



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 | 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® 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 standard deviation | 61.9 ± 7.2 | 61.7 ± 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 spirometric 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 spirometric 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 ($RV = TLC - SV_{Chighest}$). 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 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 ^[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 on Tiotropium 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 described 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: