Clinical trial results:
A randomized, double-blind, parallel group, 26-week study evaluating the efficacy, safety and tolerability of NVA237 given once or twice daily, in patients with moderate and severe chronic obstructive pulmonary disease

Summary

EudraCT number	2014-004818-28
Trial protocol	DE FI HU BE SE GB BG PL RO IT
Global end of trial date	16 November 2016

Results information

Result version number	v1 (current)
This version publication date	30 November 2017
First version publication date	30 November 2017

Trial information

Trial identification

Sponsor protocol code	CNVA237A2320,

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02371629
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	16 November 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the efficacy of NVA237 22 µg twice daily (b.i.d.) versus 44 µg once daily (o.d.) (both delivered via a Concept1) in terms of trough forced expiratory volume in the first second (FEV1) (defined as mean evaluation at 23 hours 15 minutes and 23 hours 45 minutes post-dose) following 12 weeks of treatment in patients with stable, symptomatic chronic obstructive pulmonary disease (COPD) with moderate to severe airflow limitation (Stages 2 and 3) according to Global Initiative for Chronic Obstructive Lung Disease (GOLD 2014).

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	24 June 2015
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	Belgium: 19
Country: Number of subjects enrolled	Bulgaria: 152
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	Germany: 192
Country: Number of subjects enrolled	Hungary: 85
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Poland: 94
Country: Number of subjects enrolled	Romania: 103
Country: Number of subjects enrolled	Russian Federation: 107
Country: Number of subjects enrolled	Sweden: 16
Worldwide total number of subjects	776
EEA total number of subjects	663

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)	418
From 65 to 84 years	358
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1020 patients were screened for participation in this study; 776 were randomized.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	NVA237 Twice daily

Arm description:

Patients randomized to this arm received an NVA237 22 µg capsule in the morning and evening for 26 weeks. All participants received salbutamol as rescue medicine.

Arm type	Experimental
Investigational medicinal product name	glycopyrronium bromide
Investigational medicinal product code	NVA237
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Dosage and administration details:

NVA237 44 µg

Arm title	NVA237 Once daily

Arm description:

Patients randomized to this arm received an NVA237 44 µg capsule in the morning and a placebo capsule in the evening for 26 weeks. All participants received salbutamol as rescue medicine.

Arm type	Experimental
Investigational medicinal product name	glycopyrronium bromide
Investigational medicinal product code	NVA237
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Dosage and administration details:

NVA237 22 µg

Number of subjects in period 1	NVA237 Twice daily	NVA237 Once daily
Started	388	388
Completed	362	363
Not completed	26	25
Adverse event, serious fatal	1	1
Patient decision	14	10
Physician decision	2	3
Adverse event, non-fatal	8	8
Protocol deviation	-	1
Noncompliance with study treatment	1	-
Lack of efficacy	-	2

Baseline characteristics

Reporting groups	
Reporting group title	NVA237 Twice daily
Reporting group description:	
Patients randomized to this arm received an NVA237 22 µg capsule in the morning and evening for 26 weeks. All participants received salbutamol as rescue medicine.	
Reporting group title	NVA237 Once daily
Reporting group description:	
Patients randomized to this arm received an NVA237 44 µg capsule in the morning and a placebo capsule in the evening for 26 weeks. All participants received salbutamol as rescue medicine.	

Reporting group values	NVA237 Twice daily	NVA237 Once daily	Total
Number of subjects	388	388	776
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)	216	202	418
From 65-84 years	172	186	358
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	63.2	63.6	
standard deviation	± 7.71	± 7.66	-
Gender, Male/Female Units: Subjects			
Female	122	111	233
Male	266	277	543

End points

End points reporting groups

Reporting group title	NVA237 Twice daily
Reporting group description:	
Patients randomized to this arm received an NVA237 22 µg capsule in the morning and evening for 26 weeks. All participants received salbutamol as rescue medicine.	
Reporting group title	NVA237 Once daily
Reporting group description:	
Patients randomized to this arm received an NVA237 44 µg capsule in the morning and a placebo capsule in the evening for 26 weeks. All participants received salbutamol as rescue medicine.	

Primary: Change from baseline in Trough Forced Expiratory Volume in 1 Second (FEV1) at Week 12

End point title	Change from baseline in Trough Forced Expiratory Volume in 1 Second (FEV1) at Week 12
End point description:	
Spirometry testing was performed in accordance with American Thoracic Society standards. Trough FEV1 defined as the mean of two measurements at 23 hours 15 minutes and 23 hour 45 minutes post dosing. Baseline FEV1 was defined as the average of the -45 minutes and -15 minutes FEV1 values taken on Day 1. An analysis-of-covariance (ANCOVA) for repeated measurements, also known as mixed model for repeated measures (MMRM), was performed for the change from baseline of trough FEV1 at Week 12. The model included treatment, COPD severity, baseline smoking status, baseline ICS use, region, and visit (Day 1, and Weeks 12 and 26) as factors and baseline FEV1 as a covariate.	
End point type	Primary
End point timeframe:	
Baseline, Week 12	

End point values	NVA237 Twice daily	NVA237 Once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358	360		
Units: Liters				
least squares mean (standard error)	0.092 (± 0.0126)	0.059 (± 0.0125)		

Statistical analyses

Statistical analysis title	Trough Forced (FEV1) at Week 12
Comparison groups	NVA237 Twice daily v NVA237 Once daily
Number of subjects included in analysis	718
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.051
Method	Mixed model for repeated measure (MMRM)
Parameter estimate	Mean difference (net)
Point estimate	0.033

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.066
Variability estimate	Standard error of the mean
Dispersion value	0.0169

Secondary: Change from baseline in Area Under The Curve (AUC) for Forced Expiratory Volume in one second (FEV1) for different time spans post dosing at Week 12

End point title	Change from baseline in Area Under The Curve (AUC) for Forced Expiratory Volume in one second (FEV1) for different time spans post dosing at Week 12

End point description:

The standardized Area Under the Curve (AUC) for Forced Expiratory Volume in one second (FEV1) is assessed for different time spans (0-12h, 0-24h, 12-24h) within the overall serial measurement post dosing at week 12 of treatment. Baseline FEV1 was defined as the average of the -45 minutes and -15 minutes FEV1 values taken on Day 1.

End point type	Secondary

End point timeframe:

Baseline, 0-12 hour, 0-24 hour , 12-24 hour post dose at Week 12

End point values	NVA237 Twice daily	NVA237 Once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	373		
Units: Liters				
least squares mean (standard error)				
AUC (0-12 hour) (n=373, 373)	0.136 (± 0.0119)	0.106 (± 0.0118)		
AUC (0-24 hour) (n=373, 373)	0.085 (± 0.0121)	0.043 (± 0.0120)		
AUC (12-24 hour) (n=371, 371)	0.035 (± 0.0125)	-0.019 (± 0.0124)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Area Under The Curve (AUC 0-12 hour) for Forced Expiratory Volume in one second (FEV1) post dosing at Day 1

End point title	Change from baseline in Area Under The Curve (AUC 0-12 hour) for Forced Expiratory Volume in one second (FEV1) post dosing at Day 1

End point description:

The standardized Area Under the Curve (AUC) for Forced Expiratory Volume in one second (FEV1) is assessed for 0-12 hour, post dosing at Day 1 of treatment. Baseline FEV1 was defined as the average of

the -45 minutes and -15 minutes FEV1 values taken on Day 1.

End point type	Secondary

End point timeframe:

Baseline, 0-12 hour post dose at Day 1

End point values	NVA237 Twice daily	NVA237 Once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	387		
Units: Liters				
least squares mean (standard error)	0.143 (± 0.0089)	0.139 (± 0.0087)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Area Under The Curve (AUC) for Forced Expiratory Volume in one second (FEV1) for different time spans post dosing at Week 26

End point title	Change from baseline in Area Under The Curve (AUC) for Forced Expiratory Volume in one second (FEV1) for different time spans post dosing at Week 26

End point description:

The standardized Area Under the Curve (AUC) for Forced Expiratory Volume in one second (FEV1) is assessed for different time spans (0-12h, 0-24h, 12-24h) within the overall serial measurement post dosing at week 26 of treatment. Baseline FEV1 was defined as the average of the -45 minutes and -15 minutes FEV1 values taken on Day 1.

End point type	Secondary

End point timeframe:

Baseline, 0-12 hour, 0-24 hour , 12-24 hour post dose at Week 26

End point values	NVA237 Twice daily	NVA237 Once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	364		
Units: Liters				
least squares mean (standard error)				
AUC (0-12 hour) (n=360, 363)	0.123 (± 0.0121)	0.091 (± 0.0120)		
AUC (0-24 hour) (n=360, 364)	0.076 (± 0.0122)	0.030 (± 0.0121)		
AUC (12-24 hour) (n=357, 361)	0.032 (± 0.0127)	-0.028 (± 0.0126)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in total St. George's Respiratory Questionnaire (SGRQ) score at week 12 and week 26

End point title	Change from baseline in total St. George's Respiratory Questionnaire (SGRQ) score at week 12 and week 26

End point description:

The health status, as reported by the patients, is assessed using the St. George's Respiratory Questionnaire (SGRQ). The SGRQ contains 50 items divided into 2 parts covering 3 aspects of health related to COPD: • Part I covers "Symptoms" and is concerned with respiratory symptoms, their frequency and severity • Part II covers "Activity" and is concerned with activities that caused or are limited by breathlessness • Part II is also concerned with "Impacts", which covers a range of aspects concerned with social functioning and psychological disturbances resulting from airways disease. A score was calculated for each of these three subscales and the total score was calculated. In each case, the lowest possible value was 0 and the highest 100. Higher values corresponded to greater impairment of health status.

End point type	Secondary

End point timeframe:

Baseline, 12 Weeks, 26 Weeks

End point values	NVA237 Twice daily	NVA237 Once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	388		
Units: score on a scale				
least squares mean (standard error)				
Change from Baseline to WK 12 (n=369, 369)	-5.320 (± 0.6000)	-3.563 (± 0.5987)		
Change from Baseline to WK 26 (n=357, 359)	-6.587 (± 0.6543)	-4.644 (± 0.6527)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with a clinically significant improvement in St George Respiratory Questionnaire at week 12 and week 26

End point title	Percentage of patients with a clinically significant improvement in St George Respiratory Questionnaire at week 12 and week 26

End point description:

The health status, as reported by the patients, is assessed using the St. George's Respiratory Questionnaire (SGRQ). The SGRQ contains 50 items divided into 2 parts covering 3 aspects of health related to COPD: • Part I covers "Symptoms" and is concerned with respiratory symptoms, their frequency and severity • Part II covers "Activity" and is concerned with activities that caused or are limited by breathlessness • Part II is also concerned with "Impacts", which covers a range of aspects concerned with social functioning and psychological disturbances resulting from airways disease. A score was calculated for each of these three subscales and the total score was calculated. In each case, the lowest possible value was 0 and the highest 100. A clinically significant improvement is defined as ≥ 4 unit improvement from baseline score (a decrease of ≥ 4).

End point type	Secondary

End point timeframe:

Baseline, 12 Weeks, 26 Weeks

End point values	NVA237 Twice daily	NVA237 Once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	388		
Units: percentage of patients				
number (not applicable)				
Change from Baseline to WK 12 (n=369, 369)	54.5	46.9		
Change from Baseline to WK 26 (n=357, 359)	59.4	49.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Transitional Dyspnea Index (TDI) focal score at Week 12 and Week 26

End point title	Change from baseline in Transitional Dyspnea Index (TDI) focal score at Week 12 and Week 26

End point description:

Breathlessness at Week 12 and Week 26 is measured using the Transition Dyspnea Index (TDI). On day 1, breathlessness is assessed by the Baseline Dyspnea Index (BDI). Baseline Dyspnea Index (BDI)/Transition Dyspnea Index (TDI) focal score is based on three domains: functional impairment, magnitude of task and magnitude of effort and captures changes from baseline. BDI was measured at day 1 prior to the first dose with domain scores ranging from 0=very severe to 4=no impairment and a total score ranging from 0 to 12(best). TDI captures changes from baseline. Each domain is scored from -3=major deterioration to 3=major improvement to give an overall TDI focal score of -9 to 9. Higher numbers indicate a better score.

End point type	Secondary

End point timeframe:

Baseline, 12 Weeks, 26 Weeks

End point values	NVA237 Twice daily	NVA237 Once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	388		
Units: score on a scale				
least squares mean (standard error)				
Change from Baseline to WK 12 (n=360, 356)	1.346 (± 0.1430)	0.849 (± 0.1433)		
Change from Baseline to WK 26 (n=347, 348)	1.523 (± 0.1539)	1.170 (± 0.1534)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with a clinically important improvement on Transitional Dyspnea Index (TDI) focal score at Week 12 and Week 26

End point title	Percentage of patients with a clinically important improvement on Transitional Dyspnea Index (TDI) focal score at Week 12 and Week 26

End point description:

Breathlessness at Week 12 and Week 26 is measured using the Transition Dyspnea Index (TDI). On day 1, breathlessness is assessed by the Baseline Dyspnea Index (BDI). Baseline Dyspnea Index (BDI)/Transition Dyspnea Index (TDI) focal score is based on three domains: functional impairment, magnitude of task and magnitude of effort and captures changes from baseline. BDI was measured at day 1 prior to the first dose with domain scores ranging from 0=very severe to 4=no impairment and a total score ranging from 0 to 12(best). TDI captures changes from baseline. Each domain is scored from -3=major deterioration to 3=major improvement to give an overall TDI focal score of -9 to 9. Higher numbers indicate a better score. Clinically important improvement indicates ≥ 1 unit in the TDI focal score at Weeks 12 and 26 in comparison to BDI focal score (an increase of ≥ 1).

End point type	Secondary

End point timeframe:

Baseline, 12 Weeks, 26 Weeks

End point values	NVA237 Twice daily	NVA237 Once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	388		
Units: Percentage of patients				
number (not applicable)				
Change from Baseline to WK 12 (n=360, 356)	56.9	52.0		
Change from Baseline to WK 26 (n=347, 348)	61.1	54.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Trough Forced Expiratory Volume in 1 Second (FEV1) at Day 1 and Week 26

End point title	Change from baseline in Trough Forced Expiratory Volume in 1 Second (FEV1) at Day 1 and Week 26

End point description:

Spirometry testing was performed in accordance with American Thoracic Society standards. Trough

FEV1 defined as the mean of two measurements at 23 hours 15 minutes and 23 hour 45 minutes post dosing. Baseline FEV1 was defined as the average of the -45 minutes and -15 minutes FEV1 values taken on Day 1. An analysis-of-covariance (ANCOVA) for repeated measurements, also known as mixed model for repeated measures (MMRM), was performed for the change from baseline of trough FEV1. The model included treatment, COPD severity, baseline smoking status, baseline ICS use, region, and visit (Day 1, and Weeks 12 and 26) as factors and baseline FEV1 as a covariate.

End point type	Secondary

End point timeframe:

Baseline, Day 1, Week 26

End point values	NVA237 Twice daily	NVA237 Once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	388		
Units: Liters				
least squares mean (standard error)				
Change from baseline to Day 1 (n= 381, 381)	0.119 (± 0.0099)	0.070 (± 0.0097)		
Change from baseline to Week 26 (n= 341, 349)	0.104 (± 0.0129)	0.056 (± 0.0128)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Forced Vital Capacity (FVC) at individual timepoints at week 26

End point title	Change from baseline in Forced Vital Capacity (FVC) at individual timepoints at week 26

End point description:

Mixed model for repeated measures was used to analyze change from baseline in FVC. Baseline FVC is defined as the average of the -45 min and -15 min FVC values taken on Day 1 prior to first dose.

End point type	Secondary

End point timeframe:

Baseline, Week 26 (Day 183)

End point values	NVA237 Twice daily	NVA237 Once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	388		
Units: Liters				
least squares mean (standard error)				
Day 183/-45 min: (n= 334, 342)	0.079 (± 0.0195)	0.025 (± 0.0192)		
Day 183/-15 min: (n= 340, 345)	0.102 (± 0.0193)	0.029 (± 0.0191)		
Day 183/5 min: (n= 335, 337)	0.159 (± 0.0194)	0.085 (± 0.0194)		

Day 183/15 min: (n= 333, 334)	0.177 (± 0.0195)	0.132 (± 0.0195)		
Day 183/30 min: (n= 344, 346)	0.194 (± 0.0192)	0.144 (± 0.0191)		
Day 183/1 h: (n= 335, 343)	0.190 (± 0.0194)	0.154 (± 0.0192)		
Day 183/2 h:(n= 340, 345)	0.229 (± 0.0193)	0.200 (± 0.0191)		
Day 183/3 h: (n=327, 344)	0.229 (± 0.0197)	0.186 (± 0.0192)		
Day 183/4 h: (n=335, 347)	0.216 (± 0.0194)	0.169 (± 0.0191)		
Day 183/6 h:(n= 330, 347)	0.146 (± 0.0196)	0.116 (± 0.0191)		
Day 183/8 h: (n= 331, 341)	0.137 (± 0.0195)	0.085 (± 0.0193)		
Day 183/10 h: (n= 323, 345)	0.071 (± 0.0198)	0.039 (± 0.0191)		
Day 183/12 h:(n= 318, 331)	0.041 (± 0.0200)	0.026 (± 0.0196)		
Day 183/13 h: (n= 320, 326)	0.096 (± 0.0199)	0.004 (± 0.0197)		
Day 184/16 h: (n= 295, 298)	-0.014 (± 0.0207)	-0.081 (± 0.0206)		
Day 184/22 h: (n=323, 333)	-0.036 (± 0.0198)	-0.076 (± 0.0195)		
Day 184/23 h 15 min: (n=314, 336)	0.075 (± 0.0201)	0.031 (± 0.0194)		
Day 184/23 h 45 min: (n=325, 329)	0.129 (± 0.0197)	0.077 (± 0.0196)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Inspiratory Capacity (IC) at individual timepoints at week 26

End point title	Change from baseline in Inspiratory Capacity (IC) at individual timepoints at week 26
End point description:	
Mixed model for repeated measures was used to analyze change from baseline in IC.	
End point type	Secondary
End point timeframe:	
Baseline, Week 26 (Day 183)	

End point values	NVA237 Twice daily	NVA237 Once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	388		
Units: Liters				
least squares mean (standard error)				

Day 183/-20 min: (n= 225, 224)	0.094 (± 0.0221)	0.054 (± 0.0221)		
Day 183/25 min: (n= 220, 237)	0.181 (± 0.0224)	0.173 (± 0.0215)		
Day 183/1 h 55 min:: (n= 222, 232)	0.193 (± 0.0223)	0.171 (± 0.0218)		
Day 183/3 h 55 min: (n= 215, 225)	0.163 (± 0.0226)	0.159 (± 0.0221)		
Day 183/7 h 55 min: (n= 213, 223)	0.108 (± 0.0228)	0.110 (± 0.0222)		
Day 183/11 h 55 min: (n= 210, 231)	0.042 (± 0.0229)	0.030 (± 0.0218)		
Day 184/23 h 40 min:(n= 203, 221)	0.045 (± 0.0233)	0.062 (± 0.0224)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Forced Expiratory Volume in one second (FEV1) at individual timepoints at week 26

End point title	Change from baseline in Forced Expiratory Volume in one second (FEV1) at individual timepoints at week 26

End point description:

Mixed model for repeated measures was used to analyze change from baseline in FEV1. Baseline FEV1 is defined as the average of the -45 min and -15 min FEV1 values taken on Day 1 prior to first dose.

End point type	Secondary

End point timeframe:

Baseline, Week 26 (Day 183)

End point values	NVA237 Twice daily	NVA237 Once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	388		
Units: Liters				
least squares mean (standard error)				
Day 183/-45 min: (n= 334, 342)	0.058 (± 0.0120)	0.012 (± 0.0119)		
Day 183/-15 min: (n= 340, 345)	0.086 (± 0.0119)	0.034 (± 0.0118)		
Day 183/5 min: (n= 335, 337)	0.111 (± 0.0120)	0.070 (± 0.0119)		
Day 183/15 min: (n= 333, 334)	0.145 (± 0.0120)	0.106 (± 0.0120)		
Day 183/30 min: (n= 344, 346)	0.155 (± 0.0118)	0.122 (± 0.0118)		
Day 183/1 h: (n= 335, 343)	0.158 (± 0.0120)	0.132 (± 0.0118)		
Day 183/2 h:(n= 340, 345)	0.194 (± 0.0119)	0.163 (± 0.0118)		
Day 183/3 h: (n=327, 344)	0.179 (± 0.0121)	0.154 (± 0.0118)		

Day 183/4 h: (n=335, 347)	0.166 (± 0.0120)	0.132 (± 0.0118)		
Day 183/6 h:(n= 330, 347)	0.110 (± 0.0121)	0.080 (± 0.0118)		
Day 183/8 h: (n= 331, 341)	0.118 (± 0.0121)	0.064 (± 0.0119)		
Day 183/10 h: (n= 323, 345)	0.067 (± 0.0122)	0.038 (± 0.0118)		
Day 183/12 h:(n= 318, 331)	0.056 (± 0.0123)	0.024 (± 0.0121)		
Day 183/13 h: (n= 320, 326)	0.093 (± 0.0123)	0.000 (± 0.0121)		
Day 184/16 h: (n= 295, 298)	-0.001 (± 0.0128)	-0.063 (± 0.0127)		
Day 184/22 h: (n=323, 333)	-0.012 (± 0.0122)	-0.043 (± 0.0120)		
Day 184/23 h 15 min: (n=314, 336)	0.076 (± 0.0124)	0.032 (± 0.0120)		
Day 184/23 h 45 min: (n=325, 329)	0.122 (± 0.0122)	0.067 (± 0.0121)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the percentage of days with no rescue medication use over the 26 weeks

End point title	Change from baseline in the percentage of days with no rescue medication use over the 26 weeks

End point description:

Patients report the number of puffs of rescue medication (salbutamol / albuterol) using an electronic diary. change from baseline in percentage of days without rescue medication usage over 26 weeks was analyzed.

End point type	Secondary

End point timeframe:

Baseline, 26 Weeks

End point values	NVA237 Twice daily	NVA237 Once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	383	377		
Units: percentage of days				
least squares mean (standard error)	16.574 (± 2.3519)	15.363 (± 2.3927)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean daily symptom score at Week 26

End point title	Change from baseline in mean daily symptom score at Week 26

End point description:

Patients reported symptoms by using an electronic diary. The mean daily total symptom score, the mean morning symptom score and the mean evening symptom score were calculated for each patient over 26 weeks. Only the scores for the 6 COPD symptoms (respiratory symptoms, cough, wheeze, production of sputum, sputum color, and breathlessness) were used to derive the total symptom score. Each symptom measured in a numeric rating scale of 0-10; 0 indicates no symptom and 10 indicates severe symptom. The daily score for an individual symptom score was the worst of the morning and evening scores on a particular day. If either the morning or evening score was missing for a symptom then the non-missing value was taken as the worst. A negative change indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, 26 Weeks

End point values	NVA237 Twice daily	NVA237 Once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	383	377		
Units: score on a scale				
least squares mean (standard error)				
Change in mean daily(n= 383, 377)	-1.336 (± 0.1141)	-1.107 (± 0.1160)		
Change in mean morning (n=374, 374)	-1.032 (± 0.1304)	-0.828 (± 0.1318)		
Change in mean evening (n= 372, 375)	-1.205 (± 0.1141)	-1.056 (± 0.1152)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with adverse events, serious adverse events and death

End point title	Number of patients with adverse events, serious adverse events and death

End point description:

This endpoint reports patients affected by any adverse events (AE), serious adverse events (SAE) and death. Only treatment emergent AE, SAE, deaths are reported for this endpoint.

