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Inspiromatic-safety and efficacy study of a new generation dry powder inhaler in asthmatic children

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Abstract

Background: Dry powder inhalers (DPI) are effective but forceful inhalation required to fluidize the powder may be difficult for children and patients with airway disease. Inspiromatic is a new generation active DPI that actively suspends drugs in synchrony with inhalation. We evaluated safety and efficacy of Formoterol delivery via Inspiromatic, compared to Aerolizer, a conventional DPI, in pediatric asthmatic subjects.

Methods: A phase I/II, randomized, single-center, double-blind, double-dummy, placebo-controlled, cross-over study. Subjects aged 8-18 years with FEV_1 40-80% predicted were included. Patients were randomized to inhale Formoterol via the Inspiromatic, immediately followed by the placebo via the Aerolizer or vice versa, in a double-blind fashion. Spirometry, blood pressure, and heart rate were measured at baseline and 15, 30, and 60 min after drug administration. Capsule emptying, comfort of use, confidence in efficacy, and patient satisfaction were assessed. At a subsequent visit, three months later, patients inhaled the active drug via the other DPI.

Results: Twenty-nine patients, aged 12.6 (±2.3) years, mean (SD), completed the study. Baseline FEV_1 was 69.1 (±6.7) % at visit one and 65.3 (±9) % at visit two. Maximal FEV_1 increase was 16.6 (±7.1) % with Inspiromatic and 15.5 (±7.5) % with Aerolizer ($P = 0.47$). No differences in heart rate or blood pressure were observed; 24/28 capsules were emptied using the Inspiromatic and 19/28 with the Aerolizer ($P = 0.5$); 21/28 preferred the Inspiromatic and 7/28 the Aerolizer ($P < 0.001$). There were no adverse events.

Conclusions: Formoterol inhalation via the Inspiromatic is safe and as efficacious as with the Aerolizer. The device is well accepted by asthmatic subjects.

KEYWORDS
active device, breath synchronized, dry powder inhaler, new generation

1 | INTRODUCTION

Asthma can be treated effectively using inhaled medications, but the benefit depends greatly on route and technique of administration. The broad gamut of available devices can be divided into three groups, each with its drawbacks: Nebulizers are bulky and deliver drugs slowly with deposition that varies with humidity, atmospheric pressure, compressor strength, cup structure, and breathing technique.[1] Pressurized metered dose inhalers (pMDI) are small and portable and deliver a predetermined dose. However, the dose is released at extremely high

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speed, impacting the oral cavity, and resulting in ingestion and systemic absorption.[2] Hence, spacer devices are a necessary adjunct to pMDIs for young children and those with poor coordination.[3]

Dry powder inhalers (DPIs) are attractive devices for a number of reasons. The drugs are stable in all weather conditions and have a long shelf-life. As particle size correlates with targeted lung regions, pulmonary distribution can be predicted more accurately than with pMDI devices.[4] DPIs employ breath activation and are hence synchronized with the patient's inspiration, which reduces particle deposition in the pharynx. However, with current DPIs, in particular low resistance devices, aerosol performance is often flow-rate dependent and optimal inhalation flow is difficult to achieve.[5,6] Shallow inhalations result in insufficient fine particle de-agglomeration and may result in increased oropharyngeal deposition.[7–10] In their current formulation, DPIs are not suitable for infants, and small children who depend on valved holding chamber for drug delivery.

Lung deposition is further determined by the internal device design and physicochemical properties of the powder.[11] Current particle packaging methods lead to formation of particle clusters, which require forceful and rapid inhalation to fluidize the powder and separate the active particle ingredient (API) from its carrier.[5,6] This is not easily achieved by children, who tend to inhale with suboptimal effort, technique, and coordination.[12] New generation active DPIs are being developed to respond to this need. They utilize additional electrical or mechanical energy to disperse powder prior to inhalation, reducing the inspiratory flow required.

The "Inspiromatic" (Inspiro Medical, Nes Ziona, Israel), Figure 1, is a proprietary battery-operated microprocessor-controlled DPI designed to actively suspend dry powder drugs in synchrony with inspiration, even with minimal active cooperation. The "Aerolizer" (Plastiape S.p.A., Osnago, Italy) is a passive DPI suitable for children with low inspiratory flows.

In the present phase I/II study, we aimed to establish the safety of the Inspiromatic and compare efficacy of Formoterol delivery in asthmatic children to that using the Aerolizer. For this first in-human, proof of concept study, we chose older, stable asthmatic children fully able to cooperate with the required respiratory maneuvers using both devices. The primary outcome measure was change in FEV_1, hypothesizing that the Inspiromatic would be non-inferior to the Aerolizer. Secondary outcome measures were blood pressure and heart rate as surrogate markers for a systemic effect, device performance assessed by capsule emptying, patient satisfaction, and preference.

2 | MATERIALS AND METHODS

This phase I/II, randomized, single-center, double blind, double dummy, placebo controlled cross over study evaluated the safety, and efficacy of Formoterol delivery using the Inspiromatic device in children with asthma. It was conducted at the Pulmonary Institute of a tertiary hospital, Schneider Children's Medical Center of Israel. Approval was gained from the Institutional Review Board, number 0401-11-RMC. Informed written consent was obtained from eligible patients and their caretakers prior to study enrolment.

2.1 | Study population

We included patients between 8-18 years with a physician diagnosis of asthma, consecutively attending our pulmonology clinic for routine follow up during stability. We stipulated that baseline FEV_1 had to be in the range of 40-80% predicted using the equations of Polgar and Veruni.[13] Maintenance treatment was continued throughout the study period, as deemed necessary by the treating physician to preserve asthma control. Those with higher FEV_1 at baseline underwent an exercise challenge test using a treadmill and a standardized exercise challenge test protocol according to ECSC/ERS exercise guidelines[14] and were included if the post-exercise FEV_1 met the inclusion criteria.

Exclusion criteria were inability to cooperate, pregnancy, milk allergy (as lactose was the carrier molecule for Formoterol), other obstructive airway disease (eg, cystic fibrosis, bronchiectasis, bronchiolitis obliterans, chronic lung disease of prematurity), and any previous exposure to the Aerolizer inhaler.

2.2 | The inspiromatic

The Inspiromatic (Figure 1) is an active DPI, designed to suspend drugs in synchrony with inhalation, thus increasing fine particle lung deposition. It is initiated by loading a prefilled size three standard gelatin drug capsule in a chamber, where it is manually pierced using a built-in microneedle. A thermal flow sensor registers the patient's inspiratory flow, sampling every 20 ms, and sends a signal to a microcontroller in the control unit within the electronic circuit. As soon as a flow rate of 7 L/min is detected, a solenoid valve opens, releasing a pulsed vortex flow, generated by a miniature electric air pump. The flow reaches the inside of the drug capsule via the holes previously pierced and creates a spinning motion within it, generating high sheer forces on the drug particles (Figure 2), separating the active pharmaceutical ingredient (API) from the lactose carrier and delivering the drug out of the capsule. A small particle cloud is created adjacent to the mouthpiece during the first 20 ms of inhalation. The remainder of the inspiratory limb is used to disperse the powder in the lung. The relationship between pulse length and amount of drug dispersed is shown in e-image of the online Supplementary Figure S1.

As an active DPI, the Inspiromatic is not entirely flow rate dependent as, once the inspiratory flow exceeds 7 L/min and the active de-agglomeration mechanism via the vortex flow is triggered, the particle cloud is released irrespective of further flow rate increase. However, as with all DPIs it is likely that oropharyngeal deposition increases with increasing inspiratory flow rates. The microcontroller within the electronic circuit monitors drug delivery time and provides real time feedback indicating the required inspiratory flow rate using a traffic light signal. The threshold for changing the light from red to green is an inspiratory flow rate at or above 10 L/min. The attached data logger utilizes an erasable programmable read-only memory chip (EPROM) and provides detailed information on the patient's performance.

The capsule chamber and breathing tunnel are made of polyoxymethyline (Derlin). A protective stainless steel net is located at the proximal end of the breathing tunnel at the mouthpiece. The cost of goods

Item	Description
1	Inhaler
2	Data Logger
3	LCD
4	On/Off switch
5	Keyboard
6	Memory chip
7	Battery
8	PCB and Microcontroller
9	USB connector
10	Battery level indicator
11	User inhalation indicator
12	Electric airpump
13	Piercing needle
14	Drug capsule
15	Mouthpiece
16	Flow sensor

	Inhaler	Data logger
Size	12cm x 7cm x 5cm	20cm x 11cm x 7cm
Weight	360g	900g

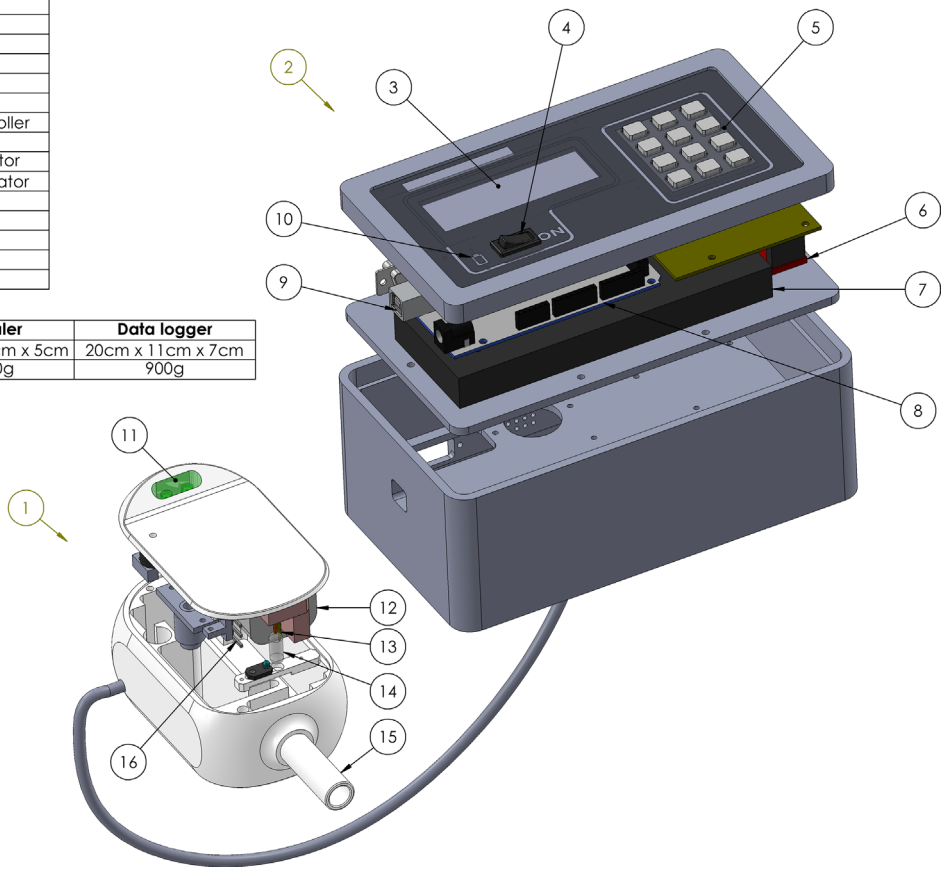

FIGURE 1 Schematic illustration of the Inspiromatic (Inspiro Medical) device

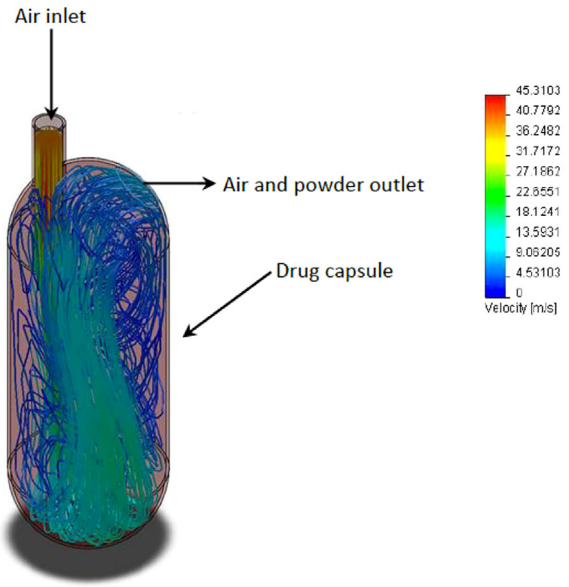

FIGURE 2 Simulation of forced vortex flow in standard drug capsule. A forced vortex flow is actively applied to the drug capsule, creating a spinning motion within, generating high sheer forces, and separating the active particle ingredient from the lactose carrier molecule

sold (COGS) of the Inspiromatic device in the current format, not including the medication itself, is estimated at below $10 per unit for bulk supply. It may rise with the future use of durable and disposable units.

2.3 | The aerolizer inhaler

The aerolizer is a passive DPI with medium intrinsic resistance,[10] generating a pressure drop of 4 kPa at 60 L/min. It weighs 23 g at a size of 7 × 4 × 2 cm. It releases 70% of the metered dose at an inspiratory flow of 28 L/min, achieving a particle size of 7.9 µm. Increasing the flow to 40 L/min, the average particle size decreases to 4.4 µm.[15] It is a single dose system that uses gelatin capsules for drug formulation. Originally developed as a unique patented design, it later became available as a delivery platform for many original inhalation products.[15,16] The Aerolizer was chosen for comparison, because of its proven track record of effective and reliable drug delivery at relatively low flow rates[17] as well as its use of gelatin filled capsules. These characteristics were similar to the Inspiromatic.

2.4 | Study protocol

Patients were instructed to discontinue any controller medications 24 h prior to the clinic visits and avoid beta-agonists on the mornings

of attendance. Demographic details, medical history, spirometry parameters, blood pressure, and heart rate were recorded at baseline. Patients were trained in the use of both devices and asked to perform one inhalation with each inhaler in immediate sequence, one containing 12 mcg Formoterol and the other placebo according to a double blind sequential computer randomized protocol, run centrally by the contract research organization. The placebo capsule contained the same amount of the carrier molecule, lactose, as the Formoterol capsule, so that its taste was identical. The outer coating of the placebo capsule employed, (size 3) and weight, were also identical to the one containing the study drug. Both capsules were prefilled and pre-labelled by the contract research organization, and physicians, lung function technicians, and patients remained blinded to the nature of the capsules. Inhalations were performed under the close guidance of the lung function technician, who punctured the capsules. Patients were trained in how to use the inhalers as follows: for the Inspiromatic, breathing instructions were to: a) perform a full expiration down to residual volume; b) attach the lips to the mouth piece; and c) inhale slowly up to total lung capacity. Patients were asked to keep at the inspiratory flow that triggered the green light feedback response. For the Aerolizer, subjects were instructed to: a) perform a full expiration down to residual volume; b) attach the lips to the mouth piece; and c) perform a rapid and deep inspiration maneuver, in accordance with the manufacturer's directions. If no whirring noise, indicating powder release, was heard, patients were asked to open the inhaler, and loosen the capsule so it could spin freely.

Pulmonary function was measured in the lung function laboratory of the Pulmonary Institute at Schneider Children's Medical Center of Israel according to the American Thoracic Society guidelines.[18] Spirometry was performed with a ZAN 100 flow sensor (ZAN Messgerate, nSpire Health, Inc., Longmont, CO) at baseline and 15, 30, and 60 min after drug and placebo administration to determine clinical efficacy. Results were expressed as a percent of predicted normal values using the equations of Polgar.[13] Blood pressure and heart rate were also measured at these time points as indirect indicators of oral absorption and systemic beta agonist effect. For patients who underwent exercise challenge, pre-exercise heart rate, and blood pressure were used as baseline measurements.

Drug clearance was determined qualitatively by the technician who inspected the capsule content after each use classifying it as "empty," that is, no or almost no visible powder left, or "not empty." Patients' inspiratory flow rates were recorded over a period of 6 s from the onset of inhalation through the Inspiromatic and downloaded from its data logger. After the first visit, patients were asked to rate comfort of use with each DPI as "uncomfortable," "reasonably comfortable," or "very comfortable." Patients were also asked to state whether they were "convinced it works," "convinced it does not work" or "unsure." Finally, they were prompted to indicate which device they would prefer to use. A second visit was carried out within 3 months of the first visit, following the same protocol, this time with the patient inhaling the active drug via the DPI that had been used for placebo during visit one.

2.5 | Statistics

Considering the primary outcome variable to be the change in percent predicted FEV_1, we tested the null hypothesis that the mean difference within pairs (each child being treated with the two inhalers) would be zero. The criterion for significance (Alpha) was set at 0.05. We used a two-tailed test meaning that an effect in either direction would be interpreted. With a proposed sample size of 30 cases, we found that the study would have a power of 94.2% to detect a statistically significant difference.

Demographic and baseline condition related characteristics were tabulated. Continuous variables such as age, FEV_1, blood pressure, and heart rate were summarized by mean and standard deviation; categorical variables by count and percentage. For comparison of means (continuous variables), the paired samples *t*-test or the Wilcoxon signed-rank test was used, as appropriate. To examine changes in spirometry parameters over time, time trend analysis was performed using One-way ANOVA following post hoc analysis using Tukey's procedure. Where sample size was small, we used Fisher's exact test for contingency analysis. Statistical analysis was performed using IBM SPSS statistics for Windows, version 24 (IBM Corp., Armonk, NY).

3 | RESULTS

3.1 | Patients

Thirty-one patients were recruited. One patient failed to achieve effective inhalation with either device and was excluded from the study. A second patient was diagnosed with bronchial adenocarcinoma during the study period and removed from the analysis. Nine (31%) patients using the active drug via the Inspiromatic and 12 (41.4%) patients via the Aerolizer underwent exercise tests prior to dropping FEV_1 to below 80% ($P = 0.249$). Baseline characteristics of the 29 included patients are shown in Table 1.

3.2 | Relief of airway obstruction with formoterol via inspiromatic versus aerolizer

Treatment with Formoterol via both inhalers achieved a clinically significant mean improvement in airflow of more than 12% at every time point, see Table 2. Maximal improvement in FEV_1 was noted one hour post inhalation with both devices. At none of the time points was there a significant difference in FEV_1 between the devices (Figure 3).

3.3 | Systemic response

Clinical signs of systemic response, evaluated using blood pressure and heart rate measurements at 15, 30, and 60 min post bronchodilator compared to baseline are shown in Table 3. No significant differences were observed between the devices.

3.4 | Device performance

Of the 29 patients, one discarded the capsule prior to the inspection and was therefore removed from this analysis. For the remaining 28, capsules were emptied following active drug delivery in 24 (86%) with the Inspiromatic and 19 (68%) with the Aerolizer ($P = 0.205$). In all four

TABLE 1 Baseline characteristics for entire group, independent of which inhaler delivered the active drug ($n = 29$)

Age (years)	
Mean (SD)	12.6 (2.3)
Median (range)	13 (8-17)
Anthropometry	
Height (cm)	155.9 (12.3)
Weight (kg)	47.1 (10.4)
BMI (kg/m^2)	19.2 (2.7)
Gender	
Male, *n* (%)	18 (62.1)
Female, *n* (%)	11 (37.9)
FVC % predicted	
Visit 1	86.6 (8.7)
Visit 2	84.1 (9.6)
FEV_1 % predicted	
Visit 1	69.1 (6.7)
Visit 2	65.3 (9)
FEF_{25-75} % predicted	
Visit 1	50.3 (16.9)
Visit 2	46.4 (17.6)

Values are expressed as mean (SD) unless indicated otherwise.

cases in which capsules had not been fully emptied with the Inspiromatic, FEV_1 values at 15 min post treatment had still improved by >12%. For only two of the nine patients who failed to completely empty the capsule using the Aerolizer, did the FEV_1 improve >12% at 15 min post treatment ($P = 0.021$). All seven who failed to improve at 15 min did improve by >12% at 30 and 60 min post Formoterol.

The average inspiratory flow rate over 6 s of inspiration, downloaded from the Inspiromatic data logger on all 58 test occasions for release of Formoterol and placebo, was 21.3 (±9.3) L/min, mean (SD). Average flow rates of below 15 L/min were observed on 17 test occasions in 11 patients. On 15 of these occasions, the capsule was emptied nevertheless. Peak flow rate was 28.7 L/min (± 11.7), mean (SD). On all occasions, peak flow exceeded the 7 L/min required for triggering the vortex flow.

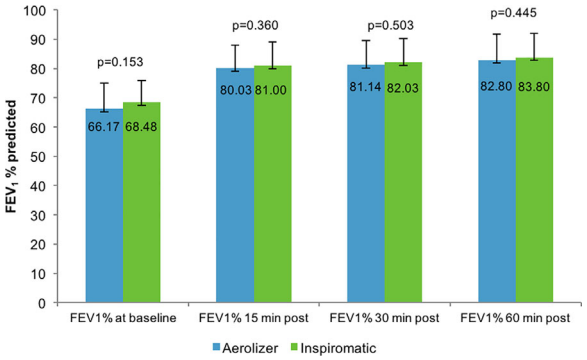

FIGURE 3 Effect of Formoterol administered via Inspiromatic versus Aerolizer on FEV1% predicted at baseline, 15, 30, and 60 min post-inhalation. Values shown represent mean with SD displayed in brackets. *P*-value indicates between-group differences at every time point

3.5 | Patient satisfaction

The questionnaire was completed by 28 of the 29 subjects. For the Inspiromatic, 26 (89.7%) were convinced it had delivered the drug effectively, none thought drug delivery was ineffective and 3 (10.3%) were unsure. Twenty-one (72.4%) of 28 were convinced the Aerolizer had delivered the drug effectively, 2 (6.9%) thought drug delivery was ineffective, and 6 (20.7%) were unsure. There was no statistical difference between the groups, $P = 0.171$. Of the 28 responders, 19 (67.9%) rated the experience with the Inspiromatic as "very comfortable," 9 (32.1%) "reasonably comfortable" and 0 "uncomfortable." Fourteen (50%) found the Aerolizer "very comfortable" to use, 11 (39.3%) "reasonably comfortable" and 3 (10.7%) "uncomfortable." Although more patients rated the Inspiromatic comfortable, the differences did not reach statistical significance ($P = 0.138$). Twenty-one (75%) overall preferred the Inspiromatic and 7 (25%) the Aerolizer ($P < 0.001$).

3.6 | Adverse events

No adverse events were reported following drug delivery with either inhaler.

TABLE 2 Change in spirometry parameters from baseline following inhalation of Formoterol from Inspiromatic and Aerolizer