (DPI) for 12 weeks. Participants also received albuterol/salbutamol via MDI or nebulas as needed throughout the study.

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

Dosage and administration details:

Single dose of glycopyrronium bromide (GLYCO) 44 mcg in morning via dry powder inhaler for 12 weeks

Number of subjects in period 1^[1]	UMEC 62.5 mcg QD	GLYCO 44 mcg QD
Started	516	518
Completed	490	484
Not completed	26	34
Adverse event, serious fatal	1	2
Adverse event, non-fatal	9	14
Protocol deviation	3	5
Withdrew consent	9	4
Lost to follow-up	-	2
Lack of efficacy	4	7

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 1290 par. were screened; 1037 par. were randomized and 1034 were in the intent-to-treat ITT population which comprised all par. randomized to treatment who received at least one dose of randomized study medication. Two par. were randomized in error and 1 par. was randomized, but did not take any study medication.

Baseline characteristics

Reporting groups

Reporting group title	UMEC 62.5 mcg QD
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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) for 12 weeks. Participants also received albuterol/salbutamol via metered-dose-inhaler (MDI) or nebulas as needed throughout the study.

Reporting group title	GLYCO 44 mcg QD
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Reporting group description:

Participants received glycopyrronium bromide (GLYCO) inhalation capsules 44 mcg QD in morning via an alternative dry powder inhaler (DPI) for 12 weeks. Participants also received albuterol/salbutamol via MDI or nebulas as needed throughout the study.

Reporting group values	UMEC 62.5 mcg QD	GLYCO 44 mcg QD	Total
Number of subjects	516	518	1034
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	64.1 ± 8.35	64 ± 8.26	-
Gender categorical Units: Subjects			
Female	161	168	329
Male	355	350	705
Race, Customized Units: Subjects			
Central/South Asian Heritage (HRTG)	3	0	3
Japanese/East Asian Heritage/South East Asian HRTG	0	1	1
White	513	517	1030

End points

End points reporting groups

Reporting group title	UMEC 62.5 mcg QD
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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) for 12 weeks. Participants also received albuterol/salbutamol via metered-dose-inhaler (MDI) or nebulas as needed throughout the study.

Reporting group title	GLYCO 44 mcg QD
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Reporting group description:

Participants received glycopyrronium bromide (GLYCO) inhalation capsules 44 mcg QD in morning via an alternative dry powder inhaler (DPI) for 12 weeks. Participants also received albuterol/salbutamol via MDI or nebulas as needed throughout the study.

Primary: Change from Baseline in trough FEV1 on Day 85

End point title	Change from Baseline in trough FEV1 on Day 85
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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 measurements were taken electronically by spirometry on Days 2, 28, 56, 84 and 85. 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 Baseline 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. The least squares mean changes are presented here. Per Protocol (PP) Population: Participants in the Intent-To-Treat (ITT) Population who did not have a full protocol deviation considered to impact efficacy.

End point type	Primary
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End point timeframe:

Baseline (BL) and Day 85

End point values	UMEC 62.5 mcg QD	GLYCO 44 mcg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	431 ^[1]	425 ^[2]		
Units: Liter				
least squares mean (standard error)	0.123 (± 0.0105)	0.099 (± 0.0105)		

Notes:

[1] - PP population

[2] - PP population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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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	UMEC 62.5 mcg QD v GLYCO 44 mcg QD
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Number of subjects included in analysis	856
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
P-value	= 0.1
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.054

Notes:

[3] - Alternate hypothesis: the difference between the treatment means (umeclidinium minus glycopyrronium) 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 glycopyrronium. If the lower CI (2.5% 1-sided significance) of the statistical testing exceeded 0 then, umeclidinium may be deemed statistically superior to glycopyrronium.

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).

Adverse event reporting additional description:

On-treatment SAEs and non-serious AEs were reported for the Intent-To Treat Population comprised all participants randomized to treatment who received at least one dose of randomized study medication in the treatment period.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	GLYCO 44 mcg QD
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Reporting group description:

Participants received glycopyrronium bromide (GLYCO) inhalation capsules 44 mcg QD in morning via an alternative dry powder inhaler (DPI) for 12 weeks. Participants also received albuterol/salbutamol via MDI or nebulas as needed throughout the study.

Reporting group title	UMEC 62.5 mcg QD
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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) for 12 weeks. Participants also received albuterol/salbutamol via metered-dose-inhaler (MDI) or nebulas as needed throughout the study.

Serious adverse events	GLYCO 44 mcg QD	UMEC 62.5 mcg QD	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 518 (2.90%)	17 / 516 (3.29%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Laryngeal cancer			
subjects affected / exposed	1 / 518 (0.19%)	0 / 516 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm malignant			
subjects affected / exposed	0 / 518 (0.00%)	1 / 516 (0.19%)	
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			

Ankle fracture			
subjects affected / exposed	0 / 518 (0.00%)	1 / 516 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 518 (0.19%)	0 / 516 (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	1 / 518 (0.19%)	0 / 516 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 518 (0.19%)	1 / 516 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 518 (0.19%)	0 / 516 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 518 (0.19%)	0 / 516 (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	0 / 518 (0.00%)	1 / 516 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 518 (0.00%)	1 / 516 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ischaemic stroke			
subjects affected / exposed	0 / 518 (0.00%)	1 / 516 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden cardiac death			
subjects affected / exposed	0 / 518 (0.00%)	1 / 516 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden death			
subjects affected / exposed	0 / 518 (0.00%)	1 / 516 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 518 (0.19%)	0 / 516 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth ulceration			
subjects affected / exposed	0 / 518 (0.00%)	1 / 516 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 518 (0.19%)	0 / 516 (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	5 / 518 (0.97%)	7 / 516 (1.36%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	1 / 518 (0.19%)	0 / 516 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 518 (0.19%)	0 / 516 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Foot deformity			
subjects affected / exposed	1 / 518 (0.19%)	0 / 516 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 518 (0.00%)	2 / 516 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 518 (0.19%)	0 / 516 (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			
Hyponatraemia			
subjects affected / exposed	1 / 518 (0.19%)	0 / 516 (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	GLYCO 44 mcg QD	UMEC 62.5 mcg QD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 518 (15.44%)	77 / 516 (14.92%)	
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	51 / 518 (9.85%) 86	42 / 516 (8.14%) 70	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	39 / 518 (7.53%) 42	42 / 516 (8.14%) 43	

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