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Extrafine beclomethasone/formoterol combination via a dry powder inhaler (NEXThaler®) or pMDI and beclomethasone monotherapy for maintenance of asthma control in adult patients: A randomised, double-blind trial

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ABSTRACT

Background: The fixed combination of extrafine beclomethasone dipropionate and formoterol fumarate (BDP/FF) pMDI (Foster®) is approved for treatment of adult asthmatic patients. In order to provide an alternative drug delivery system for BDP/FF to physicians and patients, a dry powder inhaler (NEXThaler®) has been developed, capable to deliver extrafine particles to the lungs and therefore improve the dosing of the drugs, especially in patients with poor hand-breath coordination.
Objective: This trial was performed to compare efficacy and safety of extrafine BDP/FF NEXThaler® with extrafine BDP/FF pMDI or non-extrafine BDP DPI alone in adult patients with controlled asthma.
Methods: In this 8-week randomised, double-blind, parallel-group trial, patients were randomized to receive either extrafine BDP/FF NEXThaler® 100/6 μg bid, extrafine BDP/FF 100/6 μg pMDI bid or non-extrafine BDP DPI 100 μg bid. The primary efficacy variable was change from baseline to the entire 8-week randomised treatment period in average pre-dose morning PEF.
Results: The ITT population comprised 754 patients. Extrafine BDP/FF NEXThaler® was non-inferior (pre-defined margin: −15 L/min) relative to extrafine BDP/FF pMDI (mean difference: −1.84; 95% CI: −6.73, 3.05) in terms of the primary efficacy variable, change from baseline in average pre-dose morning PEF. Statistical superiority of both extrafine BDP/FF formulations over non-extrafine BDP DPI was demonstrated for the primary efficacy variable (providing evidence of assays sensitivity of the trial), ACQ score and percentage of rescue medication use-free days. No significant safety signals were observed.
Conclusion: NEXThaler® is an effective and well-tolerated delivery device for treatment of patients with asthma who need a regular treatment.

1. Introduction

The mainstays of therapy in patients with bronchial asthma are inhaled corticosteroids (ICS) and long acting beta2-agonists (LABA) [1]. They reduce asthmatic airway inflammation [2], improve symptoms and reduce the risk of exacerbations [3–6]. However, adherence to inhaled therapy is often poor, even in patients with difficult to treat asthma [7–9] and especially in patients with lower socio-economic status [10]. In the past several years fixed dose combinations of ICS and LABA in a single inhaler have shown to improve adherence to asthma therapy [11], and reduce costs for the health-care systems as compared to free-combinations of the single components drugs [12].

Effectiveness and adherence to therapy is also related to the patient's preference and attitude to a given device. Reasons for changes in therapy or device can be age, changes in concomitant diseases or even personal preferences. Therefore, the availability of the same medication in different formulations, i.e. pressurized metered dose inhaler (pMDI) and dry powder inhaler (DPI), may

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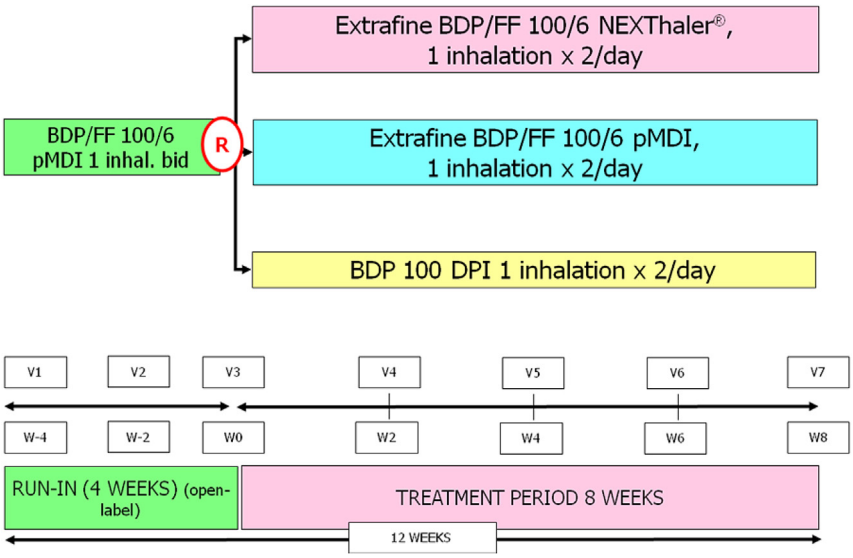

Fig. 1. Study design.

offer physicians and patients a broader range of therapeutic options to effectively treat the disease and achieve greater compliance.

Extrafine beclomethasone dipropionate (BDP)/formoterol fumarate (FF) as an HFA formulation has already been approved and marketed (Kantos®/Foster®/Kantos Master®/Inovair®) [13]. To provide an additional delivery device option an extrafine dry powder inhaler, the NEXThaler®, has been developed. Distribution of the drug within the small airways and mass median airway diameter (MMAD) of less than 2 μm defining the NEXThaler® as extrafine DPI have been previously described [14].

The aim of the present study was to demonstrate the non inferiority of BDP/FF fixed–dose combination (100/6 μg) delivered via the extrafine DPI (NEXThaler®) twice daily relative to the same dose of extrafine BDP/FF pMDI in terms of average pre-dose morning PEF in a population of adult asthmatic patients. As a secondary objective, the superiority of extrafine BDP/FF NEXThaler® over non-extrafine BDP DPI monotherapy in terms of the primary efficacy variable was evaluated to confirm the assay sensitivity of the study.

2. Materials and methods

Patients: non-smoking adult (≥18 years of age) outpatients with a diagnosis of clinically stable bronchial asthma for at least 6 months before screening and a smoking history of less than 5 pack-years, normal lung function (FEV_1>80% of the predicted normal value) after wash-out of inhaled bronchodilators, and under treatment with either regular medium dose of ICS (up to 1000 μg non-extrafine BDP/day or equivalent) or fixed combination of ICS/LABA (up to fluticasone/salmeterol 500/100 μg/day or equivalent) were included. They had to show a positive response to inhaled beta2-agonists (defined as an increase in FEV_1 of at least 12% and 200 mL 30 min after inhalation of 400 μg salbutamol) within 6 months prior to screening, and an ACQ-7 score < 1.25 as index of asthma control.

The study was performed according to the current ethical guidelines for clinical trials as described in the Declaration of Helsinki and Good Clinical Practice, and was approved by the ethical committees of the respective countries; all patients gave written informed consent prior to screening.

Study design: this was a multinational (104 centres in 7 European countries), randomised, double-blind, triple-dummy, three-arm, active comparator, parallel-group study (ClinicalTrials.gov identifier: NCT01345916).

After successful screening, patients underwent a four-week run-in period, during which they received extrafine BDP/FF 100/6 μg via pMDI (Foster®) 1 inhalation twice daily (BID) replacing their current therapy (Fig. 1).

Patients meeting the randomisation criteria (FEV_1 >80% of the predicted normal value after an adequate wash-out from bronchodilators, ACQ-7 score < 1.25 and no moderate or severe exacerbations during the run-in period) at the end of the run-in period were randomised by an Interactive Voice and Web Response System (IVRS/IWRS) to receive one of the three study treatments. Patients received one inhalation of either extrafine BDP/FF 100/6 μg via NEXThaler® or via pMDI (Foster®), or non-extrafine BDP 100 μg via DPI (Clenil® Pulvinal®) over an eight-week, twice-daily treatment regimen. A computer-generated randomisation list stratified by country with a 1:1:1 allocation ratio was used. As much as possible, the time of dosing remained constant for each patient throughout the duration of the study. Only salbutamol was allowed for symptom relief.

2.1. Efficacy and safety assessments

Visits occurred at screening, 2 weeks after screening, at the end of the 4-week run-in period (randomisation) and every two weeks up to 2 months after randomisation.

At each visit, spirometry was recorded using a standardised and centralised spirometry system (MasterScope CT, eResearchTechnology, Germany) according to current clinical guidelines published by ATS/ERS [15]; predicted values were calculated according to Quanjer et al. [16]. Patients were instructed not to take salbutamol or other short acting beta2-agonists (SABAs) in the 6 h before spirometry (unless absolutely necessary) and the morning dose of run-in or study medication prior to the visits.

The Asthma Control Questionnaire (ACQ-7) was administered at screening, at randomisation and at the Week 8 visit (end of treatment) or at the discontinuation from the study.

A hand-held electronic peak flow meter and electronic diary (AM3, eResearchTechnology, Germany [17]) was provided to the