Clinical trial results:
Multicenter, randomized, blinded, two-period cross-over study to assess the effect of glycopyrronium (44 micrograms QD) versus tiotropium (18 micrograms QD) on morning symptoms and pulmonary function in patients with moderate to severe COPD.

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Summary

EudraCT number	2013-002483-84
Trial protocol	DE GB IT ES
Global end of trial date	27 October 2014

Results information

Result version number	v1 (current)
This version publication date	12 July 2018
First version publication date	12 July 2018

Trial information

Trial identification

Sponsor protocol code	CNVA237A3401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01959516
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	27 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate that glycopyrronium QD is superior to tiotropium QD in terms of FEV1 AUC0-4h after first dose of treatment.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 February 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	Germany: 69
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 38
Worldwide total number of subjects	126
EEA total number of subjects	126

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)	55
From 65 to 84 years	71
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 126 patients were randomized to one of the two treatment sequences in a ratio of 1:1. Due to misrandomization, two patients did not receive at least one dose of the study treatment. Both, safety and ITT population included 124 patients.

Period 1

Period 1 title	Epoch 1
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	Glycopyrronium first, then Tiotropium

Arm description:

Sequence A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto) to B (Tiotropium 18 µg QD + placebo of glycopyrronium) Sequence B (Tiotropium 18 µg QD + placebo of glycopyrronium) to A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto)

Arm type	Experimental
Investigational medicinal product name	Seebri® SDDPI / Glycopyrronium bromide
Investigational medicinal product code	CNVA237A
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Dosage and administration details:

capsule for inhalation

Arm title	Tiotropium first, then Glycopyrronium

Arm description:

Sequence B (Tiotropium 18 µg QD + placebo of glycopyrronium) to A (Glycopyrronium 44 µg QD + placebo of tiotropiumto) Sequence A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto) to B (Tiotropium 18 µg QD + placebo of glycopyrronium)

Arm type	Experimental
Investigational medicinal product name	Seebri® SDDPI / Glycopyrronium bromide
Investigational medicinal product code	CNVA237A
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Dosage and administration details:

capsule for inhalation

Number of subjects in period 1	Glycopyrronium first, then Tiotropium	Tiotropium first, then Glycopyrronium
Started	63	63
Safety population	62	62
ITT population	62	62
Completed	53	58
Not completed	10	5
Subject withdrew consent	3	2
Adverse event, non-fatal	4	1
Use of prohibited treatment	1	-
Protocol deviation	-	1
Administrative problems	1	-
Moderate or severe COPD exacerbation	-	1
unsatisfactory therapeutic effect	1	-

Period 2

Period 2 title	Epoch 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Glycopyrronium first, then Tiotropium\"

Arm description:

Sequence A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto) to B (Tiotropium 18 µg QD + placebo of glycopyrronium) Sequence B (Tiotropium 18 µg QD + placebo of glycopyrronium) to A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto)

Arm type	Experimental
Investigational medicinal product name	Seebri® SDDPI / Glycopyrronium bromide
Investigational medicinal product code	CNVA237A
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Dosage and administration details:

capsule for inhalation

Arm title	Tiotropium first, then Glycopyrronium

Arm description:

Sequence B (Tiotropium 18 µg QD + placebo of glycopyrronium) to A (Glycopyrronium 44 µg QD + placebo of tiotropiumto) Sequence A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto) to B (Tiotropium 18 µg QD + placebo of glycopyrronium)

Arm type	Experimental

Investigational medicinal product name	Seebri® SDDPI / Glycopyrronium bromide
Investigational medicinal product code	CNVA237A
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Dosage and administration details:
capsule for inhalation

Number of subjects in period 2	Glycopyrronium first, then Tiotropium\"	Tiotropium first, then Glycopyrronium
Started	53	58
Completed	51	57
Not completed	2	1
Subject withdrew consent	1	-
Moderate or severe COPD exacerbation	-	1
unsatisfactory therapeutic effect	1	-

Baseline characteristics

Reporting groups

Reporting group title	Epoch 1

Reporting group description: -

Reporting group values	Epoch 1	Total	
Number of subjects	126	126	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	55	55	
From 65-84 years	71	71	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	65.7		
standard deviation	± 8.1	-	
Gender, Male/Female Units: Participants			
Female	37	37	
Male	89	89	

Subject analysis sets

Subject analysis set title	All participants (Intent To Treat analysis,ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants who were randomized to one of the two treatment sequences in a ratio of 1:1. Participants will receive sequence A = glycopyrronium + placebo to tiotropium during 28 days, followed by a 14 day washout period, then sequence B= tiotropium + placebo to glycopyrronium for 28 days.

Subject analysis set title	Glycopyronium from sequence A to B and sequence B to A
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Sequence A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto) to B (Tiotropium 18 µg QD + placebo of glycopyrronium) Sequence B (Tiotropium 18 µg QD + placebo of glycopyrronium) to A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto)

Subject analysis set title	Tiotropium from sequence A to B and sequence B to A
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Sequence B (Tiotropium 18 µg QD + placebo of glycopyrronium) to A (Glycopyrronium 44 µg QD + placebo of tiotropiumto)Sequence A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto) to B (Tiotropium 18 µg QD + placebo of glycopyrronium)

Reporting group values	All participants (Intent To Treat analysis,ITT)	Glycopyronium from sequence A to B and sequence B to A	Tiotropium from sequence A to B and sequence B to A
Number of subjects	126	126	126
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	55
From 65-84 years	0	0	71
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	65.7		
standard deviation	± 8.1	±	±
Gender, Male/Female Units: Participants			
Female	37		
Male	89		

End points

End points reporting groups

Reporting group title	Glycopyrronium first, then Tiotropium
Reporting group description:	
Sequence A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto) to B (Tiotropium 18 µg QD + placebo of glycopyrronium) Sequence B (Tiotropium 18 µg QD + placebo of glycopyrronium) to A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto)	
Reporting group title	Tiotropium first, then Glycopyrronium
Reporting group description:	
Sequence B (Tiotropium 18 µg QD + placebo of glycopyrronium) to A (Glycopyrronium 44 µg QD + placebo of tiotropiumto) Sequence A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto) to B (Tiotropium 18 µg QD + placebo of glycopyrronium)	
Reporting group title	Glycopyrronium first, then Tiotropium\"
Reporting group description:	
Sequence A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto) to B (Tiotropium 18 µg QD + placebo of glycopyrronium) Sequence B (Tiotropium 18 µg QD + placebo of glycopyrronium) to A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto)	
Reporting group title	Tiotropium first, then Glycopyrronium
Reporting group description:	
Sequence B (Tiotropium 18 µg QD + placebo of glycopyrronium) to A (Glycopyrronium 44 µg QD + placebo of tiotropiumto) Sequence A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto) to B (Tiotropium 18 µg QD + placebo of glycopyrronium)	
Subject analysis set title	All participants (Intent To Treat analysis,ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All participants who were randomized to one of the two treatment sequences in a ratio of 1:1. Participants will receive sequence A = glycopyrronium + placebo to tiotropium during 28 days, followed by a 14 day washout period, then sequence B= tiotropium + placebo to glycopyrronium for 28 days.	
Subject analysis set title	Glycopyronium from sequence A to B and sequence B to A
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Sequence A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto) to B (Tiotropium 18 µg QD + placebo of glycopyrronium) Sequence B (Tiotropium 18 µg QD + placebo of glycopyrronium) to A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto)	
Subject analysis set title	Tiotropium from sequence A to B and sequence B to A
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Sequence B (Tiotropium 18 µg QD + placebo of glycopyrronium) to A (Glycopyrronium 44 µg QD + placebo of tiotropiumto)Sequence A (Glycopyrronium 44 µg QD+ placebo of tiotropiumto) to B (Tiotropium 18 µg QD + placebo of glycopyrronium)	

Primary: Forced Expiratory Volume in 1 second (FEV1) AUC0-4h after first dose of treatment.

End point title	Forced Expiratory Volume in 1 second (FEV1) AUC0-4h after first dose of treatment.
End point description:	
Forced Expiratory Volume in 1 second (FEV1) Area Under the Curve (AUC) will measured via spirometry and calculated from 0 to 4 hours post-dose on day 1 of study treatment.	
End point type	Primary
End point timeframe:	
Day 1	

End point values	Glycopyronium from sequence A to B and sequence B to A	Tiotropium from sequence A to B and sequence B to A		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	124		
Units: Liters*hours				
least squares mean (confidence interval 95%)	1.7432 (1.7132 to 1.7732)	1.7132 (1.683 to 1.7434)		

Statistical analyses

Statistical analysis title	Forced Expiratory Volume in 1 second
Comparison groups	Glycopyronium from sequence A to B and sequence B to A v Tiotropium from sequence A to B and sequence B to A
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.025
Method	Mixed models analysis

Secondary: Comparison of glycopyrronium QD versus tiotropium QD on symptoms outcome

End point title	Comparison of glycopyrronium QD versus tiotropium QD on symptoms outcome

End point description:

Comparison of symptoms outcome between glycopyrronium QD versus tiotropium QD will be conducted via the PROMorning COPD Symptoms questionnaire. This questionnaire will be completed by participants at waking-up, pre-inhalation of study treatment (at home), and they will complete Part 2 of PRO-Morning COPD Symptoms questionnaire at site, 3hours post-inhalation of study treatment. The PRO-Morning COPD Symptoms Questionnaire is a self-administered patient reported outcome (PRO) instrument developed by the sponsor to evaluate patients' experience of early morning symptoms of COPD. The questionnaire consists of two parts : predose and postdose. Each part has 6 questions and for each question a scale of 0 to 10 can be reached. For the predose and postdose part of the questionnaire you will have then each a total score of 0-60 by adding the sub-scores for each question, higher scores represent worse severity of COPD morning symptoms

End point type	Secondary

End point timeframe:

day 1 (baseline) and week 4

End point values	Glycopyronium from sequence A to B and sequence B to A	Tiotropium from sequence A to B and sequence B to A		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	124		
Units: Scores on a scale				
least squares mean (confidence interval 95%)				
3h post-dose (Day 1)	9.7068 (8.7294 to 10.6841)	10.3974 (9.4036 to 11.3913)		
3h post-dose (Week 4)	10.4641 (9.3786 to 11.5496)	10.3193 (9.2286 to 11.41)		

Statistical analyses

Statistical analysis title	Comparison of glycopyrronium versus tiotropium
Comparison groups	Glycopyronium from sequence A to B and sequence B to A v Tiotropium from sequence A to B and sequence B to A
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1439
Method	Mixed models analysis

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Tiotropium
Reporting group description:	
Tiotropium	
Reporting group title	Glycopyrronium
Reporting group description:	
Glycopyrronium	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: AEs are validated

Serious adverse events	Tiotropium	Glycopyrronium	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 124 (1.61%)	2 / 124 (1.61%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Lumbar vertebral fracture			
subjects affected / exposed	1 / 124 (0.81%)	0 / 124 (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			
Dyspnoea			
subjects affected / exposed	0 / 124 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 124 (0.81%)	0 / 124 (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	0 / 124 (0.00%)	1 / 124 (0.81%)	
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: 5 %

Non-serious adverse events	Tiotropium	Glycopyrronium	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 124 (0.00%)	0 / 124 (0.00%)	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: