



Clinical trial results:

A multicentre, randomized double-blind placebo-controlled 3-period complete cross-over study to assess the bronchodilator effects and safety of glycopyrronium bromide (NVA237) (25 g and 50 g o.d.) in asthma patients

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	2015-005565-23
Trial protocol	DE BE LV LT
Global end of trial date	29 December 2017

Results information

Result version number	v1 (current)
This version publication date	22 December 2018
First version publication date	22 December 2018

Trial information

Trial identification

Sponsor protocol code	CQVM149B2204
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03137784
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, novartis.email@novartis.com

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	29 December 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the bronchodilator effects of NVA237 delivered by the Concept1 single-dose dry-powder inhaler in patients with asthma in terms of trough forced expiratory volume in one second (trough forced expiratory volume in one second (FEV1), mean of 23 h 15 min and 23 h 45 min post-dose) following one week of treatment, by comparing NVA237 at a dose of 25 µg and 50 µg o.d. with Placebo.

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	04 May 2017
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: 6
Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	Japan: 16
Country: Number of subjects enrolled	Latvia: 12
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	United States: 68
Worldwide total number of subjects	148
EEA total number of subjects	64

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	145
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study used a randomized, double-blind, placebo controlled, 3-period cross-over clinical trial design.

Period 1

Period 1 title	Overall study
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	1(NVA237 50 ug/NVA237 25 ug/placebo)

Arm description:

Treatment sequence: NVA 237 50 ug, 25 ug and placebo

Arm type	Sequence 1
Investigational medicinal product name	glycopyrronium bromide
Investigational medicinal product code	NVA237
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Oral use

Dosage and administration details:

50 ug

Arm title	2(NVA237 50 ug/placebo/NVA237 25 ug)
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Arm description:

Treatment sequence: NVA 237 50 ug, placebo and 25 ug

Arm type	Sequence 2
No investigational medicinal product assigned in this arm	

Arm title	3 (NVA237 25 ug/NVA237 50 ug/placebo)
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Arm description:

Treatment sequence: NVA237 25 ug, 50 ug and placebo

Arm type	Sequence 3
No investigational medicinal product assigned in this arm	

Arm title	4 (NVA237 25 ug/placebo/NVA237 50 ug)
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Arm description:

Treatment sequence: NVA 237 25 ug, placebo and 50 ug

Arm type	Sequence 4
No investigational medicinal product assigned in this arm	

Arm title	5 (placebo/NVA237 50 ug/ NVA237 25 ug)
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Arm description:

Treatment sequence: Placebo, NVA237 50 ug and 25 ug

Arm type	Sequence 5
No investigational medicinal product assigned in this arm	

Arm title	6 (placebo/ NVA237 25 ug/NVA237 50 ug)
Arm description:	
Treatment sequence: placebo, NVA237 25 ug and 50 ug	
Arm type	Sequence 6
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	1(NVA237 50 ug/NVA237 25 ug/placebo)	2(NVA237 50 ug/placebo/NVA237 25 ug)	3 (NVA237 25 ug/NVA237 50 ug/placebo)
Started	24	25	25
Completed	22	24	25
Not completed	2	1	0
Adverse event, non-fatal	1	1	-
Non-compliance with study treatment	-	-	-
Subject/guardian decision	1	-	-

Number of subjects in period 1	4 (NVA237 25 ug/placebo/NVA237 50 ug)	5 (placebo/NVA237 50 ug/ NVA237 25 ug)	6 (placebo/ NVA237 25 ug/NVA237 50 ug)
Started	24	25	25
Completed	24	24	25
Not completed	0	1	0
Adverse event, non-fatal	-	-	-
Non-compliance with study treatment	-	1	-
Subject/guardian decision	-	-	-

Period 2

Period 2 title	Baseline
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Arm title	Baseline
Arm description: -	
Arm type	Baseline

Investigational medicinal product name	glycopyrronium bromide
Investigational medicinal product code	NVA237
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Oral use
Dosage and administration details:	
50 ug	
Investigational medicinal product name	NVA237 50 ug/NVA237 25 ug/placebo
Investigational medicinal product code	NVA237 50 ug/NVA237 25 ug/placebo
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Oral use
Dosage and administration details:	
NVA237 50 ug/NVA237 25 ug/placebo	
Investigational medicinal product name	glycopyrronium bromide
Investigational medicinal product code	NVA237
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Oral use
Dosage and administration details:	
50 ug	
Investigational medicinal product name	glycopyrronium bromide
Investigational medicinal product code	NVA237
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Oral use
Dosage and administration details:	
50 ug	
Investigational medicinal product name	NVA237 50 ug/NVA237 25 ug/placebo
Investigational medicinal product code	NVA237 50 ug/NVA237 25 ug/placebo
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Oral use
Dosage and administration details:	
NVA237 50 ug/NVA237 25 ug/placebo	

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline added to complete record

Number of subjects in period 2	Baseline
Started	148
Completed	145
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	2

Baseline characteristics

Reporting groups

Reporting group title	Baseline
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Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	148	148	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	145	145	
From 65-84 years	3	3	
85 years and over	0	0	
Age Continuous			
Units: Years			
arithmetic mean	47.3		
standard deviation	± 11.8	-	
Sex: Female, Male			
Units: Subjects			
Female	75	75	
Male	73	73	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native		0	
Asian	16	16	
Native Hawaiian or Other Pacific Islander		0	
Black or African American	12	12	
White	120	120	
More than one race		0	
Unknown or Not Reported		0	

Subject analysis sets

Subject analysis set title	All participants
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Subject analysis set type	Full analysis
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Subject analysis set description:

All participants randomized to one of six treatment sequences

Subject analysis set title	NVA237 50 ug
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Subject analysis set type	Full analysis
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Subject analysis set description:

NVA237 50 g capsule

Subject analysis set title	NVA237 25 ug
Subject analysis set type	Full analysis
Subject analysis set description: NVA237 25 µg capsule	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description: Placebo	
Subject analysis set title	NVA237 50 ug
Subject analysis set type	Full analysis
Subject analysis set description: NVA237 50 g capsule	
Subject analysis set title	NVA237 25 ug
Subject analysis set type	Full analysis
Subject analysis set description: NVA237 25 µg capsule	
Subject analysis set title	NVA237 50 ug
Subject analysis set type	Full analysis
Subject analysis set description: NVA237 50 g capsule	
Subject analysis set title	NVA237 25 ug
Subject analysis set type	Full analysis
Subject analysis set description: NVA237 25 µg capsule	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description: Placebo	
Subject analysis set title	NVA237 25 ug
Subject analysis set type	Full analysis
Subject analysis set description: NVA237 25 µg capsule	
Subject analysis set title	NVA237 25 ug
Subject analysis set type	Full analysis
Subject analysis set description: NVA237 25 µg capsule	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description: Placebo	
Subject analysis set title	NVA237 50 ug
Subject analysis set type	Full analysis
Subject analysis set description: NVA237 50 g capsule	
Subject analysis set title	NVA237 25 ug
Subject analysis set type	Full analysis
Subject analysis set description: NVA237 25 µg capsule	

Reporting group values	All participants	NVA237 50 ug	NVA237 25 ug
Number of subjects	148	144	142
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	47.3		
standard deviation	± 11.8	±	±
Sex: Female, Male Units: Subjects			
Female	75		
Male	73		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	16		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	12		
White	120		
More than one race	0		
Unknown or Not Reported	0		

Reporting group values	Placebo	NVA237 50 ug	NVA237 25 ug
Number of subjects	146	146	143
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean			
standard deviation	±	±	±

Sex: Female, Male Units: Subjects			
Female Male			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

Reporting group values	NVA237 50 ug	NVA237 25 ug	Placebo
Number of subjects	141	138	143
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years arithmetic mean standard deviation	\pm	\pm	\pm
Sex: Female, Male Units: Subjects			
Female Male			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

Reporting group values	NVA237 25 ug	NVA237 25 ug	Placebo
Number of subjects	144	145	144

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	±	±	±
standard deviation			
Sex: Female, Male Units: Subjects			
Female			
Male			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

Reporting group values	NVA237 50 ug	NVA237 25 ug	
Number of subjects	147	146	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	±	±	
standard deviation			

