

EXPERT OPINION

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NEXThaler, an innovative dry powder inhaler delivering an extrafine fixed combination of beclometasone and formoterol to treat large and small airways in asthma

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Introduction: Airway inflammation and remodelling in asthma occur in the large airways and also in the small airways. The small airways are those < 2 mm in diameter and are significant sites of chronic asthmatic inflammation. It is important, therefore, to target the small as well as the large airways in any strategy for effective treatment of this disease.

Areas covered: The present review deals with the recently developed fixed dose drug combination of beclometasone dipropionate/formoterol fumarate that emits extrafine particles when delivered from an innovative dry powder inhaler (DPI), NEXThaler[®]. The aim is to present the technical and clinical aspects of aerosolized drug delivery to the lungs.

Expert opinion: The data show that the NEXThaler[®] DPI is an efficient device for the management of persistent asthma. The evaluation of the inhalation profiles through the NEXThaler[®] DPI demonstrates that device activation and consistent dose delivery occurs at patient achievable inhalation flow rates, and supports the broad utility of the NEXThaler[®] DPI in patients with asthma. Overall, all the effectiveness, efficiency and satisfaction outcomes demonstrate the NEXThaler[®] DPI is easy to use.

Keywords: asthma, beclometasone, dry powder inhaler, extrafine particles, formoterol, small airways

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1 Introduction

Asthma is a significant public health problem affecting millions of people worldwide [1], which is characterized by a chronic inflammatory process that affects the whole respiratory tract [2]. The peripheral airways, commonly referred to as the small airways, are airways with < 2 mm in internal diameter and account for a significant part of the total airflow resistance in asthmatics [3]. Often defined as the 'silent zone', the small airways are, on the contrary, not silent as this airway region has been implicated in contributing to and influencing asthma control [4,5] in clinical circumstances such as exercise-induced asthma [6,7] and nocturnal asthma [8]. Small airways are also involved in the increased risk for asthma exacerbations [6]. The traditional lung function measurements like peak expiratory flow (PEF) and the forced expiratory volume in 1 s (FEV₁) are poor reflectors of small airway abnormalities [4,5].

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Recent studies have reported that small airway abnormalities are common among patients with asthma and can also be found in patients without signs of proximal airflow obstruction [9-11]. Farah *et al.* [12] reported that ventilation heterogeneity was worse in patients with poorly controlled asthma and measures of ventilation heterogeneity were the only independent predictors, explaining 20% of the variance of a change in asthma control after inhaled corticosteroid (ICS) treatment. As a consequence, it has been postulated that asthma control can be further improved using drugs that are uniformly delivered along the entire bronchial tree, thus reaching and treating both the large and the small airways [10,11].

It has been shown that a correct inhaler technique is a key factor in ensuring that the inhaled drug reaches the bronchial tree in order to exert its pharmacological effects and also improve asthma control [13]. However, inhaler mishandling is common in real life and associated with poor disease control [14-16]. Indeed, incorrect use of inhaler devices has been associated with increased reliever use, increased use of emergency medical services, worsening asthma and higher rates of asthma instability as observed in a recent study in general practice [17,18]. What is more, physicians' knowledge of inhaler devices and inhalation techniques remains rather poor among healthcare professionals and this could be improved by improving education for healthcare providers and also by developing inhaler devices that are easy to be taught and easier to be used by patients [19,20].

Various inhalation devices, aerosolized drug formulations and inhaler technologies have been developed to improve the delivery of drugs to the bronchial tree and to improve the inhalation technique by reducing the possibility of making errors while operating the device. The present review focuses on the recently developed fixed dose drug combination of ICS/long-acting β_2 -agonist (LABA), beclomethasone dipropionate/formoterol fumarate (BDP/F), that emits extrafine particles when delivered from an innovative dry powder inhaler (DPI), NEXThaler[®] DPI.

2. Rationale for the development of an innovative device

In order to effectively reach the small airways, it is necessary to inhale particles with an appropriate mass median aerodynamic diameter (MMAD) that can target the whole bronchial tree [21]. Generally particles < 5 μm have the potential to be deposited into the airways. Formulations with a small MMAD have been shown to provide higher lung deposition with better penetration into the small airways than those with a higher MMAD [2]. These small particles have MMAD of < 2 μm and are referred to as extrafine [22-24]. The first product formulated as an inhaler that emitted extrafine particles was beclomethasone in a pressurized metered dose inhaler. This has been followed by ICS/LABA combination pressurized metered dose inhaler (pMDI) that emits extrafine particles that are able to target

both the large airways and the small airways of asthmatic patients [25]. Leach *et al.* [22] used the imaging modality of single-photon emission computed tomography (computed tomography γ scintigraphy) to compare the lung deposition of inhaled drugs with different particle size formulations. They observed that 77% of the nonextrafine fluticasone-salmeterol HFA-suspension pMDI was deposited in the oropharynx and 16% in the lungs compared with 35 and 58% of the extrafine HFA-solution of beclomethasone dipropionate.

DPIs are commonly used for inhalation therapy, but until recently no DPI has been formulated to deliver extrafine particles [26]. The development of a dry powder drug device for inhalation is quite complex; the performance of the product depends on the inter-relationship of the inhaler device with the DPIs resistance and the user's inhalation maneuver to de-aggregate the drug formulation such that particles capable of lung deposition are emitted in the inhaled airstream leaving the inhaler [27]. Each DPI has a minimum threshold energy below which the de-aggregation of the drug powder from the lactose carrier molecule is inefficient and hence, only a limited or no amount of drug is effectively delivered to the lung [28]. Therefore, it is critical that the efficiency of the device is independent from the inhalation maneuver and that patients can use their device properly.

The NEXThaler[®] DPI has been designed to generate extrafine particles from a formulation of both active components to ensure consistent dose delivery independently from the patient's inhalation.

3. Main device characteristics

The NEXThaler[®] DPI is a multidose breath-actuated DPI with an inspiratory flow resistance of 0.036 kPa^{1/2} l/min corresponding to a flow rate of 55 l/min at 4 kPa. It has a label claim of 100/6 μg of BDP/F per actuation, corresponding to a delivered dose of 81.9 μg of BDP and 5.0 μg of F. The main characteristics of the device and its external and internal components are shown in Figure 1. The NEXThaler[®] DPI has a breath-actuated mechanism (BAM) guaranteeing that the dose is released only when a threshold inspiratory flow of 35 l/min is achieved. This flow ensures efficient de-aggregation of the dose (authors' personal observation). Figure 1 shows that a dose protector prevents the dose from being inhaled until the mechanism is triggered by a flow rate that allows complete de-aggregation and delivery of the full dose.

To inhale the dose, the patient follows a straightforward three-step sequence of operations. This procedure is possible because the mouthpiece cover is integrated into the dose charging system; therefore, the opening of the cover makes the drug dose available for inhalation. After an inhalation, when the cover is closed, the dose number decrements by one count after an effective inhalation of the drug; and at the same time, the device mechanism is reset becoming ready for the next inhalation.

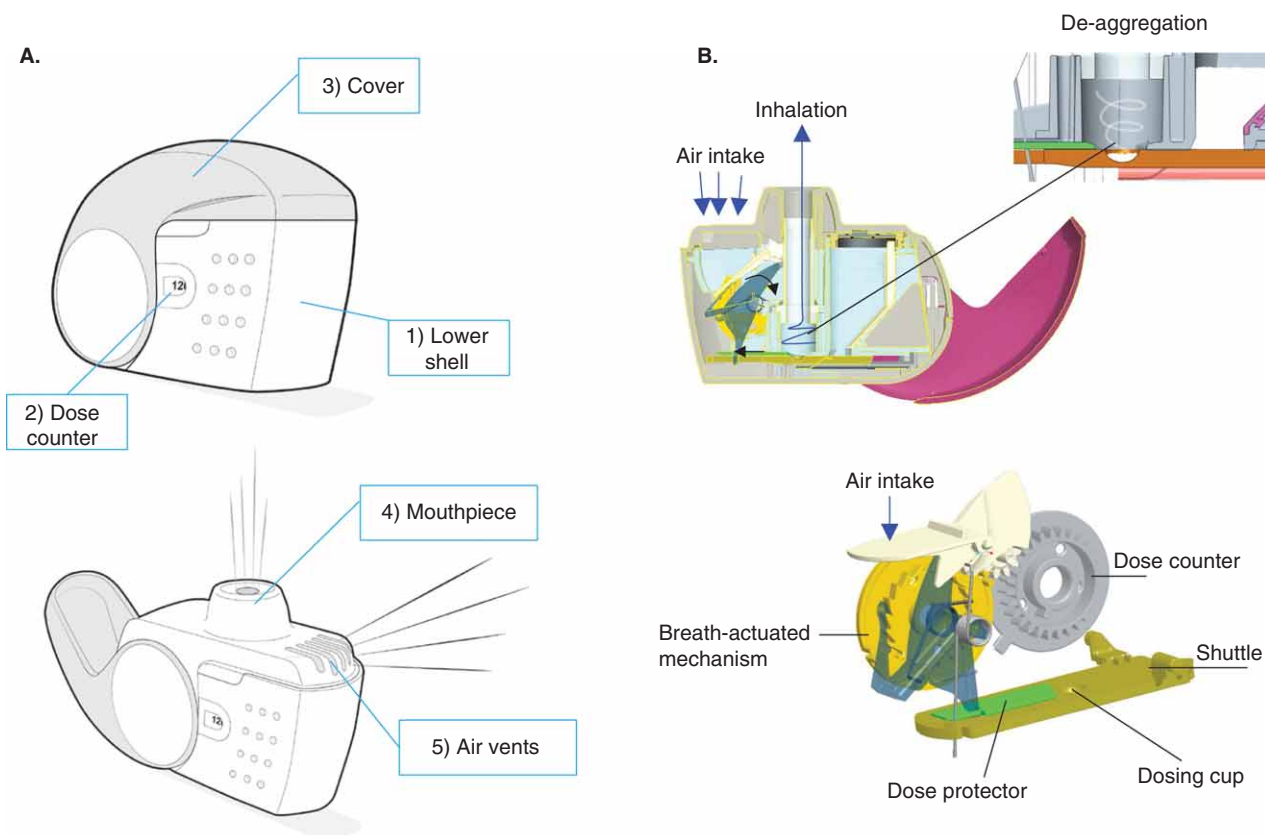


Figure 1. The NEXThaler® DPI components and mechanism of action. **A.** Outer components. The casework comprises a lower shell (1) with a dose counter (2) to display the numbers of remaining doses and an integral cover (3). When the cover is opened, it reveals a mouthpiece (4) through which the user inhales. At patient's inhalation, air flows through the air vents (5) into the inhaler. **B.** Internal components and mechanism of action. During the opening, the cover drives the shuttle ahead and the dosing cup, which is gravimetrically filled, shifts from the bottom of the reservoir to the base of the de-aggregation system. The drug is prevented to fall out from the dosing cup because of a dose protector linked with the BAM. During the inhalation, the air passes through the air vents and activates the BAM, which moves the dose protector away from the dosing cup, thus releasing a full therapeutic dose.

BAM: Breath-actuated mechanism; DPI: Dry powder inhaler

The inhalation device incorporates a feedback system for the patients user to provide them with the reassurance that a dose has been inhaled. First, a click is heard on activation of the BAM when the patient inhales through the device and the internal dose release mechanism is activated. If the inhaler is opened and then inadvertently closed without inhaling, the dose is not wasted nor does it accumulate, which avoids accidental double dosing by the patient. Second, release of the dose is confirmed through a dose counter linked to the BAM. The dose counter does not decrement after preparation of the dose but only after delivery of the full therapeutic dose. Therefore, if the patient prepares the dose but does not inhale through the device, the dose counter does not decrement. Lastly, the formulation contains lactose as a carrier, which leaves a typical taste upon inhalation of the drug from the device. This triple feedback system allows both patients and healthcare providers to be sure that the full therapeutic dose is inhaled.

Figure 2 details the emission of the dose during an inhalation. Images of drug particle entrainment and delivery were captured at three different flow rates (40, 60 and 100 l/min) [29]. For all three tested flow rates, particles are rapidly picked up and entrained into the vortex created in the central chamber of the device. Figure 2 shows that after activation of the BAM, the full-dose is released from the dosing cup within 0.35 s when using a flow of 40 l/min. Similar results were obtained at all flow rates investigated.

3.1 Extrafine delivery and lung deposition

The NEXThaler® DPI is currently the only DPI on the market delivering extrafine particles and this unique characteristic depends on two factors: i) the drug delivered from NEXThaler® DPI is designed to possess extrafine physico-chemical properties and is associated with larger lactose particles that acts as a carrier; and ii) during inhalation, the

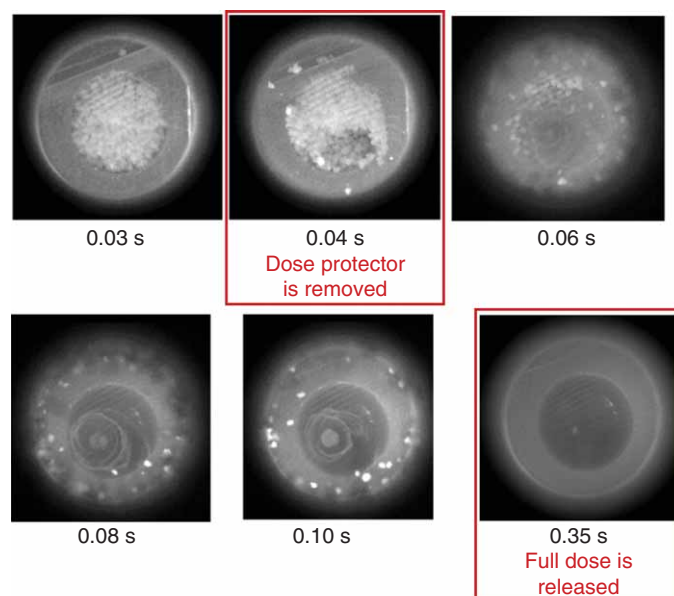


Figure 2. Particle de-aggregation and release inside the NEXThaler® DPI swirl chamber. A visual analysis was performed using a Photron APX-RS high-speed camera (10000 frames/s) in conjunction with an Oxford Lasers copper-vapor. Pictures reported here were taken at a flow rate of 40 l/min. Time shown refers to time after start of flow through the device [29].

DPI: Dry powder inhaler.

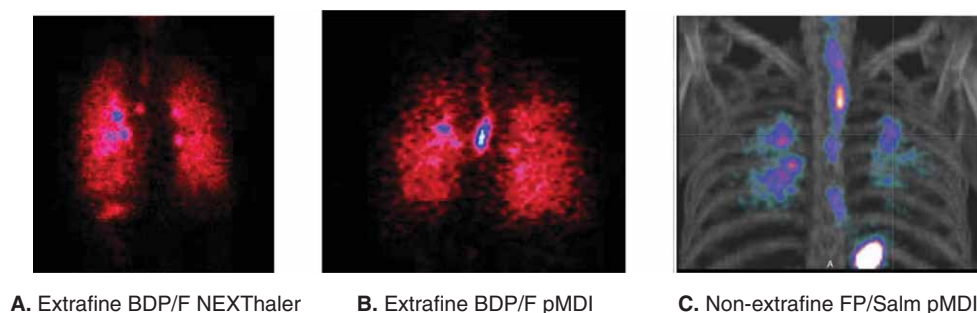
migration of large lactose carrier particles from the reservoir into the cyclone chamber of the device and the subsequent collision of particles against the chamber walls lead to the rapid release of a significant quantity of extrafine particle drug from the lactose carrier particles.

The ability of the extrafine fixed dose formulation of BDP/F to achieve peripheral and central lung deposition has been investigated in an open, single-dose, parallel group study involving 10 healthy volunteers and 9 patients with persistent asthma ($30\% \leq FEV_1 < 80\%$). The extrafine BDP/F combination was labeled with ^{99m}Tc , a γ -emitting isotope and subsequent γ camera imaging of the upper part of the body of subjects was taken [30]. The particle size distribution of BDP and F (both labeled and unlabelled) was assessed using appropriate *in vitro* methods (Andersen Cascade Impactor) [31] to verify that the radiolabeling did not modify the particle size distribution of the two drug components. In the *in vivo* patient study, the outline of the lung was ascertained in each subject using an 81m-Krypton-ventilation scan. The amount of activity in i) the entire lung region; ii) the extrathoracic region; and iii) the amount exhaled were determined by γ -scintigraphy after four inhalations of the radiolabeled BDP/F combination. Lung deposition was estimated to be 41 and 42% of the nominal dose in healthy volunteers and patients with asthma, respectively. This corresponds to 55 and 56% of the emitted dose in the healthy volunteers and patients with asthma, respectively. The approximate amount of drug exhaled ranged between 1.2 and 2.5% of the nominal dose confirming that when extrafine particles are inhaled only a very small fraction of the dose is exhaled. These results

demonstrated that a high amount of extrafine BDP/F administered via the NEXThaler® DPI was deposited in the lungs of patients with asthma. This outcome was similar to findings previously reported for extrafine BDP/F delivered via a pMDI (Figure 3). In contrast, the FP/Salm formulation, which emits particles with a higher MMAD, provided much lower lung deposition (Figure 3) [32].

3.2 Clinical efficacy

In a study investigating the clinical efficacy of extrafine BDP/F NEXThaler® DPI, 754 subjects with controlled asthma, already treated with a medium daily ICS dose or an ICS/LABA fixed combination, were randomized to receive extrafine BDP/F NEXThaler® DPI 100/6 μ g twice daily, extrafine BDP/F pMDI 100/6 μ g twice daily or nonextrafine BDP DPI 100 μ g twice daily [33]. The primary efficacy variable was the change from baseline in predose morning PEF during the 8-week treatment period. Statistical superiority of both extrafine BDP/F formulations versus nonextrafine BDP DPI was demonstrated for the primary efficacy variable, asthma control questionnaire score and percentage of rescue medication use-free days. No significant safety signals were observed. Extrafine BDP/F NEXThaler® DPI showed comparable results (predefined margin: -15 l/min) to extrafine BDP/F pMDI (mean difference: -1.84; 95% CI: -6.73 to 3.05) in terms of change from baseline in the average predose morning PEF. The results of this trial support the concept that the efficacy of treatment (in terms of disease control) with extrafine BDP/F pMDI can be obtained also using the NEXThaler® DPI device.



A. Extrafine BDP/F NEXThaler B. Extrafine BDP/F pMDI C. Non-extrafine FP/Salm pMDI

Figure 3. Scintigraphic lung deposition in asthmatic patients after inhalation of (A) extrafine BDP/F NEXThaler[®] DPI, (B) extrafine BDP/F pMDI and (C) nonextrafine FP/Salm pMDI. (A, B) Studies with extrafine BDP/F were conducted by radiolabeling the formulation with ^{99m}technetium prior to inhalation and images were taken with a planar γ camera. (C) In the study with FP/Salm, the formulation was radiolabeled with ^{99m}technetium prior to inhalation and images were taken with SPECT/CT.

A, B. From ref [32].

C. From ref [22].

Image reported in (C) is reprinted from ref [22] with permission from Elsevier.

BDP/F: Beclometasone dipropionate/formoterol; DPI: Dry powder inhaler; FP/Salm: Fluticasone propionate/salmeterol; pMDI: Pressurized metered dose inhaler; SPECT/CT: Single photon emission computed tomography/CT.

Another study compared the effects of extrafine BDP/F NEXThaler[®] DPI (one or two inhalations twice daily) and extrafine BDP/F pMDI (one or two inhalations twice daily) on lung function parameters in 69 patients with moderate to severe asthma receiving previous treatment with ICS (< 2000 μ g BDP or equivalent). The results showed a statistically and clinically significant dose-response for both formulations on the overall PEF change from baseline. In patients treated with extrafine BDP/F NEXThaler[®] DPI, the mean PEF change from baseline was significantly in favor of the 2 $\times$ 2 inhalations dose regimen versus 1 $\times$ 2 inhalations dose regimen as it was 10.5 + 47.4 l/min in subjects receiving two inhalations daily (111 patients) and 25.7 + 42.9 l/min in subjects receiving four inhalations daily (105 patients) ($p = 0.007$) [34].

3.3 Consistent full-dose release

Effective drug delivery from DPIs depends upon the formulation, the device and the characteristics of the patient's inhalation maneuver. This includes the inspiratory flow (which reacts with the resistance of a DPI to provide the energy input required to de-aggregate the powder formulation), the acceleration rate of the inhalation and inhalation volume, in order to achieve good dose delivery and deposition within the lungs. A study was undertaken to assess the capability of different diseased patients to generate a sufficient inspiratory flow to release the drug from the NEXThaler[®] DPI device [35]. The main objective of the study was to measure the inhalation profiles through the device achieved by adult asthmatic patients with varying levels of disease control. Patients were requested to make two separate inhalations through the NEXThaler[®] DPI in accordance with the patient information leaflet (PIL). The following inhalation variables were measured by acoustic monitoring: i) the inhalation flow at BAM firing; ii) peak inhalation flow (PIF); iii) initial acceleration

(rate of change of flow at inhalation start); and iv) the inhalation volume. In total, 40 adult (≥ 18 years) asthmatic patients were randomized, 20 with controlled stable disease and 20 with partly controlled or uncontrolled disease, according to GINA criteria. The study results are summarized in Figure 4. The BAM was activated by all the patients in the study, at an average flow of 35 l/min. Figure 4 also suggests that the peak inhalation flows were consistently higher than the flow required to trigger the BAM, implying that patients would be able to use the device effectively irrespective of their asthma control. The mean (SD) peak inhalation flow was 70.5 (28.2) l/min for the controlled patients and 58.8 (20.1) l/min for the uncontrolled or partially controlled patients. Furthermore, the initial acceleration, which is an additional critical factor in determining effective powder de-aggregation, was also consistent between inhalations and independent of the level of asthma control (Figure 4).

The Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products [36] recommends that DPIs show a consistent delivery performance across a specific range of inhalation flows/inspiratory effort that should be representative of the intended patient population. The *in vitro* dose emission characteristics of extrafine BDP/F NEXThaler[®] DPI 100/6 μ g have been measured at different flows with a 4 l inhalation volume and a suitable impactor, in this case the Next Generation Impactor. Similar *in vitro* dose emission characteristics have been measured for the fluticasone propionate/salmeterol (FP/Salm) combination of Seretide[®] Diskus (250/50 μ g) and for the budesonide/formoterol fumarate (BUD/F) combination in Symbicort[®] Turbuhaler (160/4.5 μ g). Figure 5 shows that the NEXThaler[®] DPI device was able to consistently release, for both BDP and formoterol, a high fine particle fraction (this is the fine particle dose expressed as a % of the delivered dose) for inhalation flows from 30 to 90 l/min. The

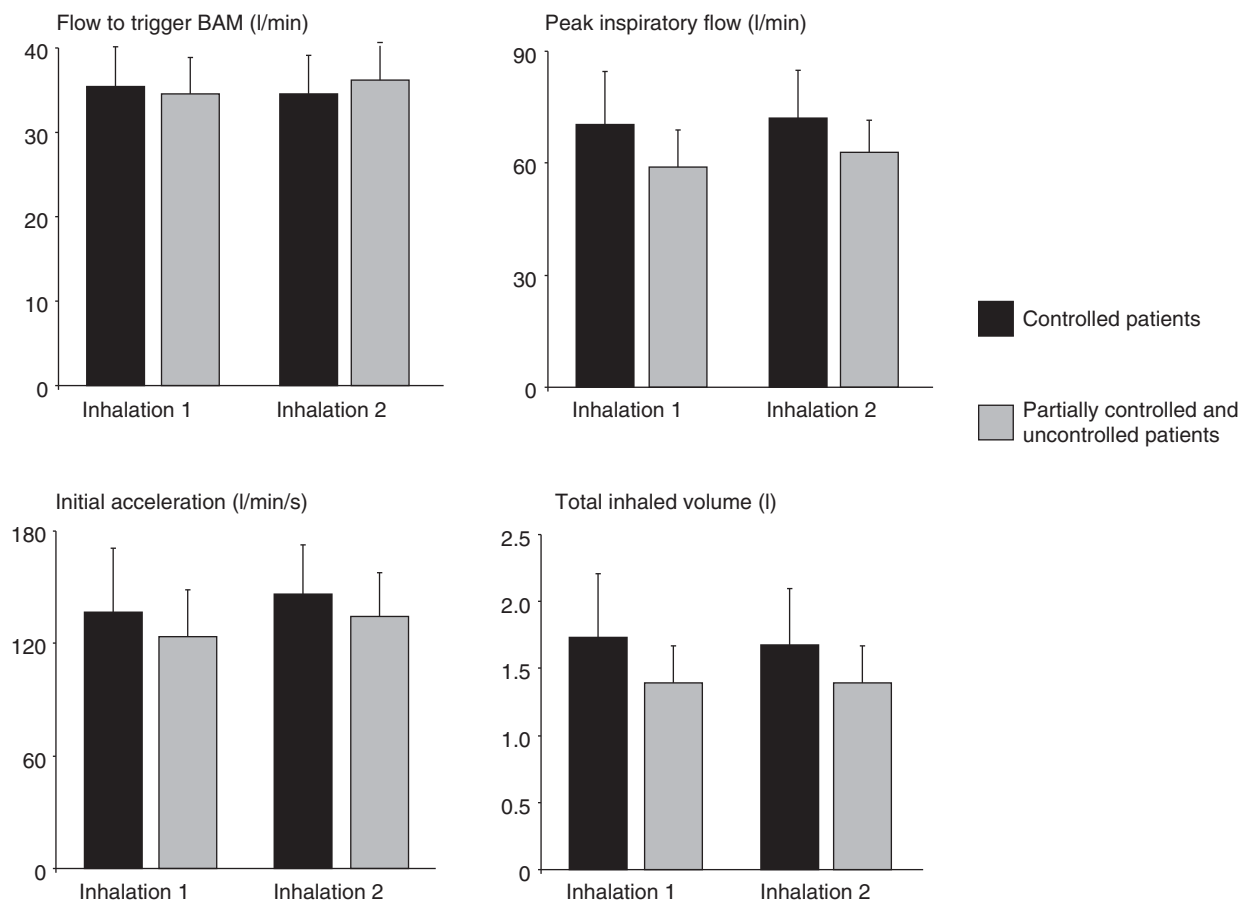


Figure 4. NEXThaler[®] DPI inhalation variables measured in patients with asthma and different level of asthma control. Data were recorded using a Sensohaler[®] acoustic monitoring technology that can monitor events and flow characteristics throughout patients' use of the device without disturbing the drug flow path. The study involved 20 patients with controlled asthma (C) and 20 patients with partially controlled or uncontrolled asthma (PC/C).

Data are reported as mean $\pm$ standard deviation [34].

results of this study, presented in Figure 5, also show that NEXThaler[®] DPI was able to generate a higher fine particle fraction in comparison to Seretide[®] Diskus at all the tested flow rates (30-40-60-90 l/min). Furthermore, the results showed that the fine particle fraction was not as flow-dependent as that of the Symbicort[®] Turbuhaler, which is a device more sensitive to changes at inhalation, flows between 30 and 60 l/min. The results in Figure 5 show that dose emission from the NEXThaler[®] DPI, like that from the Seretide[®] Diskus, is relatively independent of the inhalation flow used.

4. Improvement in the usability of the device

Table 1 provides a summary of the properties of the different DPIs containing a combination of ICS plus LABA that are currently available. The characteristics of an inhalation device and patient preference for a given device have both been shown to contribute to the level of asthma control [37]. Price *et al.* found that inhaler device selection can impact on

the clinical outcomes and the use of healthcare resources. Indeed, preference for a particular inhaler device may improve adherence to therapy, which is still reported to be suboptimal among asthma patients with rates ranging between 16 and 50 % [37].

A study has been completed to compare the usability of NEXThaler[®] DPI versus the other DPIs delivering inhaled ICS/LABA fixed combinations (Seretide[®] Diskus[®] and Symbicort[®] Turbuhaler). The study has explored patient preferences and the patients' perception of the characteristics of each device. Sixty-six adult patients with asthma and with no previous experience of using a DPI were included in a randomized cross-over comparison of the three devices [38]. The main measures of device usability by the patient were i) effectiveness: the number of steps failed for each device and the number of people who were unable to use the device successfully; ii) efficiency: the time it took patients to set up the device and the time to read the PIL; and iii) satisfaction: patient's preference. Inhaler technique was evaluated after reading the PIL leaflet.

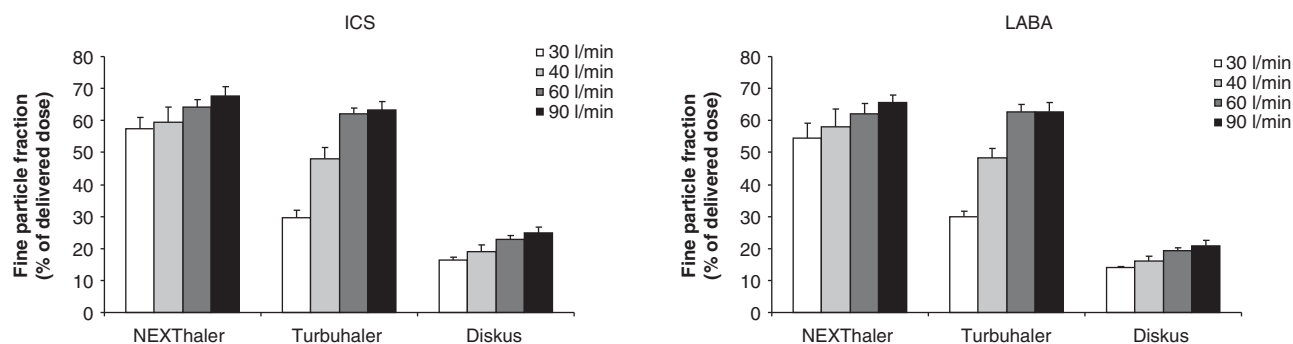


Figure 5. Fine particle fraction of ICS/LABA fixed combination DPIs tested at different inspiratory flow rates. The graph compares fine particle fraction, that is, particles < 5 μm (expressed as % of delivered dose) of different DPIs tested at several inspiratory flow rates. Measurements were obtained by using a next generation impactor following the procedure detailed in the European Pharmacopoeia (inhalation volume of 4 L).

Data are reported as mean of six repetitions (three for each of two different devices) $\pm$ standard deviation.

DPI: Dry powder inhaler; ICS/LABA: Inhaled corticosteroid/long-acting β_2 -agonist.

Table 1. Comparison of main characteristics of dry powder inhalers containing ICS/LABA fixed combinations.

	NEXThaler [®] DPI	Seretide [®] Diskus	Symbicort [®] Turbuhaler
Molecules	Beclometasone dipropionate/formoterol fumarate (BDP/F)	Fluticasone propionate/salmeterol (FP/Salm)	Budesonide/formoterol fumarate (BUD/F)
MMAD	1.4/1.5 μm (BDP/F)	3.6/3.5 μm (FP/Salm) ^{***}	3.1/3.3 μm (BUD/F) ^{***}
Extrafine delivery	yes	no	no
Inhalation steps	3	4	5
	Open	Open	Open
	Inhale	Load	Turn the grip in one direction
	Close	Inhale	Turn the grip in the other direction
		Close	Inhale
			Close
Feedback system	3	2	1 [†]
	full dose feedback system (click)	dose counter*	dose indicator*
	dose counter*	distinctive taste (lactose)	
	distinctive taste (lactose)		
Lung deposition [¶]	56% of emitted dose [#]	16% of inhaled dose ^{**}	22% of metered dose ^{††§}
Flow independency ^{##}	yes	yes	no
Patients making critical errors when using device	29% ^{§§}	35 – 41% ^{§§-¶¶}	44-53% ^{§§-¶¶}
Patients satisfied with ease of use ^{§§}	74.2%	16.7%	9.1%

*A dose counter counts each individual dose and displays the exact number of doses remaining in the inhaler; a dose indicator gives a graphical or numerical indication of the number of doses remaining in the inhaler (e.g., a graduated colored band or numerals in intervals of ten) but does not give a precise measurement.

[†]The formulation BUD/F in Symbicort[®] Turbuhaler contains lactose but this is not indicated in the SmPC as a possible feedback for the patient.

[§]No data are available for Symbicort[®] Turbuhaler lung deposition; data are referred to budesonide Turbuhaler

[¶]Data obtained in patients with asthma

[#]From ref [30].

^{**}From ref [22].

^{††}From ref [23].

^{§§}From ref [38].

^{¶¶}From ref [20].

^{##}Authors' personal observation.

^{***}From ref [25].

The NEXThaler[®] DPI was found to be superior to the other two DPIs in terms of the number of device use failures, which were significantly less ($p < 0.001$), time to set up, which was significantly quicker ($p < 0.001$) and time to read the PIL, which was significantly faster ($p < 0.001$). Additionally, the proportion of participants who completed a successful inhalation without any errors at all was significantly higher for NEXThaler[®] DPI than for Seretide[®] Diskus[®] and Symbicort[®] Turbuhaler ($p < 0.001$). Patients rated the NEXThaler[®] DPI as the easiest to use and the most preferred inhaler ($p < 0.001$). In this study, 97% of the patients who found NEXThaler[®] DPI as the easiest to use also preferred to own it as well, lending support that ease of use by the patient and patient preference are related. This would suggest that when the inhaler device is easier to use and provides accurate feedback or when a dose is successfully delivered, patients are more likely to use it correctly in accordance with their treatment program [39].

5. Conclusions

The NEXThaler[®] DPI has been specifically designed to meet the requirements of patients with persistent asthma with a regular daily treatment that can allow maximum efficacy in both the large and small airways. The available information confirms that the NEXThaler[®] DPI addresses these needs as: i) the open-inhale-close inhalation sequence makes NEXThaler[®] DPI easy to be used by patients every day; ii) the triple full-dose feedback system linked to the BAM activation permits that the full therapeutic dose is taken by the patients at each inhalation; and iii) the extrafine formulation allows the drug particles to be delivered throughout the entire bronchial tree.

6. Expert opinion

Despite the availability of many pharmacological interventions for the treatment of asthma, many patients fail to manage their asthma properly. Scientific literature has strongly suggested that optimizing device characteristics can be important to increase adherence to asthma therapy. Inhalers are the main vehicles for the effective administration of asthma medication as they permit a deep lung deposition of the drug and reduce the systemic delivery, thus reducing possible systemic side effects. pMDIs and DPIs are the devices most commonly used for drug delivery in the treatment of asthma and recent research has shown that the most important features for inhaler selection are ease of use, preference and consistent dose delivery.

In order to provide healthcare providers and patients with an alternative drug delivery system for BDP/F, NEXThaler[®] DPI has been developed and designed to address some of the critical issues associated with the currently available DPIs and it is particularly suitable for patients with persistent asthma who require regular treatment. NEXThaler[®] DPI is a breath-actuated multidose DPI that contains a fixed combination of BDP/F delivered in extrafine particles. The extrafine

formulation provides high lung deposition and enables drug particles to reach both large and small airways, thus optimizing treatment of the underlying inflammatory and remodeling process that, in asthma, takes place throughout the entire respiratory tree. The device has been designed to deliver a consistent dose at inhalation flow rates that are achieved by stable and uncontrolled adult patients with asthma.

Preclinical and clinical studies have shown that neither age nor the patients' airway disease affects the capability of asthma patients to perform adequate inspiratory flows to trigger the device. Data showed that the inhalation flows triggering the activation of the BAM were similar between controlled and uncontrolled asthmatics, indicating that the effective use of the device is independent of the level of asthma control. Furthermore, the initial acceleration of an inhalation maneuver, which is an additional critical factor in determining effective powder de-aggregation, was also consistent between inhalations and independent of the level of asthma control.

It is well known that many asthma patients do not use the correct technique when using their inhalers. All DPIs require the patient to prepare the device prior to inhalation, and patients who do not perform procedures correctly are more likely to receive no dose, or a greatly reduced dose, irrespective of the inhalation maneuver. A usability study aimed at comparing the characteristics of the NEXThaler[®] DPI with the two other combination DPIs that are on the market showed that the majority of patients found the NEXThaler[®] DPI as the easiest to use. This means that when the inhaler device is easier to use and provides accurate feedback, patients are more likely to use it correctly, thus the patient's level of adherence to the treatment will be increased. The DPI-formulated fixed combination of extrafine BDP/F might therefore offer significant advantages in the treatment of asthma due to its drug delivery properties, lung deposition profile and dose regimen. The scientific evidence demonstrates that NEXThaler[®] DPI is an effective and well-tolerated delivery device for the treatment of patients with persistent asthma who need a regular treatment and prefer the use of DPIs. The three-step operation of open, inhale and close explains why patients find the device easy to use and fits the recommendation to prescribe each patient an inhaler that they can and will use.

Declaration of interest

M. Corradi has received honoraria for presentations and consultant agreements from Chiesi Farmaceutici SpA. Dr Borja Cosio has received sponsorship for research studies, consultant agreements and honoraria for presentations from several pharmaceutical companies that market inhaled products including Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis and Menarini. Renault Louis has unrestricted research grants from GlaxoSmithKline, Novartis, AstraZeneca and Chiesi. Dr Louis has received speaker or board honoraria from GlaxoSmithKline, AstraZeneca, Chiesi and MundiPharma. Michal Pirozynski has received honoraria for

presentations and is on the advisory board for several companies including AstraZeneca (Greece, Poland, Bulgaria), Boehringer Ingelheim (Greece), Chiesi Hellas, GlaxoSmithKline (Greece, Denmark), Elpen, MSD, Novartis Hellas, UCB and Takeda. Monica Spinola is an employee of Chiesi Farmaceutici SpA. Henry Chrystyn has received sponsorship to carry out research studies together with some consultant agreements and honoraria for presentations from several companies that market inhaled products. These include Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Innovata Biomed, Meda, MundiPharma, Orion, Teva, Truddell Medical International, UCB and Zentiva. Research sponsorship has also

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