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Safety and tolerability of NVA237, a once-daily long-acting muscarinic antagonist, in COPD patients☆

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ABSTRACT

NVA237 is a novel once-daily inhaled long-acting muscarinic antagonist administered via a dry powder inhaler. This randomized, double-blind, placebo-controlled study evaluated the safety, tolerability and bronchodilator efficacy of two doses of NVA237 (100 and 200 μg), versus placebo, in patients with moderate-to-severe COPD (forced expiratory volume in 1 s [FEV_1] ≥ 30% and <80% predicted and FEV_1/forced vital capacity [FVC] < 0.7, 30 min after inhalation of 80 μg ipratropium bromide). After appropriate washout periods, patients were randomized to treatment with NVA237 100 μg ($n = 92$), NVA237 200 μg ($n = 98$) or placebo ($n = 91$) for 28 days. The primary objective was evaluation of safety, with efficacy measures included as secondary objectives. NVA237 was generally well tolerated and associated with a frequency and distribution of adverse events similar to placebo. Serious adverse events were uncommon and there was no evidence of adverse cardiovascular effects or unexpected events. Trough FEV_1 was significantly higher in those receiving NVA237 compared with placebo. For NVA237 100 μg the differences were 131 and 161 mL on Days 1 and 28, respectively ($p < 0.05$), and for NVA237 200 μg the differences were 146 and 151 mL on Days 1 and 28, respectively ($p < 0.05$). Peak FEV_1, FEV_1 at all timepoints up to 24 h after dosing, and FEV_1 area under the curve during 5 min–5 h post-dosing were also significantly higher in both NVA237 groups, compared with placebo. Patients receiving NVA237 required fewer daily puffs of rescue medication and had a higher percentage of days on which rescue medication was not required. Overall, the present study provides further evidence of the safety, tolerability and bronchodilator efficacy of once-daily treatment with NVA237 100 and 200 μg in patients with moderate-to-severe COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible [1]. Although the course of COPD varies among individuals, there is usually progressive deterioration and the condition often proves fatal. Worldwide, COPD is the fourth most frequent cause of death and results in a substantial burden of morbidity and direct and indirect healthcare costs [1].

Management of COPD requires individualized therapy to alleviate symptoms and maintain or improve quality of life [1]. Treatment with bronchodilators, either as-needed or on a long-term basis, is central to the management of COPD. Muscarinic antagonists and long-acting β_2-agonists are the principal classes of bronchodilators used in the management of COPD and are often used in combination, especially in patients with more severe disease [1]. Inhaled muscarinic antagonists such as ipratropium bromide [2,3] and tiotropium bromide [4,5] have been shown to

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improve lung function and reduce COPD symptoms, and are generally well tolerated [1].

The need for improved pharmaco-therapeutic options for COPD remains. New agents would be particularly beneficial if they could provide greater reductions in disability, improvements in quality of life and reductions in dyspnoea, while having a good safety and tolerability profile. Therapies that combine rapid and sustained efficacy with convenient dosing would be desirable.

NVA237 is a novel inhaled dry powder formulation of the long-acting muscarinic antagonist glycopyrronium bromide, and is in development as a once-daily bronchodilator for the treatment of COPD. In early studies, NVA237 was associated with a rapid onset of action and sustained 24-h bronchodilation in patients with COPD [6,7]. The results of a recent dose-ranging study indicate that NVA237 provides sustained bronchodilation with a faster onset of action and greater improvements in forced expiratory volume in 1 s (FEV_1) than tiotropium 18 μg. In addition, NVA237 appeared to be well tolerated at doses of up to 100 μg [8]. To expand upon these findings, we conducted a 28-day study in patients with moderate-to-severe COPD treated with the highest dose of NVA237 (100 μg) evaluated in the dose-ranging study [8] and at a two-fold higher dose (200 μg). The primary objective was to assess the safety and tolerability of 28 days of treatment with NVA237 100 and 200 μg once-daily, compared with placebo. Secondary objectives included assessment of bronchodilator efficacy and use of rescue medication.

2. Methods

2.1. Patients

Men and women of at least 40 years of age were enrolled in the study, which was conducted in the setting of doctors' offices or outpatient clinics. Patients were eligible if they had moderate-to-severe COPD according to the 2006 GOLD guidelines [9] and a smoking history of at least 10 pack-years (either current smokers or ex-smokers). Participants were required to have had a post-bronchodilator (30 min after the inhalation of 80 μg ipratropium bromide) $FEV_1 \geq 30\%$ and $<80\%$ of the predicted normal value and post-bronchodilator FEV_1/forced vital capacity (FVC) of <0.7.

Patients were not enrolled if they had been hospitalized for an exacerbation of airways disease or had a respiratory tract infection in the 6 weeks before screening or during the screening period. Other exclusion criteria included a history of asthma; prolonged QTc interval (>440 ms for males or >460 ms for females) at screening (or history of long QT syndrome); pregnancy or lactation; and clinically significant conditions that might have compromised safety or compliance, interfered with evaluation or precluded completion of the study. Use of the following medications was not allowed during the study: tiotropium (minimum washout period before starting study medication: 7 days), short-acting anticholinergics (8 h), long-acting β_2-agonists (48 h), short-acting β_2-agonists other than those prescribed in the study (6 h), theophylline (7 days) and combinations of short-acting anticholinergics and β_2-agonists (24 h). Patients requiring inhaled or nasal corticosteroids, cromoglycate, nedocromil or leukotriene antagonists for COPD and allied conditions had to have been using a stable dose for at least one month prior to screening. Patients using fixed combinations of β_2-agonists and inhaled corticosteroids prior to the study were transferred to the dose of inhaled corticosteroid contained in the combination product for 2 weeks prior to the second screening visit; patients continued on that dosage throughout the study. Patients were not enrolled if they were receiving β-blocking agents or had received an investigational drug within 30 days or 5 half-lives prior to enrolment. Women of child-bearing potential were excluded unless they were using appropriate contraception.

2.2. Study design

This was a three-arm, randomized, double-blind, parallel-group, placebo-controlled, multicentre study. Patients were assessed at two screening visits to confirm eligibility and permit a washout period of up to 7 days for prohibited medications, with at least 1 week between the first visit and baseline (Day 1) to allow for the collection of baseline diary data. On Day 1, eligible patients were randomized to one of three treatment groups: NVA237 100 μg, NVA237 200 μg or placebo once-daily for 28 days. Study medication was administered via a low-resistance single-dose dry powder inhaler [10]. After randomization and baseline assessments (Day 1), patients returned to the study centre to complete spirometry and safety evaluations on Days 2, 14, 28 and 29, with a follow-up visit 1 week after completion of study medication.

Patients, investigators, persons performing the assessments and data analysts remained blind to the identity of the treatment from the time of randomization until the database was locked. The blind was maintained by enforcement of confidentiality procedures and by preventing all persons involved in the study from accessing randomization data. The identity of the treatments was concealed by the use of study drugs that were identical in packaging, labelling, schedule of administration and appearance.

All patients provided written informed consent before enrolling in the study, which was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by Independent Ethics Committees or Institutional Review Boards at each study centre.

2.3. Study assessments and variables

Safety and tolerability assessment (the primary objective of the study) included recording of all adverse events (AEs) and serious adverse events (SAEs), which were categorized according to severity and relationship to study drug. Assessments included regular monitoring of haematology, blood chemistry, urinalysis, vital signs and physical condition. COPD exacerbations were identified by the investigator and reported as AEs. An exacerbation was defined as symptoms that did not resolve with the use of trial medications (and any established medication) and therefore required additional medical therapy. Patients with a COPD exacerbation during the double-blind treatment period ceased taking study medication and were withdrawn from the study. Urine samples and venous blood were collected at baseline and during the study and analyzed at a central laboratory. Electrocardiograms were recorded at baseline and during the study and reviewed by a central cardiologist. QTc interval was calculated using Fridericia's formula. Spirometry (FEV_1 and FVC) was performed at baseline and at multiple visits during the study to detect any potential AEs of study medication on lung function. FEV_1 reversibility to a standard dose of ipratropium bromide (80 μg) was assessed during screening.

As this was primarily a safety study, there was no specified primary efficacy endpoint. As a secondary objective, the bronchodilator efficacy of NVA237 was compared with placebo over 28 days of treatment based on spirometric data. The main efficacy endpoint was mean trough FEV_1 on Days 1 and 28 (trough FEV_1 was defined as the mean of two measurements at 23 h 15 min and 23 h 45 min post-dosing). Other assessments included mean trough FEV_1 on Day 14, and on Days 1, 14 and 28 the following endpoints: FEV_1 during 24 h after dosing (baseline FEV_1 was defined as the average of −45 and −15 min on Day 1), FVC during 24 h after dosing, peak FEV_1 (maximum at 5 min–5 h after dosing) and the FEV_1 area under the curve during 5 min–5 h after dosing (FEV_1 $AUC_{5\ min-5\ h}$). The use of rescue medication was also assessed.