Sex: Female, Male Units: Subjects			
Female Male			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

End points

End points reporting groups

Reporting group title	1(NVA237 50 ug/NVA237 25 ug/placebo)
Reporting group description:	
Treatment sequence: NVA 237 50 ug, 25 ug and placebo	
Reporting group title	2(NVA237 50 ug/placebo/NVA237 25 ug)
Reporting group description:	
Treatment sequence: NVA 237 50 ug, placebo and 25 ug	
Reporting group title	3 (NVA237 25 ug/NVA237 50 ug/placebo)
Reporting group description:	
Treatment sequence: NVA237 25 ug, 50 ug and placebo	
Reporting group title	4 (NVA237 25 ug/placebo/NVA237 50 ug)
Reporting group description:	
Treatment sequence: NVA 237 25 ug, placebo and 50 ug	
Reporting group title	5 (placebo/NVA237 50 ug/ NVA237 25 ug)
Reporting group description:	
Treatment sequence: Placebo, NVA237 50 ug and 25 ug	
Reporting group title	6 (placebo/ NVA237 25 ug/NVA237 50 ug)
Reporting group description:	
Treatment sequence: placebo, NVA237 25 ug and 50 ug	
Reporting group title	Baseline
Reporting group description: -	
Subject analysis set title	All participants
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants randomized to one of six treatment sequences	
Subject analysis set title	NVA237 50 ug
Subject analysis set type	Full analysis
Subject analysis set description:	
NVA237 50 g capsule	
Subject analysis set title	NVA237 25 ug
Subject analysis set type	Full analysis
Subject analysis set description:	
NVA237 25 µg capsule	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo	
Subject analysis set title	NVA237 50 ug
Subject analysis set type	Full analysis
Subject analysis set description:	
NVA237 50 g capsule	
Subject analysis set title	NVA237 25 ug
Subject analysis set type	Full analysis
Subject analysis set description:	
NVA237 25 µg capsule	
Subject analysis set title	NVA237 50 ug
Subject analysis set type	Full analysis

Subject analysis set description:

NVA237 50 g capsule

Subject analysis set title	NVA237 25 ug
Subject analysis set type	Full analysis

Subject analysis set description:

NVA237 25 µg capsule

Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Placebo

Subject analysis set title	NVA237 25 ug
Subject analysis set type	Full analysis

Subject analysis set description:

NVA237 25 µg capsule

Subject analysis set title	NVA237 25 ug
Subject analysis set type	Full analysis

Subject analysis set description:

NVA237 25 µg capsule

Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Placebo

Subject analysis set title	NVA237 50 ug
Subject analysis set type	Full analysis

Subject analysis set description:

NVA237 50 g capsule

Subject analysis set title	NVA237 25 ug
Subject analysis set type	Full analysis

Subject analysis set description:

NVA237 25 µg capsule

Primary: Trough FEV1 after one week of treatment

End point title	Trough FEV1 after one week of treatment
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End point description:

To evaluate the bronchodilator effects of NVA237 (25 ug and 50 ug) compared to placebo in terms of trough FEV1 (mean of 23h 15 min and 23 h 45 min post -dose) following 1 week of treatment in the respective treatment period. Trough FEV1 was assessed by performing spirometry measurements in the clinic for each treatment period. For the primary efficacy variable, trough FEV1 is the mean of two measurements taken at 23h 15 min and 23h 45 min post dose.

End point type	Primary
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End point timeframe:

Following 1 week of treatment

End point values	NVA237 50 ug	NVA237 25 ug	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	144	142	146	
Units: Liters				
least squares mean (standard error)	2.392 (± 0.0249)	2.392 (± 0.0250)	2.303 (± 0.0247)	

Statistical analyses

Statistical analysis title	Treatment difference
Comparison groups	NVA237 50 ug v Placebo
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	0.089
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.047
upper limit	0.132

Statistical analysis title	Treatment difference
Comparison groups	NVA237 25 ug v Placebo
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.047
upper limit	0.132

Secondary: FEV1 AUC (5 min-1 h) after one week of treatment

End point title	FEV1 AUC (5 min-1 h) after one week of treatment
End point description:	
To evaluate the bronchodilator effects of NVA237 (25 ug and 50 ug) compared with placebo in terms of Standardized FEV1 AUC following 1 week of treatment in the respective treatment period. FEV1 was measured with spirometry conducted according to internationally accepted standards. The standardized AUC FEV1 was calculated as the sum of trapezoids divided by the length of time over an entire day (AUC 5min-1h)	
End point type	Secondary

End point timeframe:
Following 1 week of treatment

End point values	Placebo	NVA237 50 ug	NVA237 25 ug	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	146	146	143	
Units: Liters				
least squares mean (standard error)	2.324 (\pm 0.0227)	2.489 (\pm 0.0226)	2.492 (\pm 0.0228)	

Statistical analyses

Statistical analysis title	Treatment difference
Comparison groups	NVA237 50 ug v Placebo
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	0.165
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.127
upper limit	0.203

Statistical analysis title	Treatment difference
Comparison groups	NVA237 25 ug v Placebo
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	0.168
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.129
upper limit	0.206

Secondary: FEV1 AUC (5 min-4 h) after one week of treatment

End point title	FEV1 AUC (5 min-4 h) after one week of treatment
End point description: To evaluate the bronchodilator effects of NVA237 (25 ug and 50 ug) compared with placebo in terms of Standardized FEV1 AUC following 1 week of treatment in the respective treatment period. FEV1 was measured with spirometry conducted according to internationally accepted standards. The standardized AUC FEV1 was calculated as the sum of trapezoids divided by the length of time over an entire day (AUC 5min-4h)	
End point type	Secondary
End point timeframe: Following 1 week of treatment	

End point values	Placebo	NVA237 50 ug	NVA237 25 ug	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	146	146	143	
Units: Liters				
least squares mean (standard error)	2.346 (\pm 0.0223)	2.522 (\pm 0.0223)	2.525 (\pm 0.0224)	

Statistical analyses

Statistical analysis title	AUC FEV1
Comparison groups	NVA237 50 ug v Placebo
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	0.176
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.141
upper limit	0.212

Statistical analysis title	AUC FEV1
Comparison groups	NVA237 25 ug v Placebo
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	0.179

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.144
upper limit	0.215

Secondary: FEV1 AUC (5 min – 23 h 45 min) after one week of treatment

End point title	FEV1 AUC (5 min – 23 h 45 min) after one week of treatment
End point description:	
To evaluate the bronchodilator effects of NVA237 (25 ug and 50 ug) compared with placebo in terms of Standardized FEV1 AUC following 1 week of treatment in the respective treatment period. FEV1 was measured with spirometry conducted according to internationally accepted standards. The standardized AUC FEV1 was calculated as the sum of trapezoids divided by the length of time over an entire day AUC (5 min – 23 h 45 min)	
End point type	Secondary
End point timeframe:	
Following 1 week of treatment	

End point values	Placebo	NVA237 50 ug	NVA237 25 ug	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	146	146	143	
Units: Liters				
least squares mean (standard error)	2.304 (± 0.0226)	2.443 (± 0.0226)	2.450 (± 0.0227)	

Statistical analyses

Statistical analysis title	Treatment difference
Comparison groups	NVA237 50 ug v Placebo
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	0.139
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.106
upper limit	0.173

Statistical analysis title	Treatment difference
Comparison groups	NVA237 25 ug v Placebo
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	0.146
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.112
upper limit	0.179

Secondary: Peak FEV1 during 4 Hours post-dose after 1 week of treatment

End point title	Peak FEV1 during 4 Hours post-dose after 1 week of treatment
End point description:	
To evaluate the bronchodilator effects of NVA237 (25 ug and 50 ug) compared with placebo in terms of Peak FEV1 following 1 week of treatment in the respective treatment period. FEV1 was measured with spirometry conducted according to internationally accepted standards. The peak effect following 1 week of treatment was defined as the maximum FEV1 during the first 4 hour on that day.	
End point type	Secondary
End point timeframe:	
Following 1 week of treatment	

End point values	Placebo	NVA237 50 ug	NVA237 25 ug	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	146	146	143	
Units: Liters				
least squares mean (standard error)	2.457 (± 0.0228)	2.621 (± 0.0228)	2.630 (± 0.0229)	

Statistical analyses

Statistical analysis title	Peak FEV1
Comparison groups	NVA237 50 ug v Placebo
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	0.164

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.127
upper limit	0.201

Statistical analysis title	Peak FEV1
Comparison groups	NVA237 25 ug v Placebo
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	0.174
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.137
upper limit	0.211

Secondary: Trough Forced Vital Capacity (FVC) after 1 week of treatment

End point title	Trough Forced Vital Capacity (FVC) after 1 week of treatment
End point description:	
To evaluate the bronchodilator effects of NVA237 (25 ug and 50 ug) compared with placebo in terms of FVC following 1 week of treatment in respective treatment period. Trough Forced Vital Capacity (FVC) following 7 Days. FVC is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. FVC was assessed via spirometry	
End point type	Secondary
End point timeframe:	
Following 1 week of treatment	

End point values	NVA237 50 ug	NVA237 25 ug	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	144	142	146	
Units: Liters				
least squares mean (standard error)	3.509 (± 0.0268)	3.530 (± 0.0269)	3.472 (± 0.0267)	

Statistical analyses

Statistical analysis title	Trough Forced Vital Capacity (FVC)
Comparison groups	NVA237 50 ug v Placebo
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.079
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	0.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.077

Statistical analysis title	Trough Forced Vital Capacity (FVC)
Comparison groups	NVA237 25 ug v Placebo
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.006
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	0.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	0.099

Secondary: FEV1/FVC ratio

End point title	FEV1/FVC ratio
End point description:	
To evaluate the bronchodilator effects of NVA237 (25 ug and 50 ug) compared with placebo in terms of FEV1/FVC ratio following 1 week of treatment in respective treatment period	
End point type	Secondary
End point timeframe:	
Following 1 week of treatment	

End point values	NVA237 50 ug	NVA237 25 ug	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	141	138	143	
Units: Ratio				
arithmetic mean (standard deviation)	0.018 (± 0.0421)	0.016 (± 0.0438)	0.003 (± 0.0398)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Morning Peak Expiratory Flow (PEF) Following the 1-week Treatment Period

End point title	Mean Morning Peak Expiratory Flow (PEF) Following the 1-week Treatment Period
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End point description:

A Peak Expiratory Flow (PEF) meter was distributed to patients at Visit 1, to be used to measure PEF twice-daily as directed. During the Screening and Treatment Periods, PEF was measured in the morning and evening every day. the morning PEF was performed within 15 minutes after waking, and the evening PEF approximately 12 hours later. Patients were encouraged to perform morning and evening PEF measurements before the use of any LABA or rescue medication. The highest of 3 values was recorded as the daily personal best. The personal best was used to calculate the mean morning PEF and mean evening PEF value collected between assessment Visits LS Mean of change from baseline in mean morning PEF is calculated with the ANCOVA model using treatment, stratification group, dosing schedule, gender, center grouping, smoking status, and baseline mean morning PEF as covariates

End point type	Secondary
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End point timeframe:

Following 1 week of treatment

End point values	Placebo	NVA237 50 ug	NVA237 25 ug	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	146	146	144	
Units: L/min				
least squares mean (standard error)	369.58 (± 2.958)	395.09 (± 2.948)	393.87 (± 2.962)	

Statistical analyses

Statistical analysis title	Peak Expiratory Flow (PEF)
Comparison groups	NVA237 50 ug v Placebo
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	25.51

Confidence interval	
level	95 %
sides	2-sided
lower limit	19.22
upper limit	31.79

Statistical analysis title	Peak Expiratory Flow (PEF)
Comparison groups	NVA237 25 ug v Placebo
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	24.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.99
upper limit	30.59

Secondary: Mean Evening peak expiratory flow rate (PEF) Following 1-week Treatment

End point title	Mean Evening peak expiratory flow rate (PEF) Following 1-week Treatment
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End point description:

A Peak Expiratory Flow (PEF) meter was distributed to patients at Visit 1, to be used to measure PEF twice-daily as directed. During the Screening and Treatment Periods, PEF was measured in the morning and evening every day. the morning PEF was performed within 15 minutes after waking, and the evening PEF approximately 12 hours later. Patients were encouraged to perform morning and evening PEF measurements before the use of any LABA or rescue medication. The highest of 3 values was recorded as the daily personal best. The personal best was used to calculate the mean morning PEF and mean evening PEF value collected between assessment Visits. LS Mean of change from baseline in mean morning PEF is calculated with the ANCOVA model using treatment, stratification group, dosing schedule, gender, center grouping, smoking status, and baseline mean morning PEF as covariates

End point type	Secondary
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End point timeframe:

Following 1 week of treatment

End point values	NVA237 50 ug	NVA237 25 ug	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	146	145	144	
Units: L/min				
least squares mean (standard error)	409.66 (± 2.928)	408.08 (± 2.934)	378.72 (± 2.949)	

Statistical analyses

Statistical analysis title	Peak Expiratory Flow (PEF)
Comparison groups	NVA237 50 ug v Placebo
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	30.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.07
upper limit	36.82

Statistical analysis title	Peak Expiratory Flow (PEF)
Comparison groups	NVA237 25 ug v Placebo
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	29.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.47
upper limit	35.26

Secondary: Mean daily number of puffs of rescue medication during 1 week of

End point title	Mean daily number of puffs of rescue medication during 1 week of
End point description:	
A day with no rescue medication use is defined from the diary data as any day where the patient recorded no rescue medicine use during the previous 12 hours. daytime and nighttime (combined) number of puffs is defined as the average of the respective number of puffs.	
End point type	Secondary

End point timeframe:
Following 1 week of treatment

End point values	Placebo	NVA237 50 ug	NVA237 25 ug	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	146	147	146	
Units: Number of puffs				
least squares mean (standard error)	1.13 (\pm 0.094)	0.98 (\pm 0.094)	1.02 (\pm 0.094)	

Statistical analyses

Statistical analysis title	Mean daily number of puffs
Comparison groups	NVA237 50 ug v Placebo
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.053
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0

Statistical analysis title	Mean daily number of puffs
Comparison groups	NVA237 25 ug v Placebo
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.163
Method	Linear Mixed Model
Parameter estimate	Linear Mixed Model (LMM)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.05

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	NVA237 50 ug
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Reporting group description:

NVA237 50 ug

Reporting group title	Placebo
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Reporting group description:

Placebo

Reporting group title	NVA237 25 ug
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Reporting group description:

NVA237 25 ug

Serious adverse events	NVA237 50 ug	Placebo	NVA237 25 ug
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 147 (0.68%)	0 / 146 (0.00%)	1 / 146 (0.68%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 147 (0.00%)	0 / 146 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Musculoskeletal and connective tissue disorders			
Patellofemoral pain syndrome			
subjects affected / exposed	1 / 147 (0.68%)	0 / 146 (0.00%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Non-serious adverse events	NVA237 50 ug	Placebo	NVA237 25 ug
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 147 (6.80%)	11 / 146 (7.53%)	11 / 146 (7.53%)
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	1 / 147 (0.68%)	2 / 146 (1.37%)	0 / 146 (0.00%)
occurrences (all)	1	2	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 147 (0.68%)	2 / 146 (1.37%)	0 / 146 (0.00%)
occurrences (all)	1	2	0
Headache			
subjects affected / exposed	5 / 147 (3.40%)	2 / 146 (1.37%)	2 / 146 (1.37%)
occurrences (all)	5	2	2
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 147 (0.00%)	0 / 146 (0.00%)	2 / 146 (1.37%)
occurrences (all)	0	0	2
Oropharyngeal pain			
subjects affected / exposed	1 / 147 (0.68%)	0 / 146 (0.00%)	2 / 146 (1.37%)
occurrences (all)	1	0	2
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 147 (0.00%)	1 / 146 (0.68%)	2 / 146 (1.37%)
occurrences (all)	0	1	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 147 (1.36%)	3 / 146 (2.05%)	1 / 146 (0.68%)
occurrences (all)	2	3	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 147 (0.68%)	1 / 146 (0.68%)	3 / 146 (2.05%)
occurrences (all)	1	1	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: