Full Novartis CTRD Results Template

Sponsor

Novartis

Generic Drug Name

NVA237

Therapeutic Area of Trial

Chronic obstructive pulmonary disease (COPD)

Approved Indication

Investigational

Protocol Number

CNVA237A2310

Title

A multi-center, randomized, double-blind, placebo-controlled, two-period crossover study to assess the effect of 50 µg inhaled NVA237 on exercise endurance in patients with moderate to severe COPD

Phase of Development

Phase III

Study Start/End Dates

09-Jun-2010 to 08-Feb-2011

Study Design/Methodology

This was a multi-centre, double-blind, randomized, placebo-controlled, two-period cross-over study design. There were two 3-week treatment periods with each treatment period being separated by a 14–day wash-out (wash-out period could be expanded up to 28 days, if required for logistical reasons). A planned number of approximately 80 patients with moderate to severe COPD were to be randomized to receive one of two treatment sequences: NVA237 followed by matched placebo or placebo followed by NVA237.

The administration of NVA237 and matched placebo under double blind conditions was performed via the Concept1 inhaler device. Administration was to be in the morning between 08.00 – 11.00 hours. Each subsequent dosing was to be at the same time as the initial dosing on Day 1 (+/- 60 minutes).

Each patient participated in a screening period (maximum 28 days) which consisted of 2 screening visits

A blinded interim sample size re-estimation was performed after at least 24 patients completed the study and made use of all the variability information on the primary endpoint collected up to that time-point from these 24 patients.

Centres

Germany (6 centers), Italy (1 centre), Romania (1 center), United Kingdom (1 center), United States (5 centers)

Publication

None

Outcome measures

Primary outcome measures(s)

Exercise Endurance Time During a Sub-maximal Constant-load Cycle Ergometry Test (SMETT) After 3 Weeks (Day 21) of Treatment

Secondary outcome measures(s)

1. Isotime Inspiratory Capacity (IC) During Sub-maximal Constant-load Cycle Ergometry Test (SMETT) After 3 Weeks of Treatment
2. Inspiratory Capacity (IC) at Rest (1 Hour Post Dose) and at Peak (End of Exercise) During Sub-maximal Constant-load Cycle Ergometry Test (SMETT) After 3 Weeks of Treatment
3. Peak and Trough (24 h Post Dose) Forced Expiratory Volume in 1 Second (FEV1) and Forced Vital Capacity (FVC)
4. Slow Vital Capacity (SVC) and Total Lung Capacity (TLC)
5. Specific Airways Conductance (SGaw)
6. Exertional Dyspnea (Borg CR10 Scale) During Sub-maximal Constant-load Cycle Ergometry Test (SMETT) After 3 Weeks Treatment
7. Exercise Endurance Time During a Sub-maximal Constant-load Cycle Ergometry Test (SMETT) on Treatment Day 1

Test Product (s), Dose(s), and Mode(s) of Administration

The investigational drug was NVA237 50 μg delivered via the Concept1 inhaler device.

Statistical Methods

All patients as randomized who received at least one dose of study drug are included in the safety analysis set. All patients who completed at least one treatment period, had an evaluable PD assessment on Day 21 of this period and had no major protocol deviation impacting the primary PD assessment were included in the PD analysis set. A secondary PD set was considered as a subset of the PD set excluding the periods where patients who have terminated the exercise endurance test for reasons not related to exhaustion or dyspnea or had relevant protocol deviations that impacted the interpretation of the test.

All PD endpoints were analyzed at each time separately with a mixed-effect analysis-of-covariance model including the sequence, period, and treatment as fixed factors, the baseline value as covariate and the patient as a random effect. The treatment least-squares means, LSmeans difference (NVA237 – Placebo) and the corresponding 95% confidence intervals were estimated. The *p*-value for the comparison of the 2 treatments was reported only for the primary and key secondary endpoints (i.e. exercise endurance time and IC at isotime at Week 3) to determine whether the treatment different is statistically significant at the two-sided 5% level.

A sensitivity analysis was carried out for the primary endpoint (exercise endurance time at Week 3) and on the key secondary endpoint (inspiratory capacity at isotime), on the secondary PD set. Patients who had terminated the test for reasons not related to exhaustion or dyspnea or had relevant protocol deviations that impacted the interpretation of the test were excluded from this analysis on the date of the test and only with respect to the primary endpoint.

Patient symptoms and rescue medication were summarized descriptively during Day 1 and Day 21 interval. The proportion of patients taking any rescue medication within that interval was compared between treatments with a logistic regression model for repeated measures, including the sequence, treatment and period as fixed effects. Treatment least-square means, differences and their 95% confidence intervals was extracted from the model and adequately transformed to report predicted proportions by treatment, odds ratio for NVA237 vs placebo and their 95% CI limits. The mean number of rescue medications taken during the Day 1 to Day 21 was compared between treatments a mixed effect analysis-of-variance model including the sequence, period, and treatment as fixed factors, and the patient as a random effect. The treatment least-squares means, LSmeans difference (NVA237 – Placebo) and the corresponding 95% confidence intervals were reported.

The assessment of safety was based mainly on the frequency of adverse events and on laboratory values that fell outside of pre-determined ranges. Vital signs and electrocardiogram data were also summarized descriptively by treatment arm for the safety population. All safety data was listed for all patients.

A blinded interim sample size re-estimation was performed after 24 patients completed the study and made use of all the variability information on the primary endpoint collected up to that time-point for these 24 patients.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Male or female adults aged ≥ 40 years, who signed an Informed Consent Form prior to initiation of any study-related procedure.
- Patients with moderate to severe stable COPD (clinical diagnosis in compliance with GOLD 2008).
- Current or ex-smokers with a smoking history ≥ 10 pack years. (Ten pack-years were defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years etc.)
- Patients with a post-bronchodilator FEV1 ≥ 40 and < 70% of the predicted normal, and postbronchodilator FEV1/FVC < 0.7 during screening. (Post referred to the highest post-bronchodilator value after inhalation of 80 µg ipratropium bromide).
- Increase in FEV1 from pre- to post-bronchodilator assessment of ≥ 5%.

Exclusion criteria

- Pregnant women or nursing mothers, women of child-bearing potential.
- Patients who had a COPD exacerbation (whether hospitalized or not) in the 6 weeks prior to Visit 1 or between Visit 1 and Visit 4
- Patients who had a lower respiratory tract infection in the 6 weeks prior to Visit 1.
- Patients requiring long term oxygen therapy on a daily basis for chronic hypoxemia
- Patients with resting (5 min) oxygen SaO2 (or SpO2) saturation on room air of < 85%.

- Patients with a Wmax value < 20 W (as determined by the incremental cycle endurance test) at Visit 2.
- Patients whose exercise endurance time at sub-maximal workload was above 25 min at baseline.
- Patients with a clinically significant abnormality on the screening or baseline ECG who in the judgment of the investigator would have been at potential risk if enrolled into the study
- Patients with a history of long QT syndrome or whose QTc was prolonged (> 450 ms for malesand > 470 ms females) at screening (Fredericia's correction).

Participant Flow

Patient disposition – n (%) of patients (All patients)

	NVA237/Placebo N=55	Placebo/NVA237 N=53	Total N=108
Patients			
Treated with NVA237	55 (100.0%)	47 (88.7%)	102 (94.4%)
Treated with Placebo	49 (89.1%)	53 (100.0%)	102 (94.4%)
Completed	49 (89.1%)	46 (86.8%)	95 (88.0%)
Completed only Period 1	3 (5.5%)	1 (1.9%)	4 (3.7%)
Discontinued	6 (10.9%)	7 (13.2%)	13 (12.0%)
Main cause of discontinuation			
Adverse Event(s)	5 (9.1%)	4 (7.5%)	9 (8.3%)
Abnormal test procedure result(s)	1 (1.8%)	0	1 (0.9%)
Patient withdrew consent	0	2 (3.8%)	2 (1.9%)
Protocol deviation	0	1 (1.9%)	1 (0.9%)

Baseline Characteristics

Table Error! No text of specified style in document.**-1 Demographic summary (Safety analysis set)**

		NVA237/Placebo N=55	Placebo/NVA237 N=53	Total N=108
Age (years)	Mean (SD)	61.3 (8.50)	59.7 (8.78)	60.5 (8.64)
	Median	61.0	59.0	59.5
	Range	42 - 80	41 - 76	41 - 80
Gender – n (%)	Male	30 (55%)	33 (62%)	63 (58%)
	Female	25 (45%)	20 (38%)	45 (42%)
Predominant race – n (%)	Caucasian	53 (96%)	51 (96%)	104 (96%)
	Black	1 (2%)	1 (2%)	2 (2%)
	Other	1 (2%)	1 (2%)	2 (2%)
Ethnicity – n (%)	Other	53 (96%)	53 (100%)	106 (98%)
	Hispanic/Latino	1 (2%)	0	1 (1%)
	Mixed Ethnicity	1 (2%)	0	1 (1%)
Height (cm)	Mean (SD)	169.8 (9.19)	171.3 (9.10)	170.5 (9.13)
	Median	170.0	172.9	171.5
	Range	150.7 - 197.0	154.0 - 191.9	150.7 - 197.0
Weight (kg)	Mean (SD)	76.3 (13.79)	79.1 (17.18)	77.7 (15.54)
	Median	76.0	77.8	76.3
	Range	54.0 - 110.6	43.4 - 113.0	43.4 - 113.0
BMI (kg/m2)	Mean (SD)	26.4 (3.79)	26.7 (4.23)	26.6 (4.00)
	Median	26.4	27.3	26.5
	Range	18.1 - 37.3	17.5 - 37.8	17.5 - 37.8
Post-bronchodilator FEV_1 (L)	Mean (SD)	1.6 (0.43)	1.7 (0.46)	1.7 (0.45)
	Median	1.5	1.7	1.6
	Range	0.9 - 3.0	1.0 - 2.6	0.9 - 3.0
Post-bronchodilator FVC (L)	Mean (SD)	3.4 (1.08)	3.6 (0.96)	3.5 (1.02)
	Median	3.2	3.6	3.4
	Range	1.6 - 8.1	1.8 - 5.5	1.6 - 8.1
Post-bronchodilator FEV_1% pred (%)	Mean (SD)	57.3 (8.25)	57.0 (8.86)	57.1 (8.52)
	Median	59.0	57.0	58.4
	Range	43.0 - 69.9	39 - 74	39 - 74
Post-bronchodilator FEV_1/FVC ratio	Mean (SD)	0.5 (0.10)	0.5 (0.08)	0.5 (0.09)
	Median	0.5	0.5	0.5
	Range	0.4 - 0.7	0.3 - 0.6	0.3 - 0.7
Reversibility (%)	Mean (SD)	19.8 (12.57)	18.6 (10.20)	19.2 (11.43)
	Median	16.0	17.8	17.0
	Range	5.1 - 57.3	5.4 - 44.9	5.1 - 57.3
Smoking status	Ex-smoker	27 (49%)	16 (30%)	43 (40%)
	Current smoker	28 (51%)	37 (70%)	65 (60%)
Packs of cigarettes/year	Mean (SD)	41.4 (18.65)	51.0 (22.70)	46.1 (21.20)
	Median	36.0	45.0	40.5
	Range	14 - 90	20 - 120	14 - 120

Outcome measures

Primary Outcome Result(s)

Exercise Endurance Time During a Sub-maximal Constant-load Cycle Ergometry Test (SMETT) After 3 Weeks (Day 21) of Treatment

Statistical analysis of exercise endurance time on Day 1 and Day 21 (PD analysis set)

Assessment		Day	NVA237 (Lsmeans 95% CI)	Placebo (Lsmeans 95% CI)	NVA237 - Placebo (Diff 95% CI)	*p*-value
Exercise endurance time(s)		1	490.92 (458.45,523.38)	447.78 (415.09,480.48)	43.13 (10.90,75.37)	
		21	505.63 (466.59,544.68)	416.70 (377.76,455.64)	88.93 (44.71,133.16)	<0.001
	+	1	498.07 (464.63,531.52)	449.94 (416.90,482.97)	48.13 (15.38,80.89)	
	+	21	509.92 (469.60,550.24)	417.06 (377.39,456.74)	92.86 (46.40,139.32)	<0.001

+ Sensitivity analysis on 2nd PD set

Secondary Outcome Result(s)

1. Isotime Inspiratory Capacity (IC) During Sub-maximal Constant-load Cycle Ergometry Test (SMETT) After 3 Weeks of Treatment

Statistical analysis of IC at isotime on Day 1 and Day 21 (PD analysis set)

Assessment	Day	NVA237 (Lsmeans 95% CI)	Placebo (Lsmeans 95% CI)	NVA237 - Placebo (Diff 95% CI)	*p*-value
IC at isotime (Liters)	1	2.25 (2.18,2.31)	2.02 (1.96,2.08)	0.23 (0.17,0.28)	
	21	2.22 (2.15,2.29)	2.02 (1.95,2.09)	0.20 (0.13,0.28)	<0.001
	1*	2.26 (2.20,2.33)	2.04 (1.97,2.11)	0.23 (0.17,0.29)	
	21*	2.24 (2.17,2.31)	2.03 (1.96,2.11)	0.21 (0.13,0.28)	<0.001

* Sensitivity analysis on 2nd PD set

2. Inspiratory Capacity (IC) at Rest (1 Hour Post Dose) and at Peak (End of Exercise) During Sub-maximal Constant-load Cycle Ergometry Test (SMETT) After 3 Weeks of Treatment

Statistical analysis of rest, peak and resting at trough IC on Day 1 and Day 21 (PD analysis set)

Assessment	Day	NVA237 (Lsmeans 95% CI)	Placebo (Lsmeans 95% CI)	NVA237 - Placebo (Diff 95% CI)
IC at peak (Liters)	1	2.23 (2.18,2.29)	2.02 (1.96,2.07)	0.22 (0.16,0.27)
	21	2.22 (2.16,2.28)	2.03 (1.97,2.10)	0.19 (0.12,0.25)
IC at rest (Bodybox) (Liters)	1	2.53 (2.46,2.61)	2.24 (2.16,2.32)	0.29 (0.19,0.40)
	21	2.49 (2.40,2.59)	2.26 (2.17,2.35)	0.23 (0.14,0.33)
IC at rest (Spirometry) (Liters)	1	2.44 (2.38,2.50)	2.18 (2.12,2.24)	0.26 (0.18,0.33)
	21	2.39 (2.33,2.45)	2.17 (2.10,2.23)	0.22 (0.15,0.30)
Resting IC at trough (Bodybox) (Liters)	1	2.34 (2.27,2.42)	2.22 (2.15,2.30)	0.12 (0.03,0.21)
	21	2.33 (2.25,2.41)	2.26 (2.18,2.34)	0.07 (-0.03,0.16)
Resting IC at trough (Spirometry) (Liters)	1	2.21 (2.16,2.27)	2.15 (2.09,2.22)	0.06 (-0.02,0.14)
	21	2.19 (2.13,2.25)	2.13 (2.07,2.19)	0.06 (-0.02,0.14)

3. Peak and Trough (24 h Post Dose) Forced Expiratory Volume in 1 Second (FEV1) and Forced Vital Capacity (FVC)

Table Error! No text of specified style in document.**-2 Statistical analysis of trough and peak FEV1 and FVC on Day 1 and Day 21 (PD analysis set)**

Assessment	Day	NVA237 (Lsmeans 95% CI)	Placebo (Lsmeans 95% CI)	NVA237 - Placebo (Diff 95% CI)
FEV_1 at peak (Liters)	1	1.59 (1.56,1.62)	1.37 (1.34,1.40)	0.22 (0.18,0.26)
	21	1.60 (1.56,1.64)	1.35 (1.31,1.39)	0.25 (0.19,0.30)
FEV_1 trough (Liters)	1	1.46 (1.43,1.49)	1.35 (1.31,1.38)	0.11 (0.06,0.16)
	21	1.44 (1.40,1.48)	1.33 (1.29,1.37)	0.11 (0.06,0.16)
FVC at peak (Liters)	1	3.33 (3.26,3.40)	3.02 (2.95,3.09)	0.31 (0.22,0.40)
	21	3.37 (3.30,3.44)	3.00 (2.93,3.06)	0.37 (0.30,0.45)
FVC trough (Liters)	1	3.25 (3.18,3.31)	2.97 (2.90,3.04)	0.28 (0.18,0.37)
	21	3.17 (3.11,3.23)	2.96 (2.90,3.02)	0.21 (0.12,0.30)

4. Slow Vital Capacity (SVC) and Total Lung Capacity (TLC)

Statistical analysis of Body plethysmography parameters on Day 1 and Day 21 (PD analysis set)

Assessment	Day	Time (h)	NVA237 (Lsmeans 95% CI)	Placebo (Lsmeans 95% CI)	NVA237 - Placebo (Diff 95% CI)
Functional residual capacity (Liters)	1	1	4.41 (4.32,4.51)	4.77 (4.67,4.86)	-0.36 (-0.49,-0.22)
	21	-1	4.61 (4.52,4.71)	4.83 (4.74,4.93)	-0.22 (-0.35,-0.09)
	21	1	4.32 (4.22,4.42)	4.78 (4.68,4.87)	-0.46 (-0.58,-0.33)
Residual volume (Liters)	1	1	3.49 (3.38,3.59)	3.92 (3.82,4.02)	-0.44 (-0.58,-0.29)
	21	-1	3.78 (3.68,3.89)	4.02 (3.92,4.13)	-0.24 (-0.38,-0.10)
	21	1	3.46 (3.36,3.55)	3.95 (3.86,4.05)	-0.50 (-0.63,-0.36)
Slow vital capacity (Liters)	1	1	3.49 (3.44,3.55)	3.16 (3.10,3.21)	0.34 (0.27,0.41)
	21	-1	3.21 (3.14,3.27)	3.14 (3.07,3.21)	0.07 (-0.02,0.15)
	21	1	3.40 (3.33,3.47)	3.14 (3.07,3.21)	0.25 (0.18,0.33)
Specific Airway Conductance (Sec (-1)*kP)	1	1	0.68 (0.65,0.71)	0.41 (0.38,0.45)	0.26 (0.22,0.30)
	21	-1	0.48 (0.45,0.51)	0.40 (0.38,0.43)	0.08 (0.04,0.12)
	21	1	0.66 (0.63,0.70)	0.42 (0.39,0.46)	0.24 (0.19,0.29)
Total lung capacity (Liters)	1	1	7.01 (6.90,7.12)	7.08 (6.97,7.19)	-0.07 (-0.22,0.08)
	21	-1	6.99 (6.88,7.09)	7.17 (7.07,7.28)	-0.19 (-0.34,-0.04)
	21	1	6.86 (6.75,6.97)	7.10 (6.99,7.21)	-0.25 (-0.39,-0.10)

5. Exertional Dyspnea (Borg CR10 Scale) During Sub-maximal Constant-load Cycle Ergometry Test (SMETT) After 3 Weeks Treatment

Statistical analysis of exertional dyspnea and leg discomfort score at isotime on Day 1 and Day 21 (PD analysis set)

Assessment	Day	NVA237 (Lsmeans 95% CI)	Placebo (Lsmeans 95% CI)	NVA237 - Placebo (Diff 95% CI)
Leg discomfort Borg score at isotime	1	6.67 (6.09,7.25)	7.24 (6.66,7.82)	-0.56 (-1.15,0.02)
	21	6.21 (5.67,6.76)	7.05 (6.51,7.60)	-0.84 (-1.45,-0.22)
Modified Borg dyspnea score at isotime	1	6.08 (5.47,6.68)	6.99 (6.39,7.60)	-0.92 (-1.48,-0.35)
	21	5.64 (5.05,6.23)	6.80 (6.20,7.39)	-1.16 (-1.89,-0.42)

Safety Results

Adverse Events by System Organ Class

Adverse events overall and frequently affected system organ classes - n (%) of patients (Safety analysis set)

Body system	NVA237 N=102 n (%)	Placebo N=102 n (%)	Total N=108 n (%)
Patients with AE(s)	**30 (29.4%)**	**25 (24.5%)**	**46 (42.6%)**
Infections and infestations	9 (8.8%)	7 (6.9%)	15 (13.9%)
Respiratory, thoracic and mediastinal disorders	11 (10.8%)	4 (3.9%)	15 (13.9%)
Musculoskeletal and connective tissue disorders	7 (6.9%)	5 (4.9%)	11 (10.2%)
Gastrointestinal disorders	5 (4.9%)	3 (2.9%)	7 (6.5%)
Nervous system disorders	3 (2.9%)	5 (4.9%)	7 (6.5%)
Cardiac disorders	1 (1.0%)	2 (2.0%)	3 (2.8%)
Investigations	2 (2.0%)	0	2 (1.9%)
Skin and subcutaneous tissue disorders	0	2 (2.0%)	2 (1.9%)
General disorders and administration site conditions	1 (1.0%)	0	1 (0.9%)
Injury, poisoning and procedural complications	0	1 (1.0%)	1 (0.9%)
Metabolism and nutrition disorders	0	1 (1.0%)	1 (0.9%)

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

Adverse events - n (%) of patients (all patients) (Safety analysis set)

	NVA237 N=102 n (%)	Placebo N=102 n (%)	Total N=108 n (%)
Patients with AE (s)	30 (29.4%)	25 (24.5%)	46 (42.6%)
Nasopharyngitis	5 (4.9%)	4 (3.9%)	9 (8.3%)
Chronic obstructive pulmonary disease	3 (2.9%)	3 (2.9%)	6 (5.6%)
Headache	3 (2.9%)	4 (3.9%)	6 (5.6%)
Back pain	3 (2.9%)	2 (2.0%)	5 (4.6%)
Cough	3 (2.9%)	1 (1.0%)	4 (3.7%)
Arthralgia	1 (1.0%)	1 (1.0%)	2 (1.9%)
Joint swelling	0	2 (2.0%)	2 (1.9%)
Oropharyngeal pain	2 (2.0%)	0	2 (1.9%)
Rhinorrhea	2 (2.0%)	0	2 (1.9%)
Toothache	1 (1.0%)	1 (1.0%)	2 (1.9%)

Serious Adverse Events and Deaths

Deaths, other serious adverse events, or discontinuations due to AEs (Safety set)

	NVA237/Placebo N=55 n (%)	Placebo/NVA237 N=53 n (%)
Any significant adverse event		
Death	0	0
SAE(s)	1 (1.8)	0
Discontinued due to AE(s)	5 (9.1)	4 (7.5)
Discontinued due to SAE(s)	1 (1.8)	0
Discontinued due to non-SAE(s)	4 (7.3)	4 (7.5)

Other Relevant Findings

Date of Clinical Trial Report

22-Jun-2011

Date Inclusion on Novartis Clinical Trial Results Database

8-Feb-2012

Date of Latest Update