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# Bronchodilatory effects of NVA237, a once daily long-acting muscarinic antagonist, in COPD patients

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## KEYWORDS

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Efficacy

## Summary

NVA237 is a novel, once daily inhaled long-acting muscarinic antagonist administered via a dry powder inhaler. This study aimed to assess the 24-h bronchodilatory effect following 14 days of treatment with inhaled NVA237 in patients with mild, moderate or severe COPD.

This was a randomized, double-blind, placebo-controlled, two-period, crossover, multi-center study. A total of 33 patients ( $\geq 40$  years; smoking history of  $\geq 10$  pack-years) were randomized to receive NVA237 50  $\mu\text{g}$  once daily followed by placebo or placebo followed by NVA237 50  $\mu\text{g}$  for 14 days. Treatment periods were separated by a 7–14 day washout period. The primary variable was the mean forced expiratory volume in 1 s ( $\text{FEV}_1$ ) derived from the area under the curve (AUC) between 0 and 24 h post-dose on Day 14.

The 24-h  $\text{FEV}_1$  profiles showed a consistent bronchodilator effect for NVA237 versus placebo on Day 14. Least square (LS) mean difference in  $\text{FEV}_1$   $\text{AUC}_{0-24 \text{ h}}$  values between NVA237 and placebo was 163 mL ( $P < 0.001$ ). There were significant increases in mean  $\text{FEV}_1$   $\text{AUC}_{0-12 \text{ h}}$  (LS mean difference 165 mL,  $P = 0.001$ ) and  $\text{FEV}_1$   $\text{AUC}_{12-24 \text{ h}}$  (161 mL,  $P < 0.001$ ) versus placebo. NVA237 significantly improved peak  $\text{FEV}_1$  (by 208 mL,  $P < 0.001$ ) and trough  $\text{FEV}_1$  (by 154 mL,  $P = 0.003$ ) versus placebo on Day 14. NVA237 was well tolerated; all adverse events were mild or moderate in intensity and not related to study drug.

NVA237 50  $\mu\text{g}$  once daily was well tolerated and showed significant and sustained 24-h bronchodilation in patients with COPD.

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## Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. It is characterized by progressive airflow limitation that is not fully

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reversible in most patients. Guidelines have recognized that COPD is both preventable and treatable; however, it is frequently under-diagnosed and under-treated in clinical practice.<sup>1,2</sup>

Management of COPD requires individualized therapy to prevent and control symptoms, reduce the frequency and severity of exacerbations, and to improve exercise tolerance and quality of life.<sup>1</sup> Treatment with bronchodilators is essential to the symptomatic management of COPD.<sup>1</sup> Inhaled muscarinic antagonists, such as ipratropium and tiotropium bromide, are one of the main classes of bronchodilators used for the treatment of COPD. Short-acting ipratropium<sup>3,4</sup> and long-acting tiotropium<sup>5,6</sup> have been shown to improve lung function and reduce COPD symptoms. Both agents are generally well tolerated in patients with COPD.<sup>1</sup>

NVA237 is a novel inhaled dry powder formulation of the long-acting muscarinic antagonist glycopyrronium bromide. It is currently in development as a once daily bronchodilator for the treatment of COPD. Preclinical studies demonstrated that NVA237 has both high affinity for and slow dissociation from muscarinic receptors; an optimal profile for prolonged bronchodilation.<sup>7</sup> NVA237 has a fast onset of effect and provides sustained 24-h bronchodilation. The safety and efficacy of NVA237 has been demonstrated studies in patients with moderate-to-severe COPD.<sup>8,9</sup> NVA237 is well tolerated at doses of up to 200 µg in this patient population.<sup>9</sup> The results of a recent dose-ranging study indicate that 50 µg NVA237 provides bronchodilation that is both statistically significant and clinically relevant (pre-defined threshold exceeded, i.e. >120 mL). The magnitude of bronchodilation observed with 50 µg NVA237 is similar to that observed with open-label tiotropium 18 µg (131 mL versus 127 mL, respectively).<sup>8</sup>

While previous studies have shown that NVA237 has a fast onset of effect that is sustained over 24 h,<sup>8,9</sup> a comprehensive 24-h bronchodilator profile of NVA237 has not been characterized to date. The present study in patients with mild, moderate or severe stable COPD was designed to assess the bronchodilatory effect of 50 µg NVA237 inhaled once daily compared with placebo, over the 24-h interval following 14 day's treatment.

## Methods

### Patients

Eligible patients were aged  $\geq 40$  years with stable mild, moderate or severe COPD according to the 2008 GOLD guidelines,<sup>10</sup> and a smoking history of at least 10 pack-years. Patients were required to have post-bronchodilator forced expiratory volume in 1 s ( $FEV_1$ )  $\geq 30\%$  of the predicted normal value and post-bronchodilator  $FEV_1$ /forced vital capacity (FVC) of  $< 0.7$  at Visit 1;  $FEV_1$  must increase by 5% or more following inhalation of ipratropium bromide in the bronchial reversibility test.

Patients were excluded if they required oxygen therapy on a daily basis for chronic hypoxemia, had a respiratory tract infection within 6 weeks prior to screening, or had been hospitalized for an exacerbation of airways disease in the 6 weeks before screening or during the screening period. Other exclusion criteria included: a history of asthma; prolonged heart-rate corrected QT interval (QTc) at screening or

a history of QT syndrome; an untoward reaction to anticholinergics or contraindications for antimuscarinic agents; pregnancy or lactation; any other clinically relevant laboratory abnormality or clinically significant condition that might have compromised patient safety or compliance.

Medications for the treatment of COPD or allied conditions were not permitted during the study and were to be discontinued for an appropriate period prior to study screening. Patients requiring inhaled corticosteroids, cromoglycate, ketotifen or nedocromil had to be using a stable dose for at least one month prior to first study treatment. Patients were not enrolled if they were unable to use the Breezhaler<sup>®d</sup> device, a single-dose dry powder inhaler (SDDPI), a pMDI (rescue medication) or perform spirometry measurements; were receiving  $\beta$ -blocking agents that were not highly  $\beta_1$  receptor-selective; or had received an investigational drug within 30 days or five half-lives prior to enrolment or dose administration. Women of child-bearing potential were excluded unless they were using appropriate contraception.

### Study design

This was a randomized, double-blind, placebo-controlled, two-period, crossover, multicenter trial (ClinicalTrials.gov identifier: NCT00856193) with a treatment duration of 14 days per period. The study consisted of a screening period (performed between 21 and 2 days prior to first dose) and the two treatment periods separated by a washout phase of 7–14 days. Study medication was administered via the Breezhaler<sup>®</sup> device, a low-resistance SDDPI suitable for use by a wide range of patients with COPD.<sup>11</sup> A study completion evaluation was performed on Day 15 of Period 2.

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 measurements were carried out on Day 1 (at 45 and 15 min pre-dose and at 5, 15 and 30 min and 1, 2, 3, 4 and 5 h post-dose), Day 7 (at 45 and 15 min pre-dose and at 5, 15 and 30 min and 1, 2, 3, 4, 5, 6, 10, 11.75, 23.25 and 23.75 h post-dose) and Day 14 (at 45 and 15 min pre-dose and at 5, 15 and 30 min and 1, 2, 3, 4, 5, 6, 10, 11.75, 13, 14, 20, 22, 23.25 and 23.75 h post-dose).

The primary efficacy variable was the standardized  $FEV_1$  area under the curve (AUC) between 0 and 24 h post-dose on Day 14. Secondary efficacy variables included  $AUC_{0-5\text{ h}}$ ,  $AUC_{0-12\text{ h}}$  and  $AUC_{12-24\text{ h}}$  for  $FEV_1$  on Day 14 (12 h was defined as the 11 h 45 min assessment), peak (defined as the highest value in the response profile on Day 1, 7 and 14, respectively) and trough  $FEV_1$  (defined as the mean of the 23 h 15 min and 23 h 45 min post-dose assessments), the standardized  $FEV_1$   $AUC_{0-5\text{ h}}$  on Day 1 and  $AUC_{0-12\text{ h}}$  on Day 7. The home monitoring device (Pikometer) for  $FEV_1$  was used as a validation

<sup>d</sup> Breezhaler is a registered trademark of Novartis Pharma AG, Basel, Switzerland.

test in this study. Profiles performed at home (Day 13) and while in the clinic (Day 14) were compared descriptively between treatment days (Day 13 versus Day 14) and with the 'standard' spirometry assessments (Pikometer versus spirometry) on Day 14.

Safety assessments included the incidence of all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to the study drug. In addition, changes in blood chemistry and hematology were monitored, and vital signs, physical condition and electrocardiograms (ECG) were regularly assessed throughout the study.

## Statistical analyses

The crossover design of this study allowed the total number of patients analyzed to be kept to a minimum. A sample size of 26 patients was estimated to provide about 90% power to detect a clinically significant increase of 120 mL in standardized  $AUC_{0-24\text{ h}}$  for  $FEV_1$  (24 h was defined as the 23 h 45 min assessment), assuming a two-sided significance level of 0.05 and standard deviation (SD) of 180 mL for within-patient differences. Originally, 32 patients were to be randomized to ensure approximately 26 completers.

All patients who completed at least one treatment period were included in the efficacy analysis. The primary efficacy analysis variable was standardized  $FEV_1 AUC_{0-24\text{ h}}$ , following 14 days of treatment; the linear trapezoidal rule was used to calculate the AUC. Standardized  $FEV_1 AUC_{0-24\text{ h}}$  was analyzed with an analysis-of-covariance (ANCOVA) model, which included: treatment sequence, treatment and period as fixed factors, baseline  $FEV_1$  value as a covariate and patient as a random effect. The least square (LS) mean difference (with 95% confidence intervals) between NVA237 and placebo was estimated. Baseline was defined as the mean of the -45 and -15 min pre-dose values on Day 1 of each treatment period. Secondary efficacy variables were analyzed in a similar manner to the primary variable.

Safety assessments were conducted in the safety population, which included all patients who received at least one dose of study medication. Safety variables are summarized descriptively.

## Results

### Disposition and baseline characteristics

A total of 33 patients were enrolled into this study (Fig. 1). Two patients were withdrawn, one for abnormal test procedure results and one who was lost to follow-up. The majority of patients were male (66.7%) and Caucasian (93.9%). Other baseline demographic and clinical characteristics are shown in Table 1.

### Efficacy

#### Primary efficacy variable

$FEV_1 AUC_{0-24\text{ h}}$  values on Day 14 were significantly ( $P < 0.001$ ) higher for NVA237 than for placebo; LS mean difference of

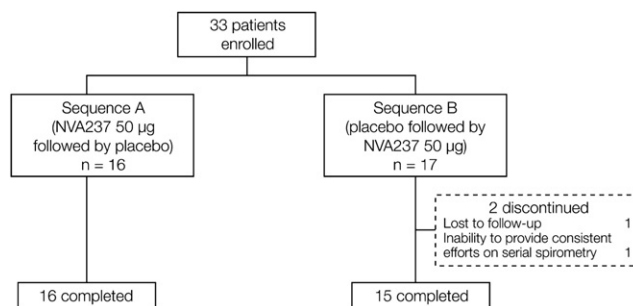


Figure 1 Patient disposition (safety population).

163 mL between NVA237 and placebo. Mean 24-h profiles of  $FEV_1$  on Day 14 (efficacy analysis set) are presented in Fig. 2.

### Secondary efficacy variables

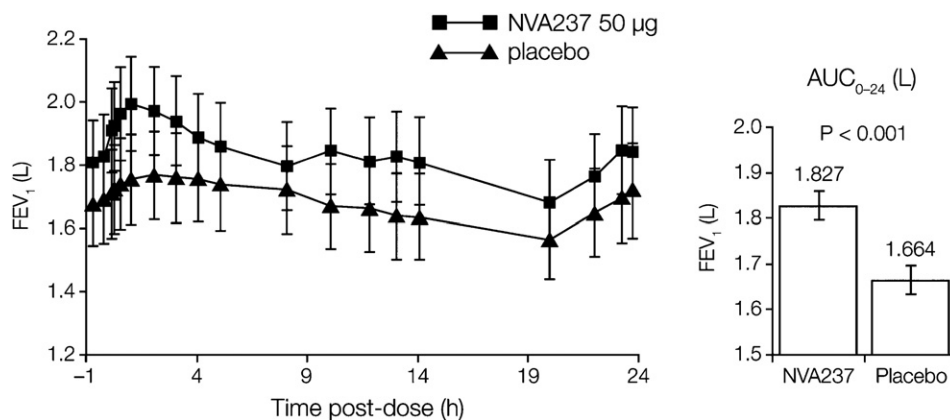
A summary of the statistical analysis of  $FEV_1 AUC$  values assessed as secondary efficacy variables is provided in Table 2.  $FEV_1$  with NVA237 was significantly higher ( $P < 0.001$ ) than placebo for all AUCs evaluated. On Day 14, there were significant increases in mean  $FEV_1 AUC_{0-5\text{ h}}$  (difference 198 mL,  $P < 0.001$ ),  $FEV_1 AUC_{0-12\text{ h}}$  (difference 165 mL,  $P = 0.001$ ) and  $FEV_1 AUC_{12-24\text{ h}}$  (161 mL,  $P < 0.001$ ) versus

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

	Total (n = 33)
Age (years), mean (SD)	60.5 (9.1)
Range	46–81
Sex, n (%)	
Male	22 (66.7)
Race, n (%)	
Caucasian	31 (93.9)
Black	2 (6.1)
Duration of COPD (years), mean (SD)	4.8 (3.8)
$FEV_1$ (L) pre-bronchodilator, mean (SD) <sup>a</sup>	1.8 (0.8)
$FEV_1$ (L) post-bronchodilator, mean (SD) <sup>a</sup>	2.1 (0.8)
$FEV_1$ % predicted pre-bronchodilator, mean (SD) <sup>a</sup>	58.9 (21.1)
$FEV_1$ % predicted post-bronchodilator, mean (SD) <sup>a</sup>	69.7 (21.1)
$FEV_1$ reversibility (%), mean (SD)	21.8 (16.0)
FVC (L) pre-bronchodilator, mean (SD) <sup>a</sup>	3.3 (1.2)
FVC (L) post-bronchodilator, mean (SD) <sup>a</sup>	3.7 (1.3)
$FEV_1/FVC$ (%) pre-bronchodilator, mean (SD) <sup>a</sup>	54.0 (10.0)
$FEV_1/FVC$ (%) post-bronchodilator, mean (SD) <sup>a</sup>	56.7 (10.6)

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

<sup>a</sup> Ipratropium bromide.



**Figure 2** Twenty-four-hour bronchodilatory effect on Day 14 (efficacy analysis set). \* FEV<sub>1</sub> = forced expiratory volume in 1 s; AUC = area under the curve. Values are expressed as mean  $\pm$  standard error. \*Only patients with FEV<sub>1</sub> values in both periods for a given time point were included.

placebo. In addition, NVA237 increased mean FEV<sub>1</sub> AUC<sub>0-12 h</sub> on Day 7 by 185 mL ( $P < 0.001$ ) and mean FEV<sub>1</sub> AUC<sub>0-5 h</sub> on Day 1 by 172 mL ( $P < 0.001$ ) versus placebo.

All primary analyses for trough FEV<sub>1</sub> comparisons showed a clinically significant effect (pre-defined threshold exceeded, i.e.  $>120$  mL) at the 5% confidence level, except for the treatment LS mean difference in trough value for NVA237 on Day 7 (91 mL; 95% CI  $-0.011$ , 0.192). The difference in trough values between NVA237 and placebo on Day 14 was 154 mL ( $P = 0.003$ ). A clinically significant effect was reported for all peak FEV<sub>1</sub> comparisons. The mean difference in peak values between NVA237 and placebo was 208 mL ( $P < 0.001$ ) on Day 14 and 173 mL ( $P = 0.011$ ) on Day 7.

### Safety

NVA237 was well tolerated. In total, five (15%) of the 33 patients experienced at least one AE (Table 3); three of these patients experienced an event only with placebo, one patient only with NVA237 and the fifth patient with both NVA237 and placebo. Almost all AEs observed in the study were of mild intensity; one AE of moderate intensity was reported: toothache (in the placebo group). No SAEs or

severe events were reported. All AEs were transient in nature and not thought to be related to the study drug. There were no clinically relevant changes in hematological or biochemical measures during the study. In addition, there were no clinically relevant changes in vital signs or ECGs.

### Discussion

The results of this study indicate that 50 µg NVA237 has a fast onset of effect, with a significant and sustained bronchodilatory effect over 24 h compared with placebo.

NVA237 significantly improved pulmonary function in patients with mild, moderate or severe stable COPD. The bronchodilatory effect was sustained for 24 h following 14 days of once daily treatment, as evidenced by significantly higher FEV<sub>1</sub> AUC<sub>0-24 h</sub> values versus placebo (primary efficacy variable). The mean difference in FEV<sub>1</sub> AUC<sub>0-24 h</sub> values between NVA237 and placebo was 163 mL ( $P < 0.001$ ). Results obtained for secondary variables also showed that the efficacy of NVA237 was sustained over the full 24-h dosing interval, as indicated by the similar bronchodilatory response over the first (0–12 h) and second (12–24 h) fraction of the dosing interval. The bronchodilator effect of NVA237 once daily appears to be sustained for at least as long

**Table 2** Statistical analysis of the FEV<sub>1</sub> AUC values assessed as secondary efficacy variables (efficacy analysis set, ANCOVA model).

Parameter	Day	Treatment	<i>n</i>	LS mean	SE	Contrast to placebo LS mean (95% CI) <sup>a</sup>	<i>P</i> value																																
AUC <sub>0-5 h</sub>	1	Placebo	33	1.849	0.0235	0.172 (0.116, 0.228)	<0.001																																
		NVA237	31	2.021	0.0242			AUC <sub>0-12 h</sub>	7	Placebo	28	1.806	0.343	0.185 (0.088, 0.282)	<0.001	NVA237	31	1.991	0.0325	AUC <sub>12-24 h</sub>	14	Placebo	32	1.714	0.0340	0.165 (0.073, 0.257)	0.001	NVA237	31	1.879	0.0346	AUC <sub>0-24 h</sub>	14	Placebo	32	1.615	0.0339	0.161 (0.079, 0.234)	<0.001
AUC <sub>0-12 h</sub>	7	Placebo	28	1.806	0.343	0.185 (0.088, 0.282)	<0.001																																
		NVA237	31	1.991	0.0325			AUC <sub>12-24 h</sub>	14	Placebo	32	1.714	0.0340	0.165 (0.073, 0.257)	0.001	NVA237	31	1.879	0.0346	AUC <sub>0-24 h</sub>	14	Placebo	32	1.615	0.0339	0.161 (0.079, 0.234)	<0.001	NVA237	31	1.776	0.0344								
AUC <sub>12-24 h</sub>	14	Placebo	32	1.714	0.0340	0.165 (0.073, 0.257)	0.001																																
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FEV<sub>1</sub> = forced expiratory volume in 1 s; AUC = area under curve; LS = least square; SE = standard error; CI = confidence interval.  
<sup>a</sup> adjusted for baseline covariate.



**Table 3** All adverse events reported in the safety population (n, %).

Adverse event	NVA237 50 µg (n = 31)	Placebo (n = 33)
Total	2 (7)	4 (12)
Abdominal discomfort	1 (3)	0
Periodontitis	0	1 (3)
Toothache	0	1 (3)
Gastroenteritis viral	0	1 (3)
Dysphonia	0	1 (3)
Pruritus	1 (3)	0

as tiotropium.<sup>12</sup> Van Noord et al. (2005) showed that tiotropium 18 µg once daily for 6 weeks increased mean FEV<sub>1</sub> AUC by 127 mL from baseline during the first 12 h post-dose, and by 43 mL 12–24 h post-dose. In comparison with ipratropium bromide, the bronchodilator effect of NVA237 once daily is sustained for longer; ipratropium bromide has a 6 h duration of action, thereby necessitating four times daily administration to maintain efficacy over 24 h<sup>13</sup>

While the results of this study clearly demonstrate that NVA237 provides significant sustained 24-h bronchodilation, moderate fluctuations in the effects of NVA237 versus placebo on Day 14 are apparent within the dosing interval. These fluctuations may be caused by the methodological variability of spirometry. Physiological fluctuations of bronchomotor tone, and thus expiratory flow, over the day could also have influenced the results; activity of the sympathetic system is postulated to be more prominent in the day, whereas parasympathetic system activity is increased during the night.<sup>14–16</sup>

Previously it has been postulated that receptor binding kinetics, in combination with *in vivo* models in dogs, may be predictive of the differences in duration of action of inhaled antimuscarinic compounds.<sup>17</sup> In these settings there were differences in the receptor dissolution and duration of action between tiotropium and NVA237. The missing link to the observations in clinical studies may be related to the fact that receptor binding kinetics are only one fractional part of compound pharmacology and can therefore not reliably predict the duration of action of a compound administered to the lung. Experimental *in vitro* settings should try to better approximate physiological conditions and utilise formulations that are representative of those used in the clinic. Clinical data of NVA237 show similar response profiles compared with tiotropium up to 24 h after dosing. The dose response pattern of NVA237 appeared to be in the same dose order early after dosing as well at 24 h after dosing, making it unlikely that the 24 h duration of action is achieved by using an unnecessarily high dose.<sup>8</sup> The clinical data presented in this paper shows that NVA237 is effective 24 h post-dose and confirm the results of previous studies in patients with COPD.<sup>8,9</sup>

NVA237 improved all other FEV<sub>1</sub> AUC values analyzed compared with placebo. On Day 14, mean FEV<sub>1</sub> AUC<sub>0–5 h</sub> increased by 198 mL ( $P < 0.001$ ). In addition, mean FEV<sub>1</sub> AUC<sub>0–5 h</sub> on Day 1 increased by 172 mL ( $P < 0.001$ ). This result provides further evidence that NVA237 has a fast onset of effect, and suggests that patients may experience rapid relief from symptoms of dyspnea after starting treatment. Peak and trough FEV<sub>1</sub> were assessed on Day 7 and Day 14 of the study.

Treatment with NVA237 was associated with a consistent, statistically significant effect versus placebo on peak FEV<sub>1</sub> values on both days. Trough values on Day 14 were also significantly greater in NVA237-treated patients. The effect on trough FEV<sub>1</sub> values was in the range of that observed with the clinical use of tiotropium and ipratropium bromide.<sup>6,13,18</sup>

Overall, the results of this study are consistent with previous findings that once daily NVA237 provides sustained 24-h bronchodilation with a fast onset of effect.<sup>8,9</sup>

NVA237 was well tolerated. Only two patients experienced AEs while receiving NVA237; all were mild and not related to the study drug. In addition, local anti-cholinergic side effects, such as dry mouth which has been reported in 15–16% of patients taking tiotropium,<sup>5,6</sup> were not observed in the present study. This might be due to the short treatment duration of this study, as a median time of onset of dry mouth of 4 weeks has previously been reported with ipratropium and tiotropium.<sup>5</sup> Overall, the safety results are consistent with previous findings demonstrating the good safety profile of NVA237.<sup>8,9</sup>

In summary, compared with placebo, NVA237 50 µg showed significant and sustained bronchodilatory efficacy in patients with mild, moderate or severe COPD, and was well tolerated. The results of the present study provide additional evidence to support the continued development of once daily NVA237 for the treatment of COPD.

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## Conflict of interest statement

Dr Fogarty has received speakers honoraria from Novartis. Helen Hattersley, Lilla Di Scala and Anton Drollmann are all employees of Novartis Pharmaceuticals.

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