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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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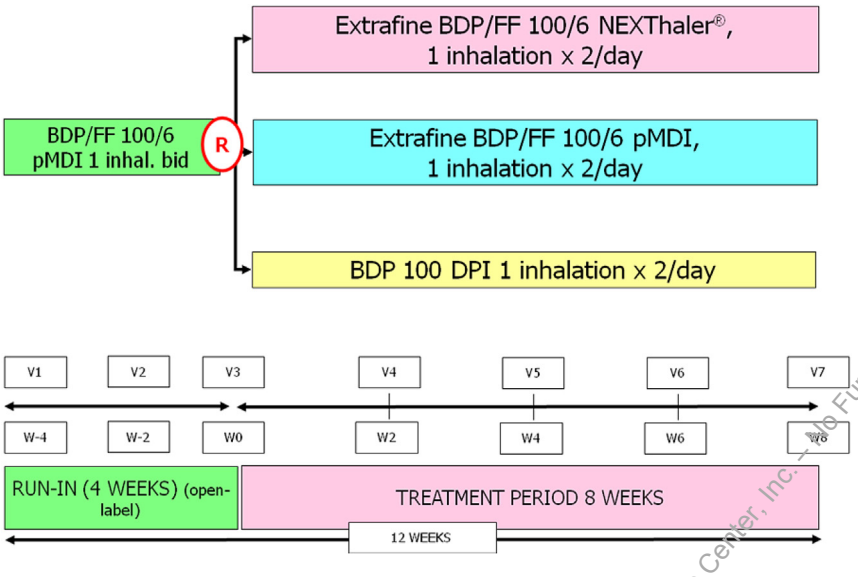

Fig. 1. Study design.

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

patients. Throughout the study, three pre-dose morning and evening PEF manoeuvres, intake of study and rescue medications, and daytime and night-time asthma symptoms were recorded daily. Each asthma symptom (cough, wheeze, chest tightness and breathlessness) was scored according to scales from 0 to 3, in which 0 represented no symptoms and 3 represented severe symptoms that prevented the patient from carrying out the usual daily activities or kept the patient awake most of the night.

At each visit, safety assessments included adverse events (AEs), vital signs (blood pressure and heart rate) and physical examination. The occurrence of moderate or severe asthma exacerbations was also recorded. A moderate asthma exacerbation was defined as deterioration in symptoms and lung function, and an increased rescue bronchodilator use for 2 days or more, but without the need of systemic corticosteroid use or hospitalisation. Emergency room (ER) visits for asthma not requiring systemic corticosteroids, were classified as moderate exacerbations. A severe asthma exacerbation was defined if it required the administration of systemic corticosteroids or an increase from a stable maintenance dose for at least 3 days, or a hospitalisation or ER visit with the use of systemic steroids [18].

2.2. Statistical analysis

The primary objective of the trial was to demonstrate that extrafine BDP/FF 100/6 μg administered via the NEXThaler® was non-inferior to the corresponding dose of extrafine BDP/FF administered via pMDI in terms of the primary efficacy variable, change from baseline to the entire 8-week randomised treatment period in average pre-dose morning PEF calculated from the daily home-based peak-flow measurements. A sample size of 177 evaluable patients per treatment group ensured approximately 90% power to demonstrate the non-inferiority, with a non-inferiority margin of −15 L/min and a one-sided significance level of 0.025, assuming no difference between treatments and a standard deviation (SD) of 43 L/min. The non-inferiority margin of −15 L/min is widely reported in previous studies [19,20], and is below the minimal patient-perceivable improvement of 18.8 L/min estimated by Santanello et al. [21]. 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.

The secondary efficacy variables included the change from baseline to each of the two-week inter-visit periods in average pre-dose morning PEF and the changes from baseline to the entire treatment period as well as to each inter-visit period in the following variables: average pre-dose evening PEF and daily PEF variability, average use of rescue medication, percentage of rescue medication use-free days, average total morning and evening asthma symptom scores, percentage of asthma symptom-free days and of asthma control days (no symptoms or rescue use). The changes from baseline in pre-dose morning FEV_1 and FVC at each clinic visit and from baseline to Week 8 in the ACQ-7 score were also evaluated in the secondary efficacy analysis.

For morning and evening PEF, the highest of the 3 measurements of each study day was considered for the statistical analysis. The total symptom scores were calculated as the sum of the severity scores for each asthma symptom. The baseline value was defined as the average of the last 14 days of the run-in period for the variables daily recorded in the electronic diary or as the measurement performed at randomisation visit for lung function and ACQ-7 score.

The Intention-to-Treat (ITT) population included all randomised patients who took at least one dose of the study medication and with post-randomisation efficacy data. The Per Protocol (PP) population included all patients of ITT population with no major protocol deviations. Safety analysis was performed in all randomised patients who took at least one dose of the double-blind study medication.

The primary efficacy variable and the secondary efficacy variables calculated over the entire treatment period and the change from baseline to Week 8 in the ACQ-7 score were analysed using an ANCOVA model including treatment, country and sex as factors and baseline as a covariate. All the secondary efficacy variables measured repeatedly during the randomised treatment period were analysed using a linear mixed model for repeated measures including the following fixed effects: treatment, country, sex, visit/period, baseline, treatment by visit/period interaction, baseline by visit/period interaction.

All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient population

A total of 932 patients were screened, of whom 755 patients were randomised (251 to extrafine BDP/FF NEXThaler® and 252 each to extrafine BDP/FF pMDI and non-extrafine BDP DPI). The most common reasons for screening failures were inclusion/exclusion criteria not met ($n = 139$) and withdrawal of informed consent ($n = 29$). Of note, the actual number of randomised patients was higher than planned due to a screening failure rate lower than expected.

During the course of the trial, 7 patients discontinued the study: 2 patients in the extrafine BDP/FF NEXThaler® group (due to an AE and lack of efficacy in 1 patient each), 3 patients in the extrafine BDP/FF pMDI group (due to inclusion/exclusion criteria not met, protocol violation and subject withdrawal in 1 patient each) and 2 patients in the non-extrafine BDP DPI group (due to inclusion/exclusion criteria not met and subject withdrawal in 1 patient each).

The patient discontinued due to inclusion/exclusion criteria not met in the BDP/FF pMDI was randomised in IVRS/IWRS by mistake and did not receive any dose of the study medication. This was the only randomised patient excluded in the ITT population and safety analysis. The PP population included a total of 740 patients (246 in the extrafine BDP/FF NEXThaler® group and 247 each in the extrafine BDP/FF pMDI and non-extrafine BDP DPI groups) (Fig. 2).

Overall, the demographic and baseline characteristics of patients were similar across the three treatment groups in the ITT population and are shown in Table 1. All patients were Caucasians except 1 Asian patient in the extrafine BDP/FF pMDI group.

As requested by the inclusion criteria, lung function was within normal ranges at screening, and patients were well controlled at screening and baseline as indicated by ACQ-7 scores (Table 1).

3.2. Results of intervention

Adherence was good for all treatment groups: mean (range) adherence to study medication was 94.9% (61.9–100.3), 94.9% (52.7–100.3) and 95.4% (69.3–101) for extrafine BDP/FF NEXThaler®, extrafine BDP/FF pMDI, and non-extrafine BPD DPI, respectively.

The switch to BDP/FF pMDI treatment during the run-in did not result in changes in asthma control (Table 1).

Changes in the primary efficacy variable, average pre-dose morning PEF, were small and non-significant between extrafine BDP/FF NEXThaler® and extrafine BDP/FF pMDI; conversely, in the non-extrafine BDP DPI group there was a statistically significant

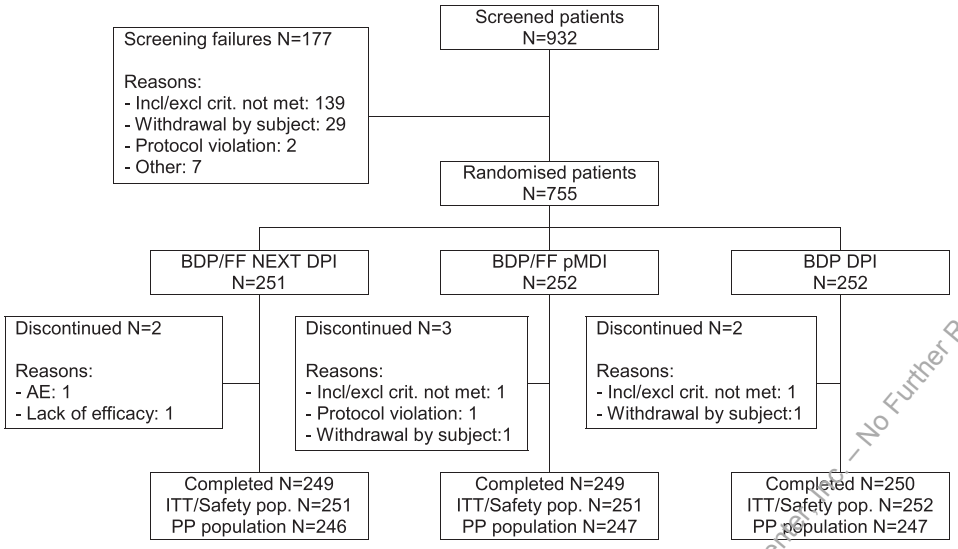

Fig. 2. Flow of patients through the study and analysis populations.

decrease in average pre-dose morning PEF from baseline to the entire treatment period (Table 2). BDP/FF NEXThaler® was found to be non-inferior to BDP/FF pMDI since the lower limit of the 95% confidence interval of the adjusted mean difference between treatments was −6.73 L/min, within the pre-defined non-inferiority margin of −15 L/min (Table 2). In the secondary efficacy analysis, the superiority of both BDP/FF NEXThaler® and BDP/FF pMDI over BDP DPI in terms of change in average pre-dose morning PEF was demonstrated, providing evidence of assay sensitivity of the trial (Table 2). These results were confirmed in the PP population, and supported by the analysis of change in average pre-dose morning PEF from baseline to each of the 2-week inter-visit periods (Fig. 3).Furthermore, there were no changes in daily pre-dose morning PEF between extrafine BDP/FF NEXThaler® and extrafine BDP/FF pMDI treatments, whereas in the group of patients treated with non-extrafine BDP DPI monotherapy a decline in PEF was shown in the first 7 days of treatment (Fig. 4).

Even if asthma was well controlled at baseline as requested by inclusion criteria, a further small, but statistically significant improvement from baseline to the entire treatment period in the adjusted means of average use of rescue medication (number of inhalations/day) and percentage of rescue medication use-free days could be observed in both extrafine BDP/FF formulations. This was not observed with the non-extrafine BDP DPI monotherapy group; differences between both extrafine BDP/FF combinations and non-extrafine BDP DPI reached statistical significance (Table 3).

For the average total day-time and night-time asthma symptom scores, there were statistically significant decreases (improvements) from baseline to the entire treatment period in adjusted mean scores with extrafine BDP/FF NEXThaler® and BDP/FF pMDI. With non-extrafine BDP DPI, a statistically significant decrease from baseline was observed for the day-time score. No significant differences between treatments were found.

A statistically significant increase from baseline to the entire treatment period in the adjusted mean percentage of asthma symptom-free days and asthma control days was observed for all treatment groups. The difference between extrafine BDP/FF pMDI and non-extrafine BDP DPI in the percentage of asthma control days reached statistical significance, in favour of the combination.

There were small decreases from baseline to the entire treatment period in adjusted mean FEV_1 and FVC observed in all treatment groups. These changes were non-significant for the two combinations, but statistically significant for BDP DPI. Treatment comparisons showed no significant difference between the combinations, but both of them were significantly better than BPI DPI.

Table 1
Demographic and baseline characteristics.

	BDP/FF next DPI $N = 251$	BDP/FF pMDI $N = 251$	BDP DPI $N = 252$
Age (years), mean (range)	43.7 (18–76)	43.9 (18–76)	44.4 (18–76)
Sex, *n* (%)			
Female	147 (58.6%)	166 (66.1%)	164 (65.1%)
BMI (kg/m^2), mean (range)	26.7 (17.0–44.6)	26.5 (16.1–43.3)	26.4 (17.1–43.0)
Time since asthma diagnosis (years), mean (range)	10.6 (0.5–43.4)	10.0 (0.6–53.3)	11.0 (0.6–50.0)
Smoking status, *n* (%)			
Non-smoker	226 (90.0%)	232 (92.4%)	234 (92.9%)
Ex-smoker	25 (10.0%)	19 (7.6%)	18 (7.1%)
FEV_1 (L), mean (SD)	3.08 (0.81)	2.98 (0.83)	2.96 (0.80)
FEV_1 % of predicted normal value, mean (SD)	97.0 (10.9)	96.2 (12.2)	96.2 (11.0)
ACQ-7 score at screening,			
Mean (SD)	0.54 (0.31)	0.51 (0.29)	0.51 (0.32)
Median	0.57	0.43	0.57
ACQ-7 score at randomisation,			
Mean (SD)	0.45 (0.32)	0.45 (0.31)	0.44 (0.33)
Median	0.43	0.43	0.43

N, number of patients in the treatment group; SD, standard deviation.

Table 2
Change from baseline to the entire treatment period in average pre-dose morning PEF (L/min).

	BDP/FF next DPI $N = 251$	BDP/FF pMDI $N = 251$	BDP DPI $N = 252$
Baseline, mean (SD)	438.24 (132.59)	419.85 (132.58)	411.20 (118.53)
Entire treatment period, mean (SD)	437.70 (131.78)	421.42 (133.27)	401.61 (115.05)
Change from baseline to the entire treatment period			
Mean (SD)	−0.53 (27.70)	1.57 (26.73)	−9.59 (30.79)
Adjusted mean (95% CI)	2.00 (−1.80, 5.81)	3.84 (−0.00, 7.69)	−7.96 (−11.75, −4.17)
Comparisons between treatments	BDP/FF next DPI vs. BDP/FF pMDI	BDP/FF next DPI vs. BDP DPI	BDP/FF pMDI vs. BDP DPI
Adjusted mean difference (95% CI)	−1.84 (−6.73, 3.05)	9.96 (5.07, 14.86)	11.81 (6.92, 16.69)
p-value	Not calculated	<0.001	<0.001

N, number of patients in the treatment group; SD, standard deviation; CI, confidence interval.

A trend for improvement from baseline to Week 8 in the adjusted mean ACQ-7 score was observed with the two fixed drug combinations; however, this was not statistically significant. Conversely, in the non-extrafine BDP DPI group there was a statistically significant increase in the ACQ-7 score (impairment). The comparison between groups showed statistically significant differences favouring both extrafine BDP/FF combinations over non-extrafine BDP DPI.

Few exacerbations were reported in the trial: in total 26 exacerbations occurred, of which 13 were graded as severe. Of these, 4 were observed in the extrafine DP/FF NEXThaler® group, 3 in the extrafine BDP/FF pMDI group, and 6 in the non-extrafine BDP DPI group.

No tremors or palpitations were observed during the study and the percentage of patients who reported treatment-related AEs was low and comparable between treatment groups (0.8% in the extrafine BDP/FF NEXThaler® group and 1.2% in the extrafine BDP/FF pMDI and non-extrafine BDP DPI groups). Other treatment emergent adverse events that occurred in more than 2 patients were headache (in 1, 4 and 5 patients in the NEXThaler-group, BDP/FF pMDI and BDP DPI-group, respectively), nasopharyngitis (in 2, 6 and 6 patients, respectively) and pharyngitis (in 7, 3 and 2 patients, respectively).

4. Discussion

This study was designed to show non-inferiority of extrafine formulation of the fixed combination of beclomethasone dipropionate and formoterol fumarate at doses of 100/6 μg BID administered via NEXThaler® DPI relative to the same dose of the fixed combination administered via pMDI.

It was demonstrated that treatment with extrafine BDP/FF using NEXThaler® DPI was non-inferior to extrafine BDP/FF administered via pMDI in terms of change from baseline in average pre-dose morning PEF. Evidence of assay sensitivity of the trial was provided, as the superiority of both combinations over non-extrafine BDP-monotherapy (100 μg BID via DPI) was shown for the primary efficacy variable.

Furthermore, the efficacy of extrafine NEXThaler® DPI and pMDI was comparable in terms of lung function (FEV_1, FVC) and symptoms (day/night-time symptoms, rescue medication use, ACQ-7 score). Significant differences favouring the extrafine BDP/FF-combinations over non-extrafine BDP were shown in terms of pulmonary function (FEV_1, FVC, PEF) and clinical parameters (rescue medication use, ACQ-7 score). Of interest, data obtained from patients' self-monitoring (pre-dose morning PEF from daily home-based measurements) were in line with lung function assessments at the respective 2-weekly clinic visits (FEV_1, FVC).

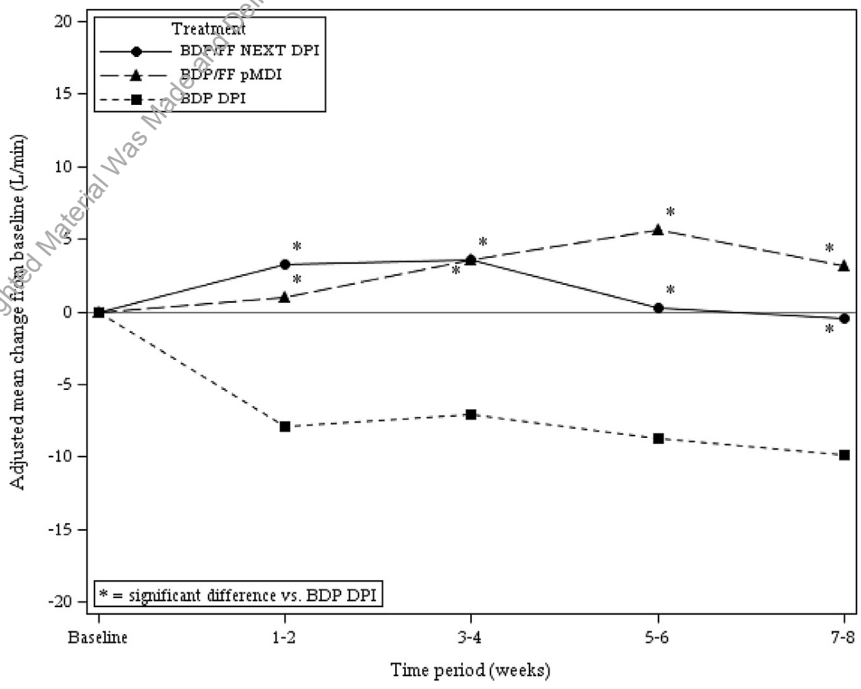

Fig. 3. Change from baseline in average pre-dose morning PEF at each two-week period.

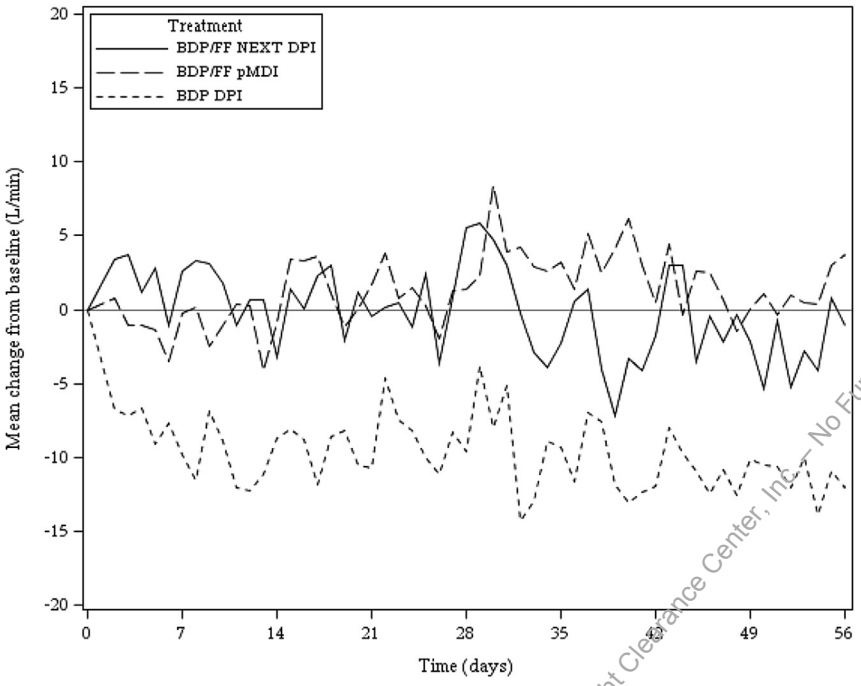

Fig. 4. Change from baseline in average pre-dose morning PEF day by day.

The use of fixed drug combinations between ICS and LABA are recommended by current guidelines at defined stages of severity (GINA stage 3 upwards) [1] and their clinical efficacy is at least in part driven by potential synergy [22]. These products are currently available as DPI (Diskus, Turbuhaler) or MDI. Preference of the patients to receive either dry powder inhalers or metered dose inhalers (either as patient actuated pressurized MDI or breath actuated devices or as soft-mist inhalers) is variable. The use and clinical effectiveness depends on various factors like manual compliance, ability to press on the canister appropriately while simultaneously inhaling slowly (MDIs), or ability to inhale forcefully with sufficient inspiratory flow to overcome delivery resistance of the device (DPIs). Due to this, the drug as well as the choice of the device has to be carefully evaluated depending on the patients' situation, age, co-morbidities and disease severity or risk of or current exacerbation.

NEXThaler® is a pocket-sized breath-actuated medium resistance multi-dose dry powder inhaler. This device has been developed to minimize the problems that occur with current DPI's in terms of dependency of drug particle size on flow rate and loss of the metered dose if the patient exhales through the device before inhaling [23,24].

The data of the current trial support the concept that efficacy of treatment (in terms of disease control) with extrafine BDP/FF pMDI can be ensured also using NEXThaler® device. This is demonstrated by the primary efficacy analysis, showing that NEXThaler® is non-inferior to the pMDI in terms of lung function as expressed as change from baseline in average pre-dose morning PEF measured at home and FEV1 measured every two weeks at clinics. In addition, the superiority of NEXThaler® vs non-extrafine BDP alone was demonstrated for both pre-dose morning PEF and FEV1 providing evidence of assay sensitivity of the trial. The results for symptoms and ACQ-7 score (as a predictor of potential future asthma exacerbations) are also in line with the non-inferiority between the two tested fixed ICS/LABA-combination therapies. There were no statistically significant differences between NEXThaler® and pMDI in any of the patient related outcomes like use of rescue medication, rescue-use free

Table 3
Change from baseline to the entire treatment period (to Week 8 for the ACQ-7 score).

	Adjusted mean change			Adjusted mean difference between treatments (95% CI)		
	BDP/FF next DPI	BDP/FF pMDI	BDP DPI	BDP/FF next DPI vs. BDP/FF pMDI	BDP/FF next DPI vs. BDP DPI	BDP/FF pMDI vs. BDP DPI
Average pre-dose evening PEF (L/min)	0.73	4.29*	−10.23*	−3.56 (−8.71, 1.60)	10.96 (5.81, 16.11)*	14.52 (9.38, 19.66)*
Average daily PEF variability (%)	−0.29	−0.24	−0.12	−0.05 (−0.56, 0.45)	−0.17 (−0.67, 0.34)	−0.11 (−0.62, 0.39)
Average use of rescue medication	−0.11*	−0.11*	−0.02	−0.00 (−0.09, 0.08)	−0.10 (−0.18,-0.01)*	−0.09 (−0.18,-0.01)*
% of rescue-use free days	5.2*	6.1*	1.9	−1.0 (−3.9, 2.0)	3.2 (0.3, 6.2)*	4.2 (1.2, 7.2)*
Average total day-time symptom score	−0.17*	−0.19*	−0.10*	0.02 (−0.09, 0.13)	−0.07 (−0.18, 0.04)	−0.09 (−0.20, 0.01)
Average total night-time symptom score	−0.13*	−0.15*	−0.05	0.02 (−0.08, 0.12)	−0.08 (−0.18, 0.02)	−0.10 (−0.20, 0.00)
% of asthma symptoms-free days	8.2*	9.1*	5.5*	−0.9 (−4.8, 2.9)	2.7 (−1.2; 6.5)	3.6 (−0.2; 7.5)
% of asthma control days	8.9*	9.6*	5.6*	−0.8 (−4.7, 3.2)	3.3 (−0.6, 7.3)	4.1 (0.1, 8.0)*
Pre-dose morning FEV_1 (L)	−0.02	−0.02	−0.07*	0.00 (−0.03, 0.04)	0.05 (0.02, 0.09)*	0.05 (0.02, 0.09)*
Pre-dose morning FVC (L)	−0.01	−0.01	−0.06*	0.01 (−0.04, 0.05)	0.05 (0.01, 0.09)*	0.04 (0.00, 0.08)*
ACQ-7 score	−0.026	−0.028	0.058*	0.002 (−0.062, 0.065)	−0.084 (−0.147,-0.021)*	−0.085 (−0.148,-0.022)*

*$p < 0.05$; CI, confidence interval.

days, asthma symptom scores, and the percentage of asthma symptom-free days and asthma control days.

The safety profile of the DPI formulation was also in line with that of available combinations of ICS and LABA and, more importantly, was not different from that of the pMDI formulation.

The current trial demonstrates that NEXThaler® is an effective and well-tolerated delivery device for treatment of patients with asthma who need a regular treatment.

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