End point type	Secondary

End point timeframe:

26 Weeks

End point values	NVA237 Twice daily	NVA237 Once daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	388		
Units: Participants				
Patients with at least one AE	203	224		
Patients with at least one SAE	33	30		
Death	1	1		

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

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	NVA237 44 mcg o.d.
Reporting group description:	
NVA237 44 mcg o.d.	
Reporting group title	NVA237 22 mcg b.i.d.
Reporting group description:	
NVA237 22 mcg b.i.d.	

Serious adverse events	NVA237 44 mcg o.d.	NVA237 22 mcg b.i.d.	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 388 (7.73%)	33 / 388 (8.51%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer recurrent			
subjects affected / exposed	0 / 388 (0.00%)	1 / 388 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	0 / 388 (0.00%)	2 / 388 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia			

subjects affected / exposed	0 / 388 (0.00%)	1 / 388 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 388 (0.26%)	0 / 388 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 388 (0.26%)	1 / 388 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic squamous cell carcinoma			
subjects affected / exposed	1 / 388 (0.26%)	0 / 388 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	1 / 388 (0.26%)	0 / 388 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Brachial plexus injury			
subjects affected / exposed	0 / 388 (0.00%)	1 / 388 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 388 (0.26%)	0 / 388 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 388 (0.00%)	1 / 388 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Aortic aneurysm			
subjects affected / exposed	0 / 388 (0.00%)	1 / 388 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	1 / 388 (0.26%)	0 / 388 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brachiocephalic artery stenosis			
subjects affected / exposed	1 / 388 (0.26%)	0 / 388 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 388 (0.00%)	2 / 388 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 388 (0.52%)	3 / 388 (0.77%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 388 (0.00%)	1 / 388 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 388 (0.00%)	1 / 388 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 388 (0.00%)	1 / 388 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	0 / 388 (0.00%)	1 / 388 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	1 / 388 (0.26%)	0 / 388 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 388 (0.00%)	1 / 388 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 388 (0.00%)	1 / 388 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudoradicular syndrome			
subjects affected / exposed	0 / 388 (0.00%)	1 / 388 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			
subjects affected / exposed	1 / 388 (0.26%)	0 / 388 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 388 (0.26%)	0 / 388 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Gastritis erosive			
subjects affected / exposed	1 / 388 (0.26%)	0 / 388 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 388 (0.00%)	1 / 388 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 388 (0.26%)	0 / 388 (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			
Acute respiratory failure			
subjects affected / exposed	0 / 388 (0.00%)	2 / 388 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	15 / 388 (3.87%)	11 / 388 (2.84%)	
occurrences causally related to treatment / all	0 / 16	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 388 (0.00%)	1 / 388 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 388 (0.00%)	2 / 388 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 388 (0.26%)	0 / 388 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	1 / 388 (0.26%)	0 / 388 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 388 (0.26%)	0 / 388 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	0 / 388 (0.00%)	1 / 388 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 388 (1.03%)	3 / 388 (0.77%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 388 (0.26%)	
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 44 mcg o.d.	NVA237 22 mcg b.i.d.	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	152 / 388 (39.18%)	126 / 388 (32.47%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 388 (3.61%)	10 / 388 (2.58%)	
occurrences (all)	14	11	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 388 (2.06%)	4 / 388 (1.03%)	
occurrences (all)	8	5	
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease			
subjects affected / exposed	99 / 388 (25.52%)	74 / 388 (19.07%)	
occurrences (all)	166	141	
Dyspnoea			
subjects affected / exposed	2 / 388 (0.52%)	9 / 388 (2.32%)	
occurrences (all)	2	10	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 388 (0.77%)	10 / 388 (2.58%)	
occurrences (all)	4	10	
Nasopharyngitis			
subjects affected / exposed	54 / 388 (13.92%)	37 / 388 (9.54%)	
occurrences (all)	67	44	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported