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Sustained 24-h efficacy of NVA237, a once-daily long-acting muscarinic antagonist, in COPD patients

C. Verkindre [a,*], Y. Fukuchi [b], A. Flémale [c], A. Takeda [d], T. Overend [e], N. Prasad [e], M. Dolker [f]

[a] *Hopital de Bethune, Beuvry, France*
[b] *Juntendo University, Tokyo, Japan*
[c] *Chirec – Parc Léopold, Service de Pneumologie, Bruxelles, Belgium*
[d] *Dohoku National Hospital, Hokkaido, Japan*
[e] *Novartis Horsham Research Centre, West Sussex, UK*
[f] *Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA*

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Summary
NVA237 is a once-daily inhaled long-acting muscarinic antagonist in development for the treatment of COPD.

This randomized, double-blind, placebo-controlled, four-period, incomplete block crossover study, with open-label active comparator (tiotropium), assessed the efficacy and safety of NVA237. Patients (≥40 years; smoking history ≥10 pack-years) with stable moderate-to-severe COPD (post-bronchodilator $FEV_1 \geq 30\%$ and <80% predicted, $FEV_1/FVC < 0.7$) received NVA237 12.5, 25, 50 or 100 μg, placebo, or tiotropium 18 μg once-daily for 7 days. The primary endpoint was mean trough (23–24 h post-dose) FEV_1 on Day 7. Secondary endpoints included mean trough FEV_1 on Day 1, and FEV_1 and FVC at individual time points post-dose on Days 1 and 7. 83 patients (mean age 64.4 years; male 83.1%; mean COPD duration 6.7 years; mean post-bronchodilator FEV_1 1.5 L/52.7% predicted) were randomized; 78 completed. Mean trough FEV_1 on Day 7 and Day 1 was significantly higher with all active treatments versus placebo ($p < 0.05$). NVA237 50 μg, 100 μg and tiotropium showed clinically relevant improvements versus placebo on Day 7 (differences of 131, 142 and 127 mL, respectively; $p < 0.0001$) and 1 (differences of 121, 135 and 112 mL, respectively; $p < 0.0001$). On Day 1, but not Day 7, FEV_1 was significantly higher ($p < 0.05$) with NVA237 50 and 100 μg versus tiotropium from 5 min up to 2 and 4 h post-dose, respectively. All doses of NVA237 and tiotropium were well tolerated.

* Corresponding author. Tel.: +33 32 164 4139; fax: +33 32 164 6350.
E-mail address: cverkindre@ch-bethune.fr (C. Verkindre).

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NVA237 once-daily was effective and well tolerated versus placebo, and demonstrated rapid and sustained 24-h bronchodilation. (ClinicalTrials.gov Identifier: NCT00501852).

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is only partially reversible and usually progressive.[1] The impact of the disease on an individual patient depends on the severity of symptoms (breathlessness and decreased exercise capacity, in particular), systemic effects, and presence of any comorbidities.[1] COPD is a disease that is both preventable and treatable, but it is frequently under-diagnosed and under-treated.[1,2] It is a leading cause of morbidity and mortality worldwide, and represents a substantial economic and social burden that is projected to increase over the coming decades.[1,2]

Pharmacotherapy for COPD is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance.[1] Breathlessness is the hallmark symptom of COPD. It is the main reason most patients seek medical attention, and is a major cause of COPD-related disability and anxiety.[1] Bronchodilators are key to the symptomatic management of COPD.[1] Antimuscarinic agents, which include ipratropium and tiotropium bromide, are one of the principal class of bronchodilators used for the treatment of COPD. Short-acting ipratropium[3,4] and long-acting tiotropium[5,6] have both demonstrated efficacy in treating COPD symptoms.

NVA237 (a novel inhaled dry-powder formulation of glycopyrronium bromide) is a once-daily long-acting muscarinic antagonist (LAMA) in development for the treatment of COPD. In preclinical studies, NVA237 demonstrated high affinity and slow dissociation from muscarinic receptors; an optimal profile for prolonged bronchodilation in patients with COPD.[7] Early single-dose[8] and multiple-dose[9] studies have shown NVA237 once-daily provides sustained 24-h bronchodilation with a rapid onset of action in patients with moderate-to-severe COPD. In addition, NVA237 is well tolerated with a good safety profile in this patient population.[8,9]

The present study in patients with stable moderate-to-severe COPD aimed to assess the efficacy and safety of four separate doses of NVA237 (given via a single-dose dry-powder inhaler [SDDPI]) in comparison with placebo and active control (open-label tiotropium) to identify a sub-therapeutic dose of NVA237 and to determine the optimal dose for further clinical evaluation. The primary study objective was to evaluate bronchodilatory efficacy in terms of trough forced expiratory volume in 1 s (FEV_1) following 7 days of treatment.

Methods

Patients

Included in this study were male or female adults aged $\geq$40 years with stable moderate-to-severe COPD[10] and a smoking history of $\geq$10 pack-years (defined as: 20 cigarettes/day for 10 years, or 10 cigarettes/day for 20 years, etc.,). Patients must have had a post-bronchodilator (following inhalation of 80 μg ipratropium bromide) $FEV_1 \geq 30\%$ and $<80\%$ of predicted normal values, and a post-bronchodilator FEV_1/forced vital capacity (FVC) < 0.7. Predicted FEV_1 was calculated according to Quanjer predictive equations for non-Japanese patients,[11] and according to Japanese Respiratory Society predictive tables for Japanese patients.[12]

Study exclusion criteria included: requiring daily oxygen therapy for chronic hypoxemia, hospitalization for exacerbation of airways disease in the 6 weeks prior to study start, respiratory tract infection (or one that had resolved $<$6 weeks previously), history of asthma, prolonged QTc interval at screening (or history of long QT syndrome), history of malignancy within the previous 5 years (except localized basal cell carcinoma of the skin), or any other clinically relevant medical condition or laboratory abnormality. Also excluded were patients unable to use any of the study devices or to perform spirometry procedures, those with history of an untoward reaction to any of the study drugs, and women of child-bearing potential not using an accepted form of contraception, pregnant women, or nursing mothers.

Use of inhaled salbutamol as rescue medication was permitted throughout the study (except immediately before and during study visits, unless absolutely necessary). Patients taking fixed combinations of inhaled corticosteroids (ICS) and long-acting β_2-agonists were transferred to the same dose of steroid contained in the fixed combination and rescue medication for a period of 2 weeks prior to starting study treatment. Patients on ICS monotherapy continued on their pre-study ICS regimen. Use of the following medications was not permitted during this study: tiotropium (minimum washout prior to starting study treatment: 7 days), short-acting anticholinergics (8 h), fixed combinations of β_2-agonists and ICS (48 h), long-acting β_2-agonists (48 h), short-acting β_2-agonists other than those prescribed in the study (6 h), any formulation of theophylline (7 days), or combinations of inhaled anticholinergics and β_2-agonists (24 h). Also prohibited were: any sympathomimetic with potential bronchodilator effect, methylxanthines, oral steroids for COPD, other anticholinergics, β-blocking agents, or other investigational drugs. Inhaled or nasal corticosteroids, cromoglycate, nedocromil and ketotifen were permitted if stabilized for $\geq$1 month prior to screening.

Study design

This was a randomized, double-blind, placebo-controlled, four-period, incomplete block crossover study, with an open-label active comparator (tiotropium). The study began with a screening period of up to 14 days to allow the

washout of prohibited medications and to ensure that current permitted medications were stable. Patients were then randomized to one of 30 treatment sequences, each comprising four 7-day treatment periods (once-daily NVA237 12.5, 25, 50 or 100 μg given via SDDPI, placebo, or open-label tiotropium 18 μg given via Handihaler®; all treatments were taken between 08:00 and 10:00 h) with a 7-day washout between each treatment period. Patients were assessed on Days 1 and 7 of each treatment period and, in total, were required to attend the study centres for 18 visits. The study was conducted in hospital/specialist respiratory clinics in Belgium, France and Japan.

A crossover study design was chosen since within-patient variability in FEV_1 is less than between-patient variability in this patient population. This design therefore allowed the total number of patients studied to be kept to a minimum. An incomplete block design was chosen to reduce the burden to patients of study visits and to reduce the number of premature discontinuations (a complete block design would have required patients to make an additional eight visits during the study).

NVA237 12.5, 25, 50 and 100 μg were provided as inhalation capsules in blisters. Placebo inhalation capsules were equally matched in size, shape and colour to NVA237 inhalation capsules. The active comparator, tiotropium bromide 18 μg, was open-labelled. The investigator assessed treatment compliance at each visit via capsule counts and information provided by the patient/caregiver.

This study was conducted according to the ethical principles of the Declaration of Helsinki. The protocol was reviewed by the Independent Ethics Committee or Institutional Review Board for each participating centre. All patients provided written informed consent before enrolling in the study.

Study assessments and variables

Efficacy was assessed via spirometry. FEV_1 and FVC were measured at 45 and 15 min prior to the first dose of study treatment (baseline), and at 5, 15 and 30 min, and 1, 2, 3, 4 and 5 h, 23 h 15 min, and 23 h 45 min post-dose on Days 1 and 7 of each treatment period. Three acceptable manoeuvres were required to be performed for each time point. The highest values measured were recorded, irrespective of whether or not they occurred on the same curve. The primary efficacy variable was trough FEV_1 (defined as the mean of the measurements taken at 23 h 15 min and 23 h 45 min post-dose) on Day 7. Secondary efficacy variables included trough FEV_1 on Day 1, and on Days 1 and 7 the following variables: peak FEV_1 (defined as the maximum FEV_1 value up to 5 h post-dose), standardized (with respect to time) FEV_1 area under the curve between 5 min and 5 h post-dose ($AUC_{5\ min-5\ h}$), and FEV_1 and FVC at the individual time points post-dose. Onset of action was assessed by comparing active treatments to placebo from 5 min post-dose on Day 1.

Safety assessments consisted of collecting adverse events (including their severity and possible relationship to study treatment), assessing vital signs, physical condition and electrocardiograms (ECGs) throughout the study. Haematology, blood chemistry and urinalysis parameters were assessed at screening, baseline and study completion.

Statistical analyses

The sample size was based on trough FEV_1 at Day 7 and was computed based on a formula for a balanced incomplete block design (6 treatments, 4 periods, 30 sequences).[13] Power was fixed at 80% to detect a treatment difference versus placebo of $\geq$120 mL (an increase in FEV_1 of 100–140 mL is generally considered to be clinically relevant)[14] at alpha 0.05/4, 2-sided (corrected by Dunnett's procedure for multiple-dose comparisons). Assuming a dropout rate of 15% at least 73 patients needed to be randomized, serving as their own controls.

The modified intent-to-treat (mITT) population included all randomized patients who received at least one dose of study medication; patients were analyzed according to the treatment they received. The mITT population was used in the analysis of all efficacy variables. The safety population was defined as patients who took at least one dose of study medication, and in this case was identical to the mITT population. The safety population was used in the analysis of all safety variables.

The primary efficacy variable (trough FEV_1 on Day 7) was analyzed using the following analysis of covariance (ANCOVA) model for a balanced incomplete (six-treatment four-period) block design: trough FEV_1 at Day 7 = patient effect (fixed) + period effect + treatment effect + (period) baseline FEV_1 + error. A similar ANCOVA model was used for all other efficacy variables. The dose-response relationship was analyzed using the trough FEV_1 values on Day 7 with multiple comparisons and modelling (MCP-Mod) procedures; the minimum effective dose was calculated using the E_{max} model. Safety variables were summarized descriptively, with clinically relevant or notable changes highlighted.

Results

Patients

In total, 83 patients were randomized into the study. Seventy-eight (94%) completed the study, providing evaluable data for 51–55 patients per treatment group (Fig. 1). The reasons for discontinuation were adverse events (AEs) ($n = 3$) and withdrawal of consent ($n = 2$). Most patients (4/5; 80.0%) discontinued whilst receiving placebo. The majority of patients were male (69/83; 83.1%) and non-Japanese (58/83; 69.9%). Other baseline demographic and clinical characteristics are shown in Table 1.

Efficacy

The primary efficacy variable, mean trough FEV_1 on Day 7, was significantly higher with all active treatments compared with placebo ($p < 0.05$; Fig. 2a). Similarly, the mean trough FEV_1 on Day 1 was significantly higher with all active treatments versus placebo ($p < 0.05$; Fig. 2b). Tiotropium significantly increased trough FEV_1 compared with the lowest dose of NVA237 (12.5 μg) on Day 1

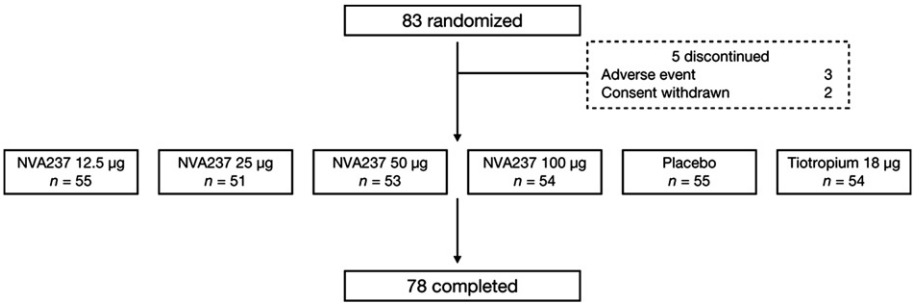

Figure 1 Patient disposition. Since this was a crossover study, a patient could be counted in more than one of the treatment groups; thus the sum of the treatment groups is greater than the number of patients randomized.

($p < 0.05$) and Day 7 ($p < 0.05$), and compared with NVA237 25 µg on Day 1 ($p < 0.05$).

On Day 7, both the 50 and 100 µg doses of NVA237 showed statistically significant improvements in mean trough FEV_1 versus placebo, which exceeded the pre-defined threshold for clinical significance (i.e., >120 mL), with differences of 131 and 142 mL, respectively ($p < 0.0001$); the difference between tiotropium and placebo was 127 mL ($p < 0.0001$). On Day 1, the 50 and 100 µg doses of NVA237 also showed clinically relevant improvements versus placebo, with differences of 121 and 135 mL, respectively ($p < 0.0001$); the difference between tiotropium and placebo was 112 mL ($p < 0.0001$).

Table 1 Patient baseline demographics and clinical characteristics (safety population).

	Total ($n = 83$)
Age (years), mean (SD)	64.4 (9.0)
Range	45–80
Sex, *n* (%)	
Male	69 (83.1)
Race, *n* (%)	
Caucasian	58 (69.9)
Asian	25 (30.1)
Duration of COPD (years), mean (SD)	6.7 (6.2)
Range	0–29
Smoking history, *n* (%)	
Ex-smoker	43 (51.8)
Current smoker	40 (48.2)
Pack-years, mean (SD)	50.1 (29.6)
FEV_1 pre-bronchodilator (L), mean (SD)	1.3 (0.4)
FEV_1 pre-bronchodilator (% predicted), mean (SD)	46.0 (12.8)
FVC pre-bronchodilator (L), mean (SD)	2.9 (0.6)
FEV_1 post-bronchodilator (L), mean (SD)	1.5 (0.4)
FEV_1 post-bronchodilator (% predicted), mean (SD)	52.7 (12.6)
FVC post-bronchodilator (L), mean (SD)	3.3 (0.6)
FEV_1 reversibility (%), mean (SD)	16.3 (13.2)
FEV_1/FVC post-bronchodilator (%), mean (SD)	46.6 (10.4)

SD = standard deviation; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity.

The results of a post-hoc analysis comparing Day 1 and Day 7 mean trough FEV_1 data for the 3 different NVA237 doses are shown in Table 2. On Day 7, the improvement in mean trough FEV_1 with 50 µg NVA237 was statistically superior ($p = 0.0070$) to 12.5 µg NVA237, although it failed marginally to show statistical significance versus 25 µg NVA237 ($p = 0.0537$). In addition, on Day 1 50 µg NVA237 was statistically superior to 25 µg ($p = 0.0009$) and 12.5 µg ($p < 0.0001$). However, the improvement in mean trough FEV_1 on Day 7 with 25 µg NVA237 was not statistically superior to 12.5 µg. Responder rates (difference of ≥120 mL in trough FEV_1 relative to placebo) for the NVA237 50, 25, and 12.5 µg groups were 61, 43, and 28%, respectively.

Serial FEV_1 data are shown in Fig. 3. FEV_1 over 24 h after dosing on Day 7 was significantly improved for all active treatments compared with placebo ($p < 0.05$) (Fig. 3a). There were no statistically significant differences between any of the NVA237 doses and tiotropium, with the exception of three post-dose time points (23 h 15 min and 23 h 45 min in the NVA237 12.5 µg group, and 5 h in the NVA237 25 µg group).

On Day 1, there were significant increases in FEV_1 with NVA237 versus placebo ($p < 0.05$) that were sustained from 5 min to 24 h post-dose, apart from for the 12.5 µg dose at a single time point (23 h 45 min). FEV_1 was significantly ($p < 0.05$) higher with NVA237 than with tiotropium at the following post-dose time points: NVA237 25 µg, from 5 min to 1 h; NVA237 50 µg, 5 min–2 h; NVA237 100 µg, 5 min–4 h. Conversely, FEV_1 was significantly higher with tiotropium than with NVA237 at the following post-dose time points: NVA237 12.5 µg, from 4 h to 23 h 45 min; NVA237 25 µg, from 23 h 15 min–23 h 45 min (Fig. 3b).

All active treatments showed statistically significant improvements over placebo on Days 1 and 7 for peak FEV_1 and standardized FEV_1 $AUC_{5\ min-5\ h}$ ($p < 0.05$; Table 3). On Day 1, values for both the 50 and 100 µg doses of NVA237 were significantly greater than those for tiotropium ($p < 0.05$).

Serial measurements of FVC followed a similar pattern to FEV_1 (data not shown).

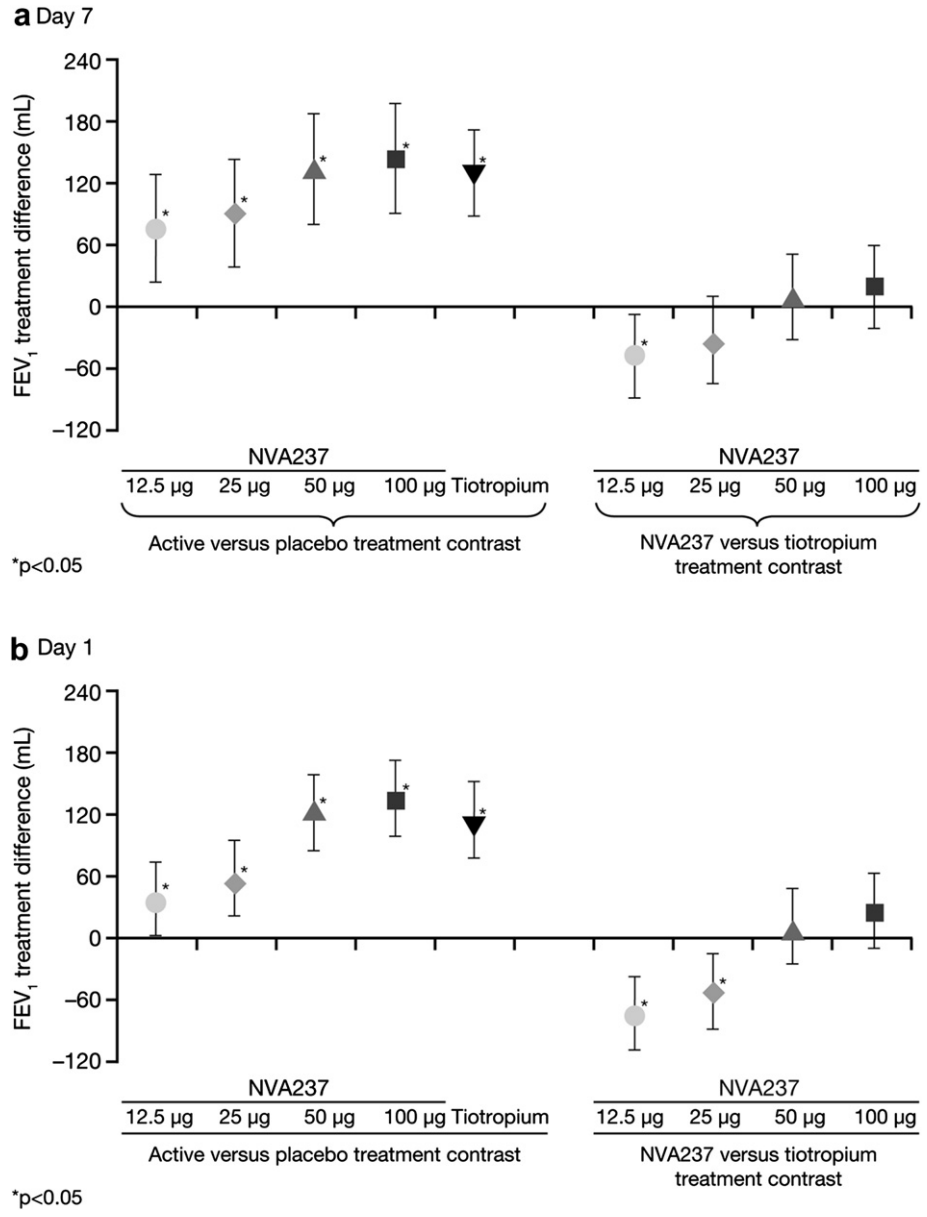

Figure 2 Trough FEV_1 treatment contrasts (active versus placebo and NVA237 versus tiotropium; least square means, 95% confidence intervals) after (a) 7 days and (b) 1 day of treatment (mITT population). FEV_1 = forced expiratory volume in 1 s; mITT = modified intent-to-treat.

Table 2 NVA237 dose comparison of mean trough FEV_1 (L) (mITT population).

NVA237 dose comparison	LS mean	SE	95% CI	*p* value
Day 1				
NVA237 50 µg−NVA237 25 µg	0.063	0.019	(0.026, 0.099)	0.0009
NVA237 50 µg−NVA237 12.5 µg	0.083	0.018	(0.047, 0.119)	<0.0001
NVA237 25 µg−NVA237 12.5 µg	0.020	0.018	(−0.016, 0.057)	0.2663
Day 7				
NVA237 50 µg−NVA237 25 µg	0.042	0.021	(−0.001, −0.084)	0.0537
NVA237 50 µg−NVA237 12.5 µg	0.057	0.021	(0.016, −0.098)	0.0070
NVA237 25 µg−NVA237 12.5 µg	0.015	0.021	(−0.026, 0.057)	0.4685

LS = least squares; SE = standard error of the mean; CI = confidence interval.

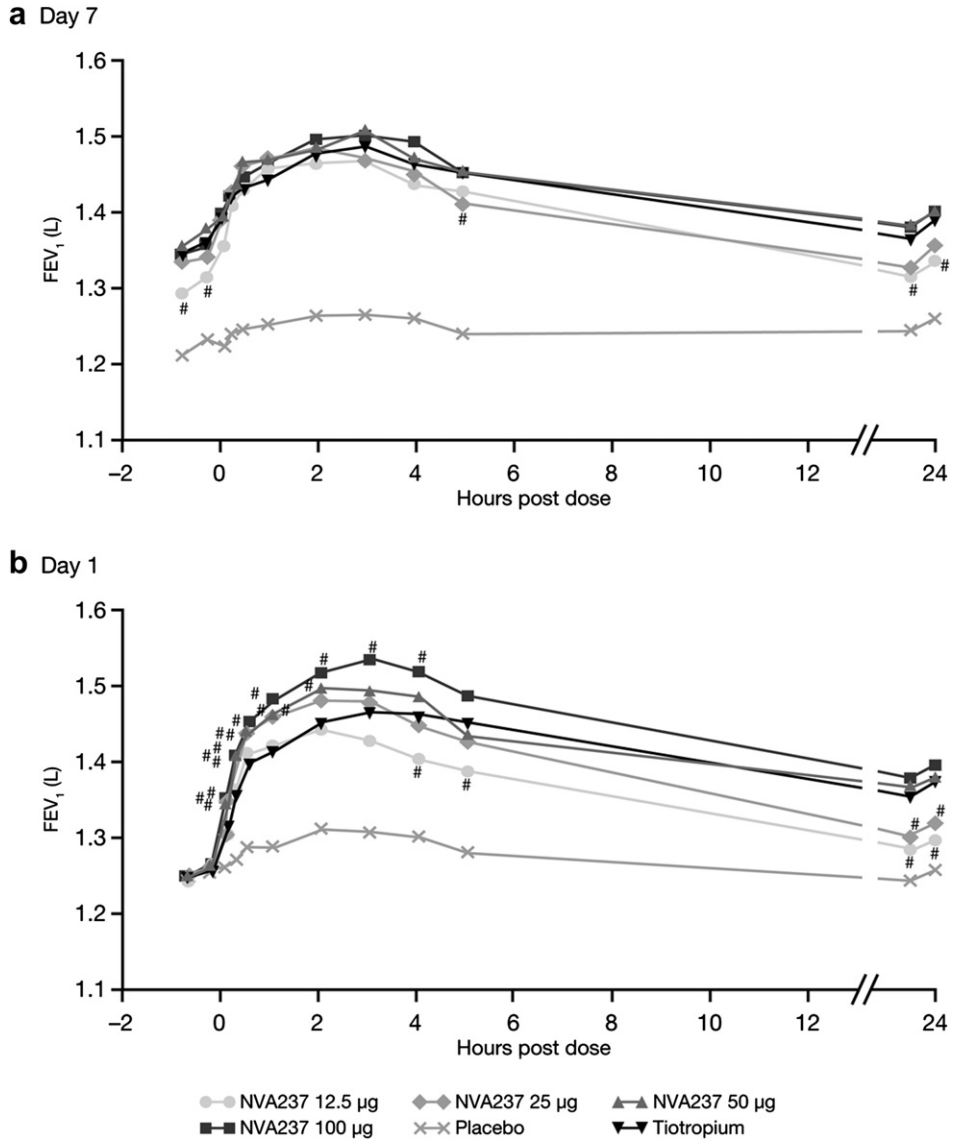

Figure 3 Twenty-4-h profile of least square means of FEV_1 on (a) Day 7 and (b) Day 1 of treatment (mITT population). a) All treatments were significant ($p < 0.05$) versus placebo; $^{\#}p < 0.05$ versus tiotropium b) All treatments were significant ($p < 0.05$) versus placebo at each post-dose time point (except NVA237 12.5 µg at 23 h 45 min); $^{\#}p < 0.05$ versus tiotropium. FEV_1 = forced expiratory volume in 1 s; mITT = modified intent-to-treat.

Safety

The most commonly reported AE during the study was headache (4/55 patients [7.3%] with NVA237 12.5 µg, 2/54 patients [3.7%] with tiotropium, and one patient with each of the other NVA237 doses; Table 4). Most AEs were mild and transient and appeared not to be dose related.

One serious adverse event (SAE) was reported: gastric cancer diagnosed in a patient taking NVA237 50 µg (not suspected to be drug related); this patient was discontinued from the study. Two other patients experienced AEs that led to premature discontinuation (COPD exacerbations, not suspected to be drug related), one during treatment with NVA237 25 µg and one with NVA237 100 µg.

There were no clinically relevant changes during the study in haematology, biochemistry or urinalysis parameters.

Mean pulse rate tended to decrease slightly with all treatments (including tiotropium and placebo), with the maximum decreases occurring approximately 1–3 h after dosing. There were no occurrences of pulse rate ≤40 bpm. The incidence of elevated pulse rate (≥90 bpm) was generally similar across the treatments.

There were no clinically relevant changes in mean systolic or diastolic blood pressure. The number of patients who had notable values for systolic blood pressure (≥140 mmHg) with NVA237 was similar to or lower than with placebo or tiotropium. For diastolic blood pressure, three patients had values ≤50 mmHg (two taking NVA237 12.5 µg

Table 3 Least square mean (SE) peak FEV_1 and standardized FEV_1 $AUC_{5\ min-5\ h}$ (mITT population).

	NVA237				Placebo ($n = 55$)	Tiotropium ($n = 55$)
	12.5 μg ($n = 55$)	25 μg ($n = 51$)	50 μg ($n = 53$)	100 μg ($n = 54$)		
Peak FEV_1 (L)						
Day 1	1.49 (0.01)[a]	1.53 (0.01)[a]	1.55 (0.01)[a,b]	1.56 (0.01)[a,b]	1.36 (0.01)	1.51 (0.01)[a]
Day 7	1.53 (0.02)[a]	1.54 (0.02)[a]	1.56 (0.02)[a]	1.56 (0.02)[a]	1.33 (0.02)	1.55 (0.02)[a]
Standardized FEV_1 $AUC_{5\ min-5\ h}$ (L)						
Day 1	1.41 (0.01)[a]	1.45 (0.01)[a]	1.47 (0.01)[a,b]	1.50 (0.01)[a,b]	1.29 (0.01)	1.44 (0.01)[a]
Day 7	1.45 (0.01)[a]	1.46 (0.02)[a]	1.48 (0.01)[a]	1.49 (0.01)[a]	1.26 (0.01)	1.47 (0.01)[a]

SE = standard error; FEV_1 = forced expiratory volume in 1 s; $AUC_{5\ min-5\ h}$ = area under the curve from 5 min to 5 h post-dose; mITT = modified intent-to-treat.
Note: results are based on patients with available data; tiotropium mITT population is 55 patients and safety population is 54 patients because one patient erroneously received tiotropium in two periods.
[a] $p < 0.05$ versus placebo.
[b] $p < 0.05$ versus tiotropium.

and one taking NVA237 100 μg). The proportion of patients with elevated diastolic blood pressure (≥90 mmHg) was lower with all doses of NVA237 (27.5–38.9%) than with tiotropium (50.9%), and was similar to placebo (36.4%).

The incidence of notable QTc interval values (Fridericia's formula; >440 ms for males and >460 ms for females) was low, with values lower for all active treatment groups (0–3.8%) than placebo (5.5%). No patient had an increase in QTcF interval of >60 ms from pre-dose to post-dose, or a clinically significant abnormality in their post-dose ECG.

Discussion

NVA237 is a once-daily inhaled LAMA in development for the treatment of COPD. The efficacy and safety of four separate doses of NVA237 (12.5, 25, 50 or 100 μg given via SDDPI) in comparison with placebo and active control (open-label tiotropium 18 μg given via Handihaler®) in patients with stable moderate-to-severe COPD were assessed in the present study.

The results indicate that following 7 days of once-daily treatment all doses of NVA237 showed sustained 24-h bronchodilation, as evidenced by significantly higher mean trough (23–24 h post-dose) FEV_1 compared with placebo ($p < 0.05$). Furthermore, the improvements in mean trough FEV_1 on Day 7 with NVA237 50 and 100 μg were clinically relevant (i.e., >120 mL versus placebo). Similar results were obtained on Day 1. The results also indicate that the onset of NVA237 effect was rapid: on both Days 1 and 7, all doses of NVA237 showed statistically significant improvements in FEV_1 values compared with placebo from 5 min post-dose ($p < 0.05$). These results are consistent with earlier findings that once-daily NVA237 provides sustained 24-h bronchodilation with a rapid onset of effect.[8,9]

One purpose of this study was to identify a suitable NVA237 dose for future studies. NVA237 demonstrated a clear dose-response relationship in this study, analysis of which estimated the minimum effective dose (i.e., the dose to result in a 120 mL increase in trough FEV_1 on Day 7) to be 42 μg once-daily. Doses greater than this (up to 100 μg once-daily) were not associated with any tolerability or safety concerns.

NVA237 50 and 100 μg and tiotropium appeared similar in terms of bronchodilatory efficacy and duration of action. However, the data indicate that NVA237 had a more rapid onset of action than tiotropium: on Day 1, FEV_1 was significantly higher with NVA237 25, 50 and 100 μg versus tiotropium from 5 min up to 1 h post-dose ($p < 0.05$). Peak FEV_1 and standardized FEV_1 $AUC_{5\ min-5\ h}$ were also significantly greater with NVA237 50 and 100 μg than with tiotropium on Day 1 ($p < 0.05$). The finding of a more rapid onset of action with NVA237 than with tiotropium is consistent with previous observations from a multiple-dose study,[9] and may represent a benefit to patients in terms of them feeling an immediate effect with treatment. In a previous study, tiotropium reached pharmacodynamic

Table 4 The total and most common (>2% in any NVA237 group) adverse events reported (safety population).

Patients, *n* (%)	NVA237				Placebo ($n = 55$)	Tiotropium ($n = 54$)
	12.5 μg ($n = 55$)	25 μg ($n = 51$)	50 μg ($n = 53$)	100 μg ($n = 54$)		
Total	11 (20.0)	11 (21.6)	11 (20.8)	8 (14.8)	7 (12.7)	7 (13.0)
Headache	4 (7.3)	1 (2.0)	1 (1.9)	1 (1.9)	0	2 (3.7)
Rhinitis	0	3 (5.9)	0	0	1 (1.8)	0
Cough	3 (5.5)	0	0	1 (1.9)	2 (3.6)	0
Nasopharyngitis	2 (3.6)	2 (3.9)	0	0	1 (1.8)	0
Toothache	0	0	2 (3.8)	0	0	1 (1.9)

steady state (in terms of both trough and acute bronchodilatory response) within 1 week of treatment.[5] This might explain why on Day 7 of the present study there were no longer any relevant differences in FEV_1 between NVA237 and tiotropium at the early time points post-dose.

NVA237 was well tolerated with a good overall safety profile. No safety signals of concern were identified from the AE data, and this is consistent with previous findings reporting the good overall safety profile of NVA237.[15] In our study, there was no observable dose-response relationship between NVA237 and AEs, and no increase in COPD-related AEs compared with placebo or tiotropium. No single AE was reported by more than 8% of patients with any particular treatment. Dry mouth, which has previously been reported in 15–16% of patients taking tiotropium,[5,6] was not observed in the present study. This may be due to the short treatment duration in this study, as a median time of onset of dry mouth of 4 weeks has previously been reported with ipratropium and tiotropium.[5] Ongoing longer-term studies will assess the incidence of dry mouth with NVA237. Laboratory findings, vital signs and ECG observations were generally unchanged during the study. These safety and tolerability observations are in-line with those from earlier NVA237 studies.[8,9]

The results of the present study support the continued development of once-daily NVA237 for the treatment of patients with COPD. However, further investigations are warranted since, in addition to spirometric variables, there are other outcome parameters — such as improvements in symptoms, exercise capacity, and quality of life — that are relevant to the patient.

In conclusion, NVA237 was effective and well tolerated for the treatment of moderate-to-severe COPD at all doses compared with placebo, and demonstrated rapid and sustained 24-h bronchodilation. Additionally, the onset of action may be more rapid with NVA237 (50 and 100 μg) than tiotropium, which might represent a benefit to patients.

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Conflict of interest statement

YF is a consultant to Novartis (Japan), Boehringer Ingelheim (Japan), AstraZeneca (Japan) and Otsuka Pharmaceutical Co. Ltd.

CV, AF and AT declare no conflicts of interest.

TO, NP and MD are employees of Novartis Pharma AG.

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