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REVIEW

Optimizing Respiratory Care with NEXThaler: Bridging Technology and Treatment

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Abstract: Inhaled therapy is central in the management of asthma and chronic obstructive pulmonary disease, with inhaler device selection significantly influencing treatment efficacy and patient adherence. NEXThaler is a breath-actuated dry powder inhaler (DPI) designed to deliver extrafine formulations of inhaled corticosteroids (ICS) and bronchodilators, ensuring consistent drug deposition across both central and peripheral airways. This review provides a clinically oriented overview of inhaler technologies, focusing on the design features and clinical performance of this breath-actuated DPI. Notably, this narrative review is based on a comprehensive analysis of peer-reviewed clinical and preclinical studies on the NEXThaler DPI. Most evidence presented is derived from non-comparative studies, modeling approaches, or sponsor-supported trials. Key features of the NEXThaler DPI include a breath-actuated mechanism, flow-independent dosing, a dose counter and a triple feedback system that enhances correct usage, and a simplified open-inhale-close mechanism. The delivery of extrafine particles (<2 µm) facilitates deeper lung penetration, improving small airway targeting and potentially allowing for lower ICS doses with maintained efficacy. Lung deposition studies demonstrate superior peripheral distribution and consistent dosing across varying inspiratory flow rates. Clinical trials and real-world studies confirm the efficacy and safety of bronchodilators and ICS combinations delivered via the NEXThaler DPI in both asthma and chronic obstructive pulmonary disease populations, showing noninferiority to pressurized metered-dose inhalers and improved outcomes in lung function, symptom control, and adherence. The device's usability and patient satisfaction further support its role in respiratory care. Additionally, its propellant-free design contributes to reducing the environmental impact of inhaler therapy. Overall, thanks to its technological innovations, the NEXThaler DPI represents a clinically validated and patient-friendly option for the delivery of inhaled therapies in chronic respiratory diseases.

Keywords: NEXThaler, dry powder inhaler, extrafine formulation, asthma, chronic obstructive pulmonary disease

Introduction

Inhaled therapy is the cornerstone of asthma and chronic obstructive pulmonary disease (COPD) management, ensuring targeted drug delivery to the lungs while minimizing systemic effects. These chronic respiratory conditions require maintenance treatment with inhaled corticosteroids (ICS) and/or bronchodilators, such as long-acting β_2-agonists (LABA) and long-acting muscarinic antagonists (LAMA), to achieve symptom control and prevent exacerbations.[1]

A range of inhalation devices is available for drug delivery, including pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), nebulizers and Soft Mist™ inhalers. Each device has distinct characteristics that can influence ease of use, patient compliance, and drug deposition, making device selection crucial to meet individual patient needs and abilities and optimize treatment outcomes.[1]

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NEXThaler is a breath-activated DPI with the capability to deliver drugs in an extrafine formulation, ensuring a consistent therapeutic dose in all administrations. Extrafine formulations have been defined as aerosols with a mass median aerodynamic diameter (MMAD) <2 μm.[2] Clinical studies have confirmed the efficacy and safety of different therapies delivered via this DPI in managing asthma and COPD. The dual-combination therapy, beclomethasone dipropionate/formoterol fumarate (BDP/FF) delivered via this DPI, is approved for both asthma and COPD, while the triple-combination therapy, which includes glycopyrronium (BDP/FF/G), is currently marketed for COPD and under development for asthma. Thanks to its advanced technology, this DPI enables the efficient deposition of extrafine particles throughout both large and small airways, enhancing disease control and reducing coordination challenges associated with inhaler use.[3–5]

The use of NEXThaler for asthma and COPD is in line with current international GINA and GOLD guidelines.[6,7] Specifically, NEXThaler BDP/FF is an ICS/LABA option for maintenance therapy for asthma patients from Step 3 onward and, where approved, for MART strategies, in line with GINA recommendations.[6] In COPD, this formulation is also recommended for selected patients with an exacerbation history and an eosinophilic profile, where ICS use is justified.[7] The extrafine single-inhaler triple therapy BDP/FF/G delivered via NEXThaler is also indicated for COPD patients with persistent symptoms and/or exacerbations despite dual therapy, particularly in those with an eosinophilic phenotype.[7]

More broadly, both GINA and GOLD emphasize that effective asthma and COPD management depend not only on pharmacological treatment but also on appropriate inhaler selection and reliable drug delivery, particularly in the context of small airway involvement.[6,7] In this context, the NEXThaler DPI incorporates design features intended to support consistent drug delivery and correct handling, aligning with guideline recommendations on individualized device selection based on inspiratory flow capability, ease of use, and error minimization.

This manuscript provides a clinically oriented review of inhaler devices used in the treatment of asthma and COPD, with particular emphasis on the NEXThaler DPI. Key device characteristics, including ease of use, dose consistency, and error minimization, are examined in comparison with other commonly used pMDIs and DPIs. Available clinical data on efficacy, safety, and patient-reported outcomes are discussed to contextualize the use of this DPI within current inhalation therapy options. Special attention is given to its performance in real-world adherence and patient handling, as well as its relevance in guideline-based respiratory care. Notably, an earlier review by Corradi et al examined the initial development and features of the NEXThaler device, highlighting its role in the management of persistent asthma.[8] The present review builds on those findings by incorporating more recent clinical, technical, and real-world evidence.

Design Features and Mechanism of Action

As compared to other devices, the NEXThaler DPI is designed with innovative feedback systems and unique features that enhance patient control over the inhalation process, aiming at improving treatment efficacy and, ultimately, disease control. The device was specifically developed to address common challenges associated with DPIs, such as the dependence of drug particle size on inhalation flow rate, the potential loss of the metered dose if the patient exhales into the device before inhaling or does not use it properly.[9–11] The key design features are summarized in Figure 1.

Breath-Actuated Mechanism

A key feature of the NEXThaler DPI is its breath-actuated mechanism (BAM), which ensures that medication is only released once the patient's inhalation flow reaches a sufficient level to detach drug particles from their carriers. This mechanical feature consists of a spring-supported dose release protector that is activated when the inhalation force exceeds the spring's resistance. The average triggering threshold is approximately 35.0 L/min, with a reported activation range of 16.3 to 52.3 L/min.[12] This mechanism minimizes the release of larger particles (>5 μm), enhances the therapeutic fine particle fraction, and promotes drug deposition in the lower respiratory tract.[13]

The impact of BAM on the aerodynamic properties of emitted drug particles has been evaluated both in vivo and in silico under varying inhalation conditions. Farkas et al compared the size distribution and deposition fractions of particles emitted by a DPI with and without BAM at three inhalation flow rates: low, moderate and high.[13] The BAM system significantly increased the fine particle fraction of both BDP and FF, with the steroid fraction rising from 24–30% to 47–51% and the bronchodilator fraction increasing from 25–34% to 52–55%. Moreover, predicted upper airway drug

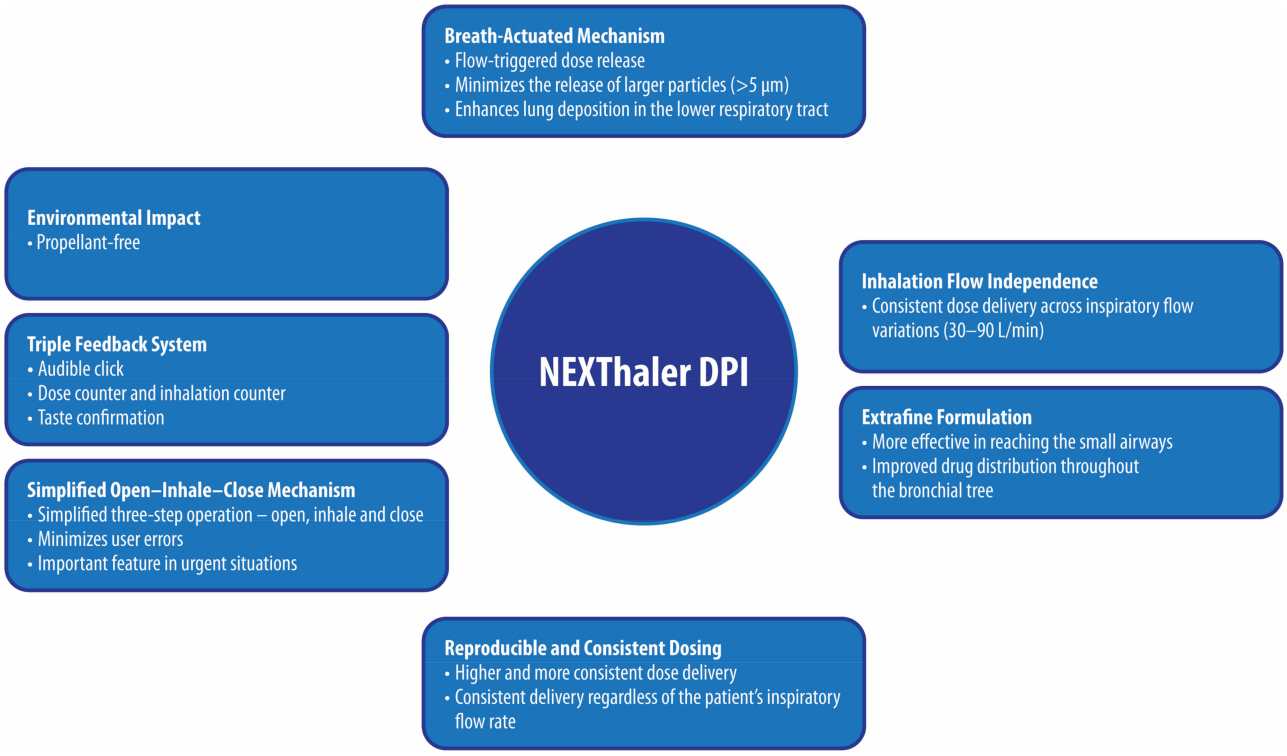

Figure 1 Key features of the NEXThaler® dry powder inhaler (DPI). The device incorporates a breath-actuated, flow-triggered dose-release mechanism that limits emission of larger particles (>5 µm) and promotes deposition in the lower respiratory tract. It provides consistent and reproducible dosing across a range of inspiratory flow rates (30–90 L/min), supported by an extrafine formulation to improve small-airway delivery and bronchial distribution. Additional usability features include a simplified open–inhale–close operation to reduce handling errors, a triple feedback system (audible click, dose/inhalation counter, and taste confirmation), and a propellant-free design with reduced environmental impact.

deposition decreased, while lung deposition increased. At the moderate flow rate, the predicted upper airway doses of the steroid and bronchodilator decreased from approximately 60% to 35–40% for both drug components, whereas lung deposition increased from about 20–35% (steroid) and from 22% to 38% (bronchodilator). Under high flow conditions, lung deposition further improved, rising from 25% to 40% for the steroid and from 29% to 47% for the bronchodilator. Even at the lowest inhalation flow rate, BAM reduced upper airway deposition by nearly 50%, while lung deposition remained comparable to DPI without BAM for both drug components.[13]

Inhalation Flow Independence

Another key feature of the NEXThaler DPI is that its performance remains unaffected by inhalation flow rate and volume, ensuring consistent drug delivery with extrafine particle mass, regardless of the patient's inhalation strength or lung capacity.[14,15] This was initially highlighted by Buttini et al, who found that the NEXThaler DPI delivering the double formulation delivered a stable dose of extrafine formulations independent of the applied flow rate (*t*-test, $p > 0.05$ within the 30–90 L/min range) or variations in inhalation volume (±15% of the specification value for 2 L vs 4 L).[14]

A clinical study further confirmed this DPI is reliable and reproducible dosing across healthy individuals, asthma patients, and those with COPD at different disease stages. Notably, this DPI in the dual-combination formulation achieved high lung deposition (ranging from 54.9% to 56.2% of the emitted BDP dose), a negligible exhaled fraction (1.6% to 3.3%), and low extra-thoracic deposition (41.8% to 43.2%) across all three study groups.[15]

The NEXThaler DPI is designed to function effectively at a minimal and optimal inspiratory flow rate of 35 L/min, which is lower than that required by many other DPIs.[16] Moreover, the dose is emitted over a very short duration (approximately 0.2–0.3 seconds), which minimizes variability in airflow during release and contributes to consistent drug delivery across different inhalation patterns.[17] Clinical evidence supports this, showing that patients with partly

controlled or uncontrolled asthma, as well as those with varying degrees of COPD severity, are able to generate sufficient inspiratory flow for the DPI actuation.[12]

The ability of this DPI to ensure consistent dose delivery regardless of inspiratory flow variations, along with its superior aerosolization performance, was also demonstrated by Buttini et al.[14] In their aerodynamic assessment of drug deposition across various inspiratory flow rates, the DPI in the dual-combination formulation maintained stable dose delivery for both drugs in its formulation, unlike other devices, whose performance was more dependent on the applied flow rate. Furthermore, compared to other tested devices, the NEXThaler DPI was the only one capable of delivering approximately 50% of extrafine particles relative to the total delivered dose, underscoring its efficiency in targeting the small airways.[14]

Extrafine Formulation

The ability of the NEXThaler DPI to deliver an extrafine formulation (particles with an MMAD of less than 2 μm^2) plays a key role in optimizing drug deposition across both central and peripheral airways.[14,18,19] Due to their smaller aerodynamic diameter, extrafine particles can more effectively reach the small airways, supporting a more homogeneous distribution of the drugs throughout the bronchial tree.[20,21] The implications of this formulation strategy – on deposition patterns, lung function parameters, and clinical outcomes – have been explored in multiple clinical, in silico and real-world studies, and are detailed in the subsequent sections.[18,19,22,23]

Reproducible and Consistent Dosing

Beyond delivering an extrafine formulation that enhances peripheral drug deposition, the technological innovations of the NEXThaler DPI allow for higher and more consistent dose delivery, regardless of the patient's inspiratory flow rate. Notably, different breath-actuated DPIs have varying minimal and optimal inspiratory flow requirements – the flow needed to overcome the internal resistance of the device and effectively release the medication – typically ranging from 30 to 60 L/min. When selecting an appropriate inhaler, it is essential to assess these device-specific flow requirements in relation to the patient's peak inspiratory flow rate, defined as the maximum inspiratory flow achieved during a forced inspiratory maneuver. Peak inspiratory flow rate may be significantly reduced in certain patient groups, particularly females and individuals with COPD, potentially resulting in suboptimal DPI performance.[16]

In terms of flow resistance, NEXThaler DPI is classified as medium resistance, which helps modulate inhalation flow and optimize particle deagglomeration. Compared with low-resistance DPIs, that require higher inspiratory flow for optimal performance, and high-resistance DPIs, that may be challenging for patients with severe airflow limitation, NEXThaler offers a balance between ease of actuation and consistent aerosol delivery.[12,14,16]

Dose-Counter and Triple Feedback System

An additional feature that supports both accurate drug administration and environmental sustainability is the integration of a dose counter. This feature enables patients to monitor their medication use while helping reduce medicine wastage, healthcare costs, and environmental impact. A recent study analyzing 2614 used pMDIs found that the proportion of inhalers returned empty was significantly higher for those equipped with dose counters compared to those without (51.3% vs. 25.1%; $p < 0.0001$). Conversely, the rate of underused inhalers was markedly lower in the group with dose counters (5.2% vs. 33.2%; $p < 0.0001$). Additionally, over half of patients using inhalers without a dose counter (55.2%) reported being uncertain about when their device was empty.[24]

The NEXThaler DPI also incorporates a triple feedback system that provides real-time confirmation of successful inhalation through (1) an audible "click of confidence" upon BAM activation; (2) a unit dose counter, which also functions as an inhalation counter; and (3) a lactose carrier whose taste confirms dose delivery.[25] Additionally, the device includes a dose protector, which ensures that the extrafine formulation is released exclusively during inhalation, minimizing the risk of drug loss due to accidental handling or improper use.[11] Finally, the NEXThaler DPI contains a full month's supply of medication, eliminating the need for manual capsule loading and reducing errors associated with single-dose, capsule-based DPIs.[26]

Simplified Open–Inhale–Close Mechanism

Correct use of DPIs is critical to ensure effective drug delivery and disease management. However, many patients misuse DPIs due to limited education, physical limitations, or improper handling. Commonly reported errors include incorrect dose metering, inadequate inhaler positioning, failure to exhale before activation, lack of breath-hold after inhalation, not verifying whether the inhaler is empty, accidental double activation, and using the device in inappropriate postures (eg, semi-lying or supine).[11]

To address these challenges, the NEXThaler DPI employs a simplified three-step operation – open, inhale, and close – which minimizes the number of required maneuvers and increases the likelihood of proper use.[11] This design eliminates the need for hand–breath coordination, a common limitation of pMDIs that require synchronization between actuation and inhalation, often affecting treatment adherence and clinical outcomes.[26] Notably, this feature becomes especially important in urgent situations such as bronchospasm attacks, where the NEXThaler DPI can be a viable alternative to pMDIs for reliever therapy.[27]

Propellant-Free

Beyond its technological features, the NEXThaler DPI offers a propellant-free alternative to pMDIs, promoting environmentally sustainable asthma and COPD management.[13,26] Hydrofluorocarbon propellants used in pMDIs contribute approximately 0.03% of global annual greenhouse gas emissions.[28] In contrast, DPIs and soft mist inhalers produce significantly lower emissions (~8 g CO_2e per actuation) compared to pMDIs (~100 g CO_2e per actuation).[29] Choosing DPI products for patients able to use them in case of suboptimal control may therefore reduce the environmental impact of inhaler therapy without compromising clinical efficacy.[30]

Lung Deposition Studies

The technological innovations of the NEXThaler DPI, coupled with its extrafine formulation, contribute to enhanced peripheral deposition, consistent dose delivery across a range of inspiratory flow rates, and superior overall drug deposition compared to DPIs delivering non-extrafine formulations.[14,18,19] Evidence from the literature has demonstrated that formulations containing extrafine particles are more effective in reaching the small airways, allowing for improved drug distribution throughout the bronchial tree (Table 1).[20,21,31] To contextualize the performance of the NEXThaler DPI, the following section presents comparative data from studies involving DPI and pMDI formulations, as extrafine BDP/FF and BDP/FF/G have been evaluated across both inhaler types. This is followed by a dedicated section focusing on studies specifically involving the NEXThaler DPI.

Studies with pMDI

In a pooled analysis of 18 studies evaluating DPIs and pMDIs delivering particles of varying sizes, Jabbal et al showed that lung deposition increased as the MMAD of the particles decreased, while the exhaled fraction remained consistently low regardless of particle size[21] The favorable lung deposition profile of extrafine triple-combination BDP/FF/G was further confirmed by Usmani et al, who reported that approximately 22–25% of the inhaled dose was deposited within the lungs. Notably, half of the deposited drug reached the peripheral lung regions, resulting in a central-to-peripheral deposition ratio of approximately 1. Importantly, deposition patterns were similar between healthy individuals and patients with asthma, suggesting that disease characteristics do not substantially affect the distribution of extrafine particles within the lungs.[32]

Thanks to their enhanced drug deposition in the small airways, extrafine formulations potentially allow for lower effective doses of ICS.[22] A systematic review and meta-analysis of real-life studies comparing extrafine- and fine-particle ICSs showed that extrafine formulations were associated with better asthma control and fewer exacerbations at significantly lower prescribed ICS doses. This dose-sparing effect is clinically relevant, as higher ICS doses are potentially linked to increased systemic adverse effects; thus, extrafine formulations may offer a safer therapeutic profile by reducing overall ICS exposure while maintaining asthma control.[22]

The extrafine formulation also showed superior lung deposition compared to non-extrafine formulations in multiple studies.[18,19,23] In a functional respiratory imaging study, Usmani et al conducted an in-silico comparison of lung deposition between extrafine BDP/FF/G and the non-extrafine combination of fluticasone furoate/vilanterol/umeclidinium (FluF/VI/UMEC) in subjects with moderate-to-severe COPD. The extrafine formulation was associated with higher ICS deposition, greater peripheral deposition of all three drug components, and a more favorable peripheral-to-central deposition ratio.[23]

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Table 1 Lung Deposition Studies of Extrafine Formulations

Study	Design/Method	Type of Inhalers	Key Results
Jabbal et al 2017[21]	Pooled analysis of 18 studies in healthy subjects and asthma patients	DPIs and pMDIs with varying MMAD	Lung deposition increased as MMAD decreased (MMAD ~1 μm yielded >50% lung deposition); exhaled fraction remained unchanged
Usmani et al 2022[32]	Gamma scintigraphy in 10 healthy subjects and nine asthma patients	BDP/FF/G pMDI	Results for healthy vs asthmatic subjects: • Mean intrapulmonary deposition: 22.7 ± 9.2% vs. 25.5 ± 6.8%; p = 0.47 • Fraction deposited in lung: 0.52 ± 0.07 vs. 0.49 ± 0.06 • C/P ratios: 0.94 ± 0.25 vs 1.06 ± 0.25
Sonnappa et al 2018[22]	Real-world systematic review and meta-analysis (seven studies, 33,453 subjects)	Extrafine vs fine ICS	Results for extrafine vs fine ICS: • OR of achieving asthma control: 13.4 (95% CI: 1.22–1.46; p < 0.0001) • Exacerbation rate ratios: 0.84 (95% CI, 0.73–0.97; p < 0.0001) • ICS dose weighted mean difference: −170 μg (95% CI, −222 to −118 μg)
Usmani et al 2020[23]	In silico functional respiratory imaging	BDP/FF/GB (extrafine) vs FluF/VI/UMEC (non-extrafine)	Results for BDP/FF/GB vs FluF/VI/UMEC; • Higher ICS deposition • Higher peripheral deposition of all three components • Greater P/C ratio: BDP = 0.48 ± 0.13, FF = 0.48 ± 0.13, GB = 0.49 ± 0.13 vs. FluF = 1.96 ± 0.84, VI = 0.97 ± 0.34, UMEC = 1.20 ± 0.48
Watz et al 2021[18]	Functional respiratory imaging study (flow rate 30–60 L/min)	NEXThaler DPI (BDP/FF extrafine) vs DPI (FluF/VI) vs. DPI (BUD/FF)	• Intrathoracic deposition of ICS/LABA is significantly higher with NEXThaler DPI vs FluF/VI DPI • Peripheral deposition at 60 L/min was higher for NEXThaler DPI vs. FluF/VI DPI (ICS 24.7% vs. 5.0%; LABA 25.3% vs. 13.0%; both p < 0.001) • C/P ratio lower with NEXThaler DPI vs. FluF/VI DPI (ICS: 0.63 vs. 1.63; LABA: 0.63 vs. 0.99). • BUD/FF DPI performance declined at lower flow
Horváth et al 2025[19]	Inhalation profiling in 113 COPD patients	NEXThaler DPI vs FluF/VI DPI	• Higher lung dose for NEXThaler DPI vs. FluF/VI DPI in 85% of patients • Bronchiolar-to-bronchial deposition ratio: 5.0 (NEXThaler DPI) vs. 2.6 (FLuF/VI DPI)
Buttini et al 2016[14]	In vitro aerodynamic performance	NEXThaler DPI (BDP/FF extrafine) vs DPI (FP/SAL) vs. DPI (BUD/FF)	• NEXThaler DPI and FP/SAL DPI: consistent dose delivery regardless of flow rate • BUD/FF DPI: significant dose reduction at <60 L/min • NEXThaler DPI delivered ~50% extrafine particles relative to the delivered dose

De Backer et al 2010[20]	Gamma scintigraphy in healthy, asthmatic, and COPD patients (n = 8 per group)	BDP/FF extrafine pMDI	• Lung deposition: 34.1 ± 9.3% (healthy), 30.9 ± 8.9% (asthma), 33.1 ± 8.9% (COPD) • Extrathoracic deposition: 53.48 ± 8.95 vs 57.64 ± 9.92% and 54.98 ± 7.01% • C/P ratios: 1.42 ± 0.32 vs 1.96 ± 0.43 vs 1.94 ± 0.69
Virchow et al, 2018[10]	Scintigraphic deposition study in healthy subjects and patients with asthma or COPD (n = 28)	NEXThaler DPI (BDP/FF extrafine)	• Mean lung deposition ~55% of emitted dose • Low exhaled fraction (1.6–3.3%) • Consistent C/P deposition across groups
Kupczyk et al, 2025[31]	In silico deposition modelling using real-life inhalation profiles (n = 104)	NEXThaler (BDP/FF extrafine) vs pMDI (BDP/FF extrafine) vs. DPI (FP/SAL non extrafine) vs. DPI (BUD/FF non extrafine)	• High lung deposition (>50%) with NEXThaler and pMDI • Performance comparable or superior to other non-extrafine DPIs • Robust delivery across a range of inspiratory profiles

Abbreviations: BDP, Beclometasone dipropionate; BUD, Budesonide; C/P ratio, Central-to-peripheral deposition ratio; DPI, Dry powder inhaler; FF, Formoterol fumarate; FluF, Fluticasone furoate; FP, Fluticasone propionate; GB, Glycopyrronium bromide; ICS, Inhaled corticosteroid; LABA, Long-acting β_2-agonist; LAMA, Long-acting muscarinic antagonist; MMAD, Mass median aerodynamic diameter; OR, Odds ratio; P/C ratio, Peripheral-to-central deposition ratio; pMDI, Pressurized metered-dose inhaler; RR, Rate ratio; SAL, Salmeterol xinafoate; UMEC, Umeclidinium bromide; VI, Vilanterol.

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Studies with the NEXThaler DPI

In a functional respiratory imaging study, Watz et al investigated the lung deposition patterns of three double-combination (ICS/LABA) DPIs across different mean inspiratory flow rates. The study found that the NEXThaler DPI achieved significantly higher intrathoracic deposition of both ICS and LABA compared to another DPI, particularly at lower flow rates. A greater proportion of the drug reached the peripheral lung (24.7% vs. 5% for ICS and 25.3% vs. 13.0% for LABA; $p < 0.001$). Moreover, the central-to-peripheral deposition ratio was lower with the NEXThaler DPI (ICS: 0.63 vs. 1.63; LABA: 0.63 vs. 0.99), indicating superior peripheral targeting and a more homogeneous distribution throughout the airways. The NEXThaler DPI also demonstrated greater consistency in drug deposition across varying inspiratory flow rates when compared to another DPI, whose deposition efficiency was more flow-dependent.[18]

Additional evidence supporting the ability of the NEXThaler DPI to deliver consistent lung drug deposition regardless of a patient's inhalation profile was provided by Horváth et al using data from 113 COPD patients with varying inhalation characteristics and disease severities, the study compared lung deposition between the NEXThaler DPI in the dual combination formulation and a DPI with a non-extrafine formulation. The NEXThaler DPI achieved a higher lung dose of the two formulations in approximately 85% of patients, with a significantly greater bronchiolar-to-bronchial deposition ratio (5.0 vs. 2.6), indicating superior drug delivery to the small airways. While this bronchiolar-to-bronchial ratio differs from the central-to-peripheral (C/P) deposition ratio reported by Walz et al,[18] the values observed in both studies were notably similar. Another key finding was that patients with exacerbations had lower overall lung deposition compared to non-exacerbating patients; however, the NEXThaler DPI consistently outperformed the other in both groups (28.8 ± 5.8% vs. 23.7 ± 3.8% in exacerbating patients and 33.7 ± 6.1% vs. 24.9 ± 3.9% in non-exacerbating patients).[19]

Notably, in addition to particle size formulation and inhalation flow, patient technique – particularly breath-hold duration – plays a critical role in optimizing lung deposition. In silico modelling data suggest that extending breath-hold duration to 10–15 seconds significantly increases deposition of extrafine particles in the distal airways through gravitational settling, especially with formulations, such as NEXThaler, that generate a high proportion of extrafine particles.[19]

Clinical Efficacy

Asthma Management

Clinical trials have demonstrated that the NEXThaler DPI is an effective and well-tolerated inhaler to deliver bronchodilators and ICS combinations for achieving disease control in patients requiring regular asthma treatment. It has shown noninferiority to pMDIs containing the same drug, achieving comparable improvements in peak expiratory flow (PEF), lung function, symptom control, and reduced reliance on rescue medication.[5,26] The main results on clinical studies on bronchodilators and ICS combinations delivered via the NEXThaler DPI for the treatment of asthma are reported in Table 2.

Table 2 Summary of Clinical Studies Evaluating the Efficacy of BDP/FF and BDP/FF/G Delivered via NEXThaler DPI in Asthma and COPD

Study	Design/Population	Intervention/Comparator	Key Findings
Asthma			
Kanniess et al 2015[5]	8-week RCT; n = 755 with controlled asthma	BDP/FF 100/6 µg bid NEXThaler DPI vs pMDI vs. BDP 100 µg bid (non-extrafine) DPI	NEXThaler DPI non-inferior to pMDI (Δ pre-dose morning PEF −1.84 L/min; noninferiority margin −15 L/min) Similar FEV1 and FVC, rescue free-days, ACQ-7, and symptom and control-free days
Zheng et al 2024[26]	12-week RCT; n≈500 Chinese adults with asthma	BDP/FF 100/6 µg bid NEXThaler DPI vs pMDI (after 4 weeks pMDI run-in)	NEXThaler DPI non-inferior to pMDI for pre-dose morning PEF Similar FEV_1, FVC, ACQ-6, rescue use and AE rates

(*Continued*)

Table 2 (Continued).

Study	Design/Population	Intervention/Comparator	Key Findings
Braido et al 2025[33] (NEWTON)	Observational study; n = 620 asthma patients	BDP/FF NEXThaler DPI 100/6 μg as MART or maintenance	ACQ-5 improved from 2.0 to 0.6 at 6 months; 56.7% achieved well-controlled asthma TAI-12 good adherence (TAI = 50) increased from 31.7% to ~50% at 3 and 6 months EQ-5D-5L increased from 0.881 to 0.970 and 1.000 at 3 and 6 months FEV_1 improved from 86% to 93%
Aung et al 2024[34]	Prospective study; n = 86 with severe asthma and high FeNO	Switch to BDP/FF NEXThaler DPI	56% FeNO suppressors after 1 month, indicating prior poor adherence FeNO suppressors had improved ACQ-6, FEV_1 and eosinophil counts 79% avoided biologics at 12 months
Singh et al 2019[35]	DB, double-dummy crossover trial; n = 65 asthma patients	BDP/FF NEXThaler DPI vs pMDI after methacholine challenge	Minimal FEV_1 difference after 5 min: 2 mL (95% CI: –0.060–0.065) Median time to 85% FEV1 recovery: 8 min (NEXThaler DPI) vs. 7.5 min (pMDI) Comparable symptom relief (Borg score)
COPD			
Hodzhev et al 2022[3]	16-week observational study; n = 441 with severe COPD	BDP/FF NEXThaler DPI vs pMDI	Both groups improved in mean FEV_1 and mean FVC; Higher response rate for NEXThaler DPI vs pMDI (45.2% vs. 25.6%)
Beeh et al 2021[4]	52-week RCT, three-way, crossover, n = 342 with COPD	BDP/FF/G 100/6/10 μg NEXThaler DPI vs BDP/FF/G pMDI vs. BDP/FF pMDI	Noninferiority met for the two triple-formulation in terms of FEV_1 $AUC_{0-12}h$ (Δ −20 mL) and trough FEV_1: (Δ+3 mL) Similar trends in health status (SGRQ) and rescue medication Triple therapy is superior to dual therapy in lung function, SGRQ and rescue medication use

Abbreviations: ACQ-5, Asthma Control Questionnaire-5; ACQ-6, Asthma Control Questionnaire-6; AE, Adverse Event; $AUC_{0-12}h$, Area Under the Curve from 0 to 12 Hours; BDP, Beclometasone Dipropionate; bid, Twice Daily; COPD, Chronic Obstructive Pulmonary Disease; DB, Double-Blind; DPI, Dry Powder Inhaler; EQ-5D-5L, EuroQol 5-Dimensions 5-Levels Questionnaire; FeNO, Fractional Exhaled Nitric Oxide; FEV_1, Forced Expiratory Volume in 1 Second; FVC, Forced Vital Capacity; G, Glycopyrronium; MART, Maintenance and Reliever Therapy; pMDI, Pressurized Metered-Dose Inhaler; PEF, Peak Expiratory Flow; RCT, Randomized Controlled Trial; SGRQ, St. George's Respiratory Questionnaire; TAI-12, 12-Item Test of Adherence to Inhalers.

In an 8-week randomized, double-blind, parallel-group trial, Kanniess et al compared three treatment arms in 755 patients with controlled asthma: extrafine BDP/FF 100/6 μg bid delivered via the NEXThaler DPI, extrafine BDP/FF 100/6 μg pMDI bid and non-extrafine BDP DPI 100 μg bid alone[5] The study demonstrated that both extrafine BDP/FF formulations were statistically superior to the non-extrafine BDP DPI in terms of pre-dose morning PEF (primary efficacy outcome; as expected for the combination of ICS/LABA vs ICS alone), asthma symptom scores (ACQ-7) and the percentage of days without rescue medication use. Furthermore, the NEXThaler DPI was shown to be non-inferior to the extrafine BDP/FF pMDI for the primary efficacy outcome, as the difference in average pre-dose morning PEF over 8 weeks was −1.84 L/min, with the lower limit of the 95% CI remaining above the predefined noninferiority margin of −15 L/min. No significant differences were also found between the NEXThaler DPI and the pMDI in lung function parameters (FEV_1 and FVC), rescue medication use, rescue-use free days, ACQ-7, and percentage of symptom-free and asthma control days.[5]

Zheng et al reported similar findings in a study evaluating the efficacy and safety of the NEXThaler DPI containing extrafine BDP/FF compared to pMDI in approximately 500 Chinese adults with controlled asthma[26] The study met its

primary endpoint, demonstrating noninferiority of the DPI vs pMDI in average pre-dose morning PEF change from baseline over 12 weeks, with results exceeding the −15 L/min noninferiority margin in both the ITT and PP populations. Notably, the DPI showed comparable efficacy to the pMDI for average pre-dose evening PEF at later timepoints and across the treatment period. Lung function parameters (pre-dose FEV_1 and FVC), asthma symptoms (mean ACQ-6), and rescue medication use were also similar between treatment groups, with observed differences being minimal and not clinically significant.[26]

The effects of BDP/FF delivered via the NEXThaler DPI in asthma management have been investigated in the multinational, multicenter, observational, prospective cohort study NEWTON, which examined the real-world impact of this treatment as maintenance therapy or maintenance and reliever therapy (MART) in patients with moderate to severe asthma. The study involved 57 respiratory medicine centers across six European countries and enrolled approximately 650 patients over 12 months (NCT05168995).[36] Of these, 423 patients completed the Asthma Control Questionnaire (ACQ-5) at baseline and during the 6-month follow-up and were included in the full analysis set. The median ACQ-5 score improved from 2.0 at baseline to 0.6 at 6 months ($p < 0.0001$), while the proportion of patients with poorly controlled asthma declined from 65.1% to 17.5%. Overall, 66.1% of patients showed improved asthma control, and 56.7% achieved well-controlled asthma status (ACQ-5 ≤ 0.75). Quality of life also improved in parallel with asthma control, as shown by the increase in the EQ-5D-5L index (from 0.881 at baseline to 0.970 and 1.000 at 3 and 6 months; $p < 0.0001$ for both). Adherence, assessed using the 12-item Test of Adherence to Inhalers (TAI-12), also improved significantly: the proportion of patients with good adherence (TAI = 50) increased from 31.7% at baseline to 50.0% at 3 months and 49.9% at 6 months ($p < 0.0001$). The mean TAI score rose from 46.0 to 49.5 at both 3 and 6 months. Lastly, in terms of lung function, FEV_1 (% predicted) improved significantly from baseline (median 86.0%) to month 6 (median 93.0%, $p < 0.0001$), along with PEF and FEF25–75%.[33]

A recent study further explored the utility of BDP/FF delivered via the NEXThaler DPI in supporting the assessment of both ICS responsiveness and treatment adherence in patients with severe asthma and FeNO levels ≥45 ppb – a marker often associated with non-adherence or non-responsiveness to ICS therapy. After 1 month of switching from a non-counting ICS/LABA to the NEXThaler DPI, 56% of patients exhibited significant FeNO suppression, suggesting that their restored FeNO levels were largely due to suboptimal adherence rather than ICS resistance. Additionally, even among FeNO non-suppressors, a small but significant reduction in FeNO levels was observed. FeNO suppressors also demonstrated significant improvements in asthma control (ACQ-6), FEV_1, and blood eosinophil counts, and 79% of them did not require biologic therapy after approximately 12 months of treatment. Notably, 56 out of 86 patients reported that the dose counter helped them adhere to treatment and monitor their clinical progress. These findings support the combined use of a dose-counting inhaler and FeNO monitoring as a practical strategy to distinguish between non-responsiveness and non-adherence, thereby guiding more appropriate treatment decisions and potentially avoiding unnecessary escalation to biologic therapies.[34]

Additionally, BDP/FF delivered via the NEXThaler DPI has been shown to be as effective as the pMDI formulation in providing rapid symptom relief for asthma patients following methacholine-induced bronchospasm. In a double-blind, double-dummy, crossover noninferiority trial involving 65 patients, both inhalers produced a rapid improvement in lung function. The adjusted mean difference in FEV_1 between BDP/FF DPI and BDP/FF pMDI was minimal (2 mL, 95% CI: –0.060; 0.065) at 5 minutes post-dose and remained similar over the 30-minute observation period. The median time to 85% FEV_1 recovery was nearly identical (8 minutes for BDP/FF DPI vs. 7.5 minutes for BDP/FF pMDI; $p = 0.554$), as was the median time to 50% recovery (4.2 minutes vs. 4 minutes, respectively). Symptom relief, assessed using the Borg dyspnea score, was comparable between the two treatments.[35]

Chronic Obstructive Pulmonary Disease

ICS/LABA and ICS/LABA/LAMA combinations delivered via the NEXThaler DPI have been shown to improve disease control, reduce symptoms and enhance lung function in patients with COPD[3,4] across different disease severities. The main results on clinical studies on ICS/LABA and ICS/LABA/LAMA combinations delivered via the NEXThaler DPI for the treatment of COPD are reported in Table 2.

A 16-week observational study evaluated the effectiveness of BDP/FF delivered via the NEXThaler DPI compared to BDP/FF pMDI in 441 patients with severe COPD, many of whom had comorbidities such as cardiovascular disease and diabetes. Both treatment groups showed significant improvements in FEV_1 and FVC, but BDP/FF DPI was superior in terms of mean FEV_1 and mean FVC, as these parameters continued to improve consistently throughout the study, whereas they plateaued at week 4 in the BDP/FF pMDI group. Moreover, patients using BDP/FF DPI were significantly more likely to be classified as treatment responders (45.2% vs. 25.6%) compared to those treated with BDP/FF pMDI.[3]

Small Airway Dysfunction

Extrafine BDP/FF delivered via the NEXThaler DPI has also been shown to significantly improve small airway dysfunction (SAD), a key feature of both asthma and COPD characterized by impairment of the distal airways (<2 mm in diameter) with inflammation, narrowing and altered airway wall stiffness and distensibility.[37] Notably, distal airway involvement is prevalent across all asthma severities, with a higher prevalence in severe disease. Studies indicate that 91% of asthmatic patients exhibit SAD, which is associated with poor disease control and increased exacerbations.[37,38] In COPD, SAD is present in over 90% of the patients, with its prevalence increasing with disease severity (as classified by GOLD guidelines) and with a close relationship with disease burden.[39]

The effects of BDP/FF delivered via the NEXThaler DPI on SAD were investigated in a study of 43 COPD patients with severe airflow obstruction and at least one moderate exacerbation in the previous year. Patients who had initiated BDP/FF DPI within the week prior to enrollment were followed for up to 12 weeks. Markers of small airway resistance (R5–R20) significantly improved, decreasing from 0.23 ± 0.09 kPa/(L/s) at baseline to 0.16 ± 0.09 at 6 weeks and 0.16 ± 0.08 at 12 weeks ($p < 0.05$). Additionally, COPD symptom burden was reduced, with CAT scores improving from 13 at baseline to 6 at 6 weeks and 4 at 12 weeks ($p < 0.05$). These improvements correlated with changes in small airway function, reinforcing the role of BDP/FF extrafine formulation in improving functional parameters related to SAD as well as the disease impact on health status.[40]

A multicenter, randomized, double-blind study further demonstrated the noninferiority of the extrafine triple therapy BDP/FF and glycopyrronium (G) delivered via the NEXThaler DPI compared to pMDI for lung function outcomes in 342 patients with COPD. Specifically, the study assessed the efficacy of BDP/FF/G 100/6/10 µg delivered via DPI or pMDI, comparing both triple therapy formulations to dual therapy (BDP/FF 100/6 µg) administered via pMDI. The study met its primary objectives, as the two triple formulations showed comparable improvements in FEV_1 $AUC_{0-12}h$ and trough FEV_1. The confidence intervals for the differences from baseline to Day 28 remained entirely within the pre-specified noninferiority margin (−50 mL): −20 mL (95% CI: −35, −6) for AUC0–12 h and 3 mL (95% CI: −15, 20) for FEV1. Similar trends were observed for health status (assessed via St. George's Respiratory Questionnaire [SGRQ]) and rescue medication use. Furthermore, both triple therapy formulations were superior to dual therapy in terms of lung function, health status, and rescue medication use.[4] Based on these findings, BDP/FF/G delivered via the NEXThaler DPI was approved in the European Union as a maintenance treatment for patients with moderate-to-severe COPD who are not adequately controlled on ICS/LABA or LABA/LAMA therapy.[4]

In a clinical study, Skloot et al[41] also reported improved airway parameters in patients with symptomatic COPD who switched from non-extrafine high-dose ICS/LABA (fluticasone propionate/salmeterol) to extrafine BDP/FF/G delivered via DPI After 6 weeks of treatment, patients showed significant improvements in distal airway parameters, including increased specific image-based airway volume (siVaw, from 39.8% to 62.6%) and reduced airway resistance (siRaw, from −51.1% to −57.2%). Additionally, there was an increase in pre-dose FEV_1 (62.2 mL, $p = 0.0690$) and an improvement in CAT total score (−3.30, $p < 0.0001$).[41]

Safety and Tolerability

Clinical trials have confirmed that the NEXThaler DPI maintains a safety and tolerability profile comparable to pMDI formulations, with similar rates of adverse events. Most adverse events reported in investigational and observational studies were mild to moderate, with few related to treatment. The percentage of patients experiencing adverse events was similar between the NEXThaler DPI and pMDI across both asthma and COPD populations, as well as for both double (BDP/FF) and triple (BDP/FF/G) therapy.[4,5,26] For example, in a study by Zheng et al, the proportion of patients

reporting at least one adverse event was 48.4% with the BDP/FF DPI compared to 49.6% with the pMDI.[26] Similarly, in a study by Beeh et al, adverse events were reported in 15.5% of patients receiving the BDP/FF/G DPI versus 18.7% with the pMDI.[4] The Newton study further confirmed the safety of BDP/FF delivered via the NEXThaler DPI, with only 10.2% of patients experiencing TEAEs, and only 4.3% of patients reporting TEAEs considered related to the medication.[33]

Notably, the use of extrafine BDP formulations appears to reduce the risk of pneumonia and upper- and lower-respiratory tract infections, adverse events frequently associated with continuous ICS therapy. A propensity-matched historical cohort study by Price et al found that fine-particle fluticasone was associated with a higher risk of pneumonia and respiratory infections in COPD patients compared to extrafine BDP.[42] Furthermore, a similar study showed that initiating extrafine BDP/LABA therapy did not increase pneumonia risk, mirroring the risk profile observed with LABA monotherapy (without ICS).[43] This lower risk with extrafine BDP may be attributed to its smaller particle size, which is thought to facilitate more effective drug deposition at lower doses while maintaining therapeutic efficacy.[42]

Patient Preference and Adherence

When selecting an inhaled therapy for asthma maintenance, it is essential to consider not only the medication itself but also the patient's ability to use the device and their overall experience with it. A user-friendly inhaler that aligns with patient needs plays a crucial role in ensuring proper drug delivery, improving adherence, and ultimately enhancing treatment outcomes.[26,44–47] Importantly, successful inhaler use depends not only on patient preference but also on the ability to generate sufficient inspiratory flow to activate the device and achieve effective drug delivery. A recent study demonstrated a linear correlation between the peak inspiratory flow (PIF) achieved through two inhalers and native spirometric PIF, suggesting that assessment of inspiratory flow may help guide device selection. By matching the inhaler to the patient's inspiratory capacity, lung deposition can be optimized and therapeutic efficiency enhanced.[48]

A survey by Contoli et al assessing the experience and satisfaction of 4000 asthmatic patients using DPIs found that while most users (61%) were generally satisfied with their device, satisfaction was lower among those with greater disease burden (55%). Key factors influencing patient preference included ease of use, the presence of a dose counter, and feedback confirming correct inhalation.[44] The NEXThaler DPI, thanks to its BAM and the triple feedback system, effectively addresses these needs and has been positively received by patients in multiple studies.[45,47,49]

In a study by Scichilone et al, 62 patients with moderate to severe COPD provided positive feedback about the NEXThaler DPI, appreciating its ease of use, low inhalation effort required for activation, and the presence of both an inhalation click and an inhalation counter.[47]

More recently, Braido et al reported high patient satisfaction with the device, with over 79% of users being completely or very satisfied with the device in general and especially regarding ease of use and the dose counter. The overall satisfaction was consistent with the improvement in adherence, suggesting that satisfaction with the device may improve patients' adherence to treatment.[33]

Comparative studies have also reported higher patient satisfaction with the NEXThaler DPI compared with other DPIs, emphasizing its practical benefits in daily management.[45,49] In a study by Voshaar et al involving 66 adult asthma patients, the NEXThaler DPI delivering the ICS/LABA formulation outperformed others in several key usability measures, including higher rates of successful inhalation completion without errors ($p < 0.001$), shorter setup time ($p < 0.001$), and faster comprehension of the instructions for use ($p < 0.001$).[45] Conversely, a study by Tinke et al, conducted in 139 patients with asthma (n = 90) and COPD (n = 45), found no significant difference in the number of critical errors between the NEXThaler DPI (n = 3) and another DPI (n = 5).[49]

Conclusion

The NEXThaler DPI represents a meaningful advancement in inhaler technology, offering an effective and user-friendly option for patients with asthma and COPD. Its ability to deliver extrafine formulations facilitates drug deposition in both large and small airways while technological features such as BAM, flow independence, and dose feedback systems further support consistent drug delivery and may enhance patient's satisfaction and treatment adherence.

Although much of the supporting data are derived from surrogate endpoints and modeling approaches, these findings provide important insights into the device's functional performance and usability. Evidence from clinical trials and real-world studies further supports the therapeutic equivalence of NEXThaler DPI to pMDI in terms of efficacy, safety, and patient satisfaction.

Overall, NEXThaler DPI appears to be a clinically validated and well-tolerated option that aligns with current treatment strategies and guideline principles in chronic respiratory disease care. Future research should focus on robust head-to-head comparative studies against other DPIs, long-term effectiveness in diverse populations, and real-world impact on exacerbation rates and disease progression.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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