Clinical trial results:
A randomized, double-blind, multicenter, 2-period single-dose cross-over study to assess the early bronchodilation of glycopyrronium bromide (44 µg o.d.) compared to tiotropium (18 µg. o.d.) 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	2013-001445-13
Trial protocol	DE
Global end of trial date	09 January 2014

Results information

Result version number	v1 (current)
This version publication date	25 July 2018
First version publication date	25 July 2018

Trial information

Trial identification

Sponsor protocol code	CNVA237ADE02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01922271
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	09 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that glycopyrronium bromide 44 µg q.d has superior efficacy compared to tiotropium 18 µg q. d. on early bronchodilation, determined by forced expiratory volume in 1 second (FEV1) area under the curve at 0 to 2 hours (AUC 0-2h), in moderate to severe chronic obstructive pulmonary disease (COPD) patients.

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. In addition, patients who experienced a moderate to severe COPD exacerbation had to be discontinued from study medication and the trial immediately. At the start of screening (Visit 1), all patients were provided with a short acting β2-agonist (salbutamol 100 µg) which they were instructed to use throughout the trial (when required) as rescue medication only. Nebulized salbutamol was not allowed as rescue medication. No other rescue treatment was permitted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 152
Worldwide total number of subjects	152
EEA total number of subjects	152

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	98
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

It was anticipated that at least 180 patients would be need to be screened to randomize 150 patients. Dropouts were not replaced. At the end of the study, 197 patients were screened and 152 patients randomized at 14 centers in Germany, with 76 patients per sequence.

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Assessor, Subject

Blinding implementation details:

A double-dummy design was used because the identity of the study drugs could not be disguised due to their different forms.

Arms

Are arms mutually exclusive?	Yes
Arm title	NVA237 Followed by Tiotropium

Arm description:

NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® on Day 1 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) on Day 8.

Arm type	Experimental
Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	NVA237 44 µg
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

NVA237 44 µg inhalation capsules o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® at Visit 3 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 4.

Investigational medicinal product name	Placebo to Tiotropium 18 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® at Visit 3 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 4.

Investigational medicinal product name	Tiotropium 18 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® at Visit 3 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 4.

Investigational medicinal product name	Placebo to NVA237 44 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® at Visit 3 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 4.

Arm title	Tiotropium Followed by NVA237

Arm description:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) on Day 1 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® on Day 8.

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

Dosage and administration details:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 3 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® at Visit 4.

Investigational medicinal product name	Placebo to NVA237 44 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 3 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® at Visit 4.

Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	NVA237 44 µg
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 3 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® at Visit 4.

Investigational medicinal product name	Placebo to Tiotropium 18 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 3 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® at Visit 4.

Number of subjects in period 1	NVA237 Followed by Tiotropium	Tiotropium Followed by NVA237
Started	76	76
Completed	76	76

Period 2

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

Blinding implementation details:

A double-dummy design was used because the identity of the study drugs could not be disguised due to their different forms.

Arms

Are arms mutually exclusive?	Yes
Arm title	NVA237 Followed by Tiotropium

Arm description:

NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® at Visit 3 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 4.

Arm type	Experimental
Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	NVA237 44 µg
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

NVA237 44 µg inhalation capsules o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® at Visit 3 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 4.

Investigational medicinal product name	Placebo to Tiotropium 18 µg
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® at Visit 3 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 4.

Investigational medicinal product name	Tiotropium 18 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® at Visit 3 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 4.

Investigational medicinal product name	Placebo to NVA237 44 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® at Visit 3 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 4.

Arm title	Tiotropium Followed by NVA237

Arm description:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 3 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® at Visit 4.

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

Dosage and administration details:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 3 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® at Visit 4.

Investigational medicinal product name	Placebo to NVA237 44 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 3 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® at Visit 4.

Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	NVA237 44 µg
Other name	

Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 3 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® at Visit 4.

Investigational medicinal product name	Placebo to Tiotropium 18 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 3 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® at Visit 4.

Number of subjects in period 2	NVA237 Followed by Tiotropium	Tiotropium Followed by NVA237
Started	76	76
Completed	75	76
Not completed	1	0
Consent withdrawn by subject	1	-

Period 3

Period 3 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

A double-dummy design was used because the identity of the study drugs could not be disguised due to their different forms.

Arms

Are arms mutually exclusive?	Yes
Arm title	NVA237 Followed by Tiotropium

Arm description:

NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® at Visit 3 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 4.

Arm type	Experimental

Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	NVA237 44 µg
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

NVA237 44 µg inhalation capsules o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® at Visit 3 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 4.

Investigational medicinal product name	Placebo to Tiotropium 18 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® at Visit 3 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 4.

Investigational medicinal product name	Tiotropium 18 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® at Visit 3 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 4.

Investigational medicinal product name	Placebo to NVA237 44 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® at Visit 3 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 4.

Arm title	Tiotropium Followed by NVA237

Arm description:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 3 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® at Visit 4.

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

Dosage and administration details:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 3 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d.

delivered via Handihaler® at Visit 4.

Investigational medicinal product name	Placebo to NVA237 44 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 3 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® at Visit 4.

Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	NVA237 44 µg
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 3 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® at Visit 4.

Investigational medicinal product name	Placebo to Tiotropium 18 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 3 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® at Visit 4.

Number of subjects in period 3	NVA237 Followed by Tiotropium	Tiotropium Followed by NVA237
Started	75	76
Completed	75	76

Baseline characteristics

Reporting groups	
Reporting group title	NVA237 Followed by Tiotropium
Reporting group description:	
NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® on Day 1 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) on Day 8.	
Reporting group title	Tiotropium Followed by NVA237
Reporting group description:	
Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) on Day 1 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® on Day 8.	

Reporting group values	NVA237 Followed by Tiotropium	Tiotropium Followed by NVA237	Total
Number of subjects	76	76	152
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	61.9	61.7	
standard deviation	± 7.2	± 8.2	-
Gender categorical			
Units: Subjects			
Female	28	26	54
Male	48	50	98

End points

End points reporting groups

Reporting group title	NVA237 Followed by Tiotropium

Reporting group description:

NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® on Day 1 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) on Day 8.

Reporting group title	Tiotropium Followed by NVA237

Reporting group description:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) on Day 1 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® on Day 8.

Reporting group title	NVA237 Followed by Tiotropium

Reporting group description:

NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® at Visit 3 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 4.

Reporting group title	Tiotropium Followed by NVA237

Reporting group description:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 3 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® at Visit 4.

Reporting group title	NVA237 Followed by Tiotropium

Reporting group description:

NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via HandiHaler® at Visit 3 and Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 4.

Reporting group title	Tiotropium Followed by NVA237

Reporting group description:

Tiotropium 18 µg o.d, delivered via the manufacturer's proprietary inhalation device (HandiHaler®) plus placebo to NVA237 o.d., delivered via a single-dose dry powder inhaler (SDDPI) at Visit 3 and NVA237 44 µg o.d., delivered via a single-dose dry powder inhaler (SDDPI), plus placebo to tiotropium o.d. delivered via Handihaler® at Visit 4.

Subject analysis set title	NVA237
Subject analysis set type	Full analysis

Subject analysis set description:

All patients on NVA237 for Period 1 and Period 2. The Full Analysis Set (FAS) consisted of all randomized patients who applied at least one dose of study medication during at least one study period.

Subject analysis set title	Tiotropium
Subject analysis set type	Full analysis

Subject analysis set description:

All patients onTiotropium for Period 1 and Period 2. The Full Analysis Set (FAS) consisted of all randomized patients who applied at least one dose of study medication during at least one study period.

Primary: Forced Expiratory Volume in 1 Second (FEV1) Area Under the Curve (AUC) 0-2 Hours in Liters

End point title	Forced Expiratory Volume in 1 Second (FEV1) Area Under the Curve (AUC) 0-2 Hours in Liters

End point description:

The AUC was calculated from the FEV1 measurements obtained at timepoints between 0 min and 2h using the trapezoidal rule and will be standardized (=divided) by the measurement time (i.e. 2h). FEV1

was collected during spriometric testing. Spirometric testing had to be performed in accordance with ATS standards. For all clinic spirometry assessments, three acceptable maneuvers (a maximum of 8 maneuvers) had to be performed for each time-point. The FEV1, FVC values recorded in the e-CRF were the highest values measured irrespective of whether or not they occurred on the same curve.

End point type	Primary

End point timeframe:

Day 1

End point values	NVA237	Tiotropium		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	151	150		
Units: liters				
arithmetic mean (standard deviation)	1.49 (± 0.4232)	1.453 (± 0.4135)		

Statistical analyses

Statistical analysis title	Analysis of Primary Variable

Statistical analysis description:

The primary endpoint is FEV1 AUC0-2h calculated at 0', 5', 15', 45', 75' and 2h using the trapezoidal rule divided by actual measurement time. The null hypothesis was that there is no difference between treatments for AUC0-2h vs. glycopyrronium has a higher FEV1 AUC0-2h compared to tiotropium. Treatment comparisons were made using an analysis of variance model for center, period, patient-within-center and treatment. The null hypothesis was tested using a 2-sided significance level of 5%.

Comparison groups	NVA237 v Tiotropium
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.059

Secondary: Forced Expiratory Volume in 1 Second (FEV1) 15 Minutes Post-Dose

End point title	Forced Expiratory Volume in 1 Second (FEV1) 15 Minutes Post-Dose

End point description:

FEV1 was collected during spriometirci testing. Spirometric testing had to be performed in accordance with ATS standards . For all clinic spirometry assessments, three acceptable maneuvers (a maximum of 8 maneuvers) had to be performed for each time-point. The FEV1, FVC values recorded in the e-CRF were the highest values measured irrespective of whether or not they occurred on the same curve.

End point type	Secondary

End point timeframe:

15 minutes post dose

End point values	NVA237	Tiotropium		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	152[1]	151[2]		
Units: Liters				
arithmetic mean (standard deviation)	1.433 (± 0.411)	1.398 (± 0.4092)		

Notes:

[1] - Full analysis set

[2] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Specific Airway Resistance (sRaw) Over Time

End point title	Specific Airway Resistance (sRaw) Over Time

End point description:

Constant-volume body plethysmography was used to assess sRaw. After having the maneuver explained to the subject, resting tidal breathing commenced during which a stable end-expiratory lung volume level and a stable tidal volume should be achieved.
After approximately 5 normal tidal breaths at a breathing frequency not exceeding 0.5 – 1 per second the pressure-flow curves were collected to determine the specific airway resistance (sRaw).

End point type	Secondary

End point timeframe:

Specific airway resistance (sRaw) was measured at -45 minutes prior to dosing and at 30 minutes, 1 hour, 1 hour 30 minutes, 2 hours 30 minutes, and 3 hours 30 minutes post dosing.

End point values	NVA237	Tiotropium		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	152[3]	150[4]		
Units: SR tot (kPa*s)				
arithmetic mean (standard deviation)				
-45 minutes (n = 152, 150)	4.203 (± 1.8102)	4.105 (± 1.8338)		
30 min (n=150, 151)	2.904 (± 1.4759)	3.089 (± 1.4555)		
1 hr (n=151, 149)	2.656 (± 1.3062)	2.877 (± 1.413)		
1 hr 30 min (n=151, 150)	2.632 (± 1.3152)	2.811 (± 1.4065)		
2 hr 30 min (n=150, 149)	2.643 (± 1.3146)	2.756 (± 1.4091)		
3 hr 30 min (n=150, 149)	2.779 (± 1.4496)	2.828 (± 1.4534)		

Notes:

[3] - Full analysis set

[4] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Residual Capacity (FRCpleth)

End point title	Functional Residual Capacity (FRCpleth)

End point description:

FRC was collected during body plethysmography. After having the maneuver explained to the subject, resting tidal breathing commenced during which a stable end-expiratory lung volume level and a stable tidal volume should be achieved. After a few breaths, the shutter of the body plethysmograph was closed and the subject continued to breathe against the closed shutter for an additional few breaths during which the pressure-volume loops were collected and FRC obtained. After four to five breaths the shutter was opened and the measurement was completed. The subject should not hold their cheeks during the maneuver. Three acceptable measurements were done and the mean entered onto the eCRF.

End point type	Secondary

End point timeframe:

Functional resistance capacity (FRC) in liters was measured at -45 minutes, 30 minutes, 1 hour, 1 hour 30 minutes, 2 hours 30 minutes, and 3 hours 30 minutes post dosing.

End point values	NVA237	Tiotropium		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	152[5]	151[6]		
Units: Liters				
arithmetic mean (standard deviation)				
-45 min (n=152, 150)	5.211 (± 1.3086)	5.142 (± 1.2656)		
30 min (n=150, 151)	4.823 (± 1.2517)	4.852 (± 1.1812)		
1 hr (n=151, 149)	4.769 (± 1.2571)	4.725 (± 1.1496)		
1 hr 30 min (n=151, 149)	4.756 (± 1.2366)	4.714 (± 1.1523)		
2 h 30 min (n= 150, 149)	4.736 (± 1.1545)	4.676 (± 1.2243)		
3 h 30 min (n= 150, 148)	4.761 (± 1.2286)	4.704 (± 1.1911)		

Notes:

[5] - Full analysis set

[6] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Residual Volume (RV)

End point title	Residual Volume (RV)

End point description:

This was collected during body plethysmography. After the inspiratory capacity maneuver the patient exhaled fully and slowly to the level of RV with verbal encouragement. The exhaled volume is the slow vital capacity (SVC). The exhalation had to be no longer than 15 s long or to fulfill the end-of-test criterion, which was less than 20 mL volume change in two consecutive seconds. The highest of the three measurements was reported and considered in RV calculation (RV = TLC – SVChighest). All volumes were reported in liters (L) under BTPS conditions (body temperature (37° C), ambient pressure, saturated with water vapor.

End point type	Secondary

End point timeframe:

Residual volume in liters was measured at -45 minutes, 30 minutes, 1 hour, 1 hour 30 minutes, 2 hou

End point values	NVA237	Tiotropium		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	152[7]	151[8]		
Units: liters				
arithmetic mean (standard deviation)				
-45 min (n=152, 150)	4.433 (± 1.2596)	4.344 (± 1.1707)		
30 min (n=150, 151)	3.996 (± 1.1862)	4.035 (± 1.0689)		
1 hr (n=151, 149)	3.891 (± 1.1997)	3.913 (± 1.0281)		
1 hr 30 min (n=151, 149)	3.91 (± 1.1534)	3.903 (± 1.0281)		
2 h 30 min (n= 150, 149)	3.893 (± 1.0486)	3.861 (± 1.1058)		
3 h 30 min (n= 150, 148)	3.97 (± 1.1576)	3.895 (± 1.074)		

Notes:

[7] - Full analysis set

[8] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Inspiratory capacity (IC)

End point title	Inspiratory capacity (IC)

End point description:

Inspiratory capacity was measured during body plethysmography. After measuring sRaw and FRC in a linked maneuver, the patient had to follow the verbal command to fill up their lungs slowly and completely to reach a plateau at the total lung capacity level.

End point type	Secondary

End point timeframe:

Inspiratory capacity in liters was measured at -45 minutes, 30 minutes, 1 hour, 1 hour 30 minutes, 2 hours 30 minutes, and 3 hours 30 minutes post dosing.

End point values	NVA237	Tiotropium		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	152[9]	151[10]		
Units: liters				
arithmetic mean (standard deviation)				
-45 min (n=152, 150)	2.169 (± 0.5548)	2.193 (± 0.5583)		
30 min (n=150, 151)	2.433 (± 0.5934)	2.422 (± 0.5996)		
1hr (n=151, 149)	2.455 (± 0.6001)	2.435 (± 0.5908)		
1hr 30 min (n=151, 150)	2.472 (± 0.62)	2.457 (± 0.5883)		
2hr 30 min (n=150, 149)	2.467 (± 0.5929)	2.474 (± 0.6051)		
3hr 30 min (n=150, 149)	2.479 (± 2.449)	2.449 (± 0.5907)		

Notes:

[9] - Full analysis set

[10] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Total Lung Capacity (TLC)

End point title	Total Lung Capacity (TLC)

End point description:

Total lung capacity was collected during body plethysmography.

End point type	Secondary

End point timeframe:

Total lung capacity in liters was measured at -45 minutes, 30 minutes, 1 hour, 1 hour 30 minutes, 2 hours 30 minutes, and 3 hours 30 minutes post dosing.

End point values	NVA237	Tiotropium		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: liters				
arithmetic mean (standard deviation)				
-45 min (n=152, 150)	7.38 (± 1.4781)	7.335 (± 1.4328)		
30 min (n=150, 151)	7.255 (± 1.4628)	7.274 (± 1.4032)		
1hr (n=151, 149)	7.224 (± 1.4294)	7.161 (± 1.4015)		
1hr 30 min (n=151, 149)	7.227 (± 1.4383)	7.165 (± 1.369)		
2hr 30 min (n=150, 149)	7.203 (± 1.37)	7.149 (± 1.4476)		
3hr 30 min (n=150, 148)	7.24 (± 1.4297)	7.149 (± 1.3963)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	NVA237

Reporting group description:

All patients on NVA237 for Period 1 and Period 2. The Full Analysis Set (FAS) consisted of all randomized patients who applied at least one dose of study medication during at least one study period.

Reporting group title	Tiotropium

Reporting group description:

All patients onTiotropium for Period 1 and Period 2. The Full Analysis Set (FAS) consisted of all randomized patients who applied at least one dose of study medication during at least one study period.

Serious adverse events	NVA237	Tiotropium	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 152 (1.32%)	2 / 151 (1.32%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (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	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Surgical and medical procedures			
Nephrectomy			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
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: 2 %

Non-serious adverse events	NVA237	Tiotropium	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 152 (1.97%)	4 / 151 (2.65%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 152 (1.97%)	4 / 151 (2.65%)	
occurrences (all)	3	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 August 2013	Amendment was issued after inclusion of 33% of patients. Spirometry decribed that patients with a decrease in post bronchodilator FEV1 compared to pre-bronchodilator FEV1 should be screen failed. This was now added to exclusion criterion.

Notes:

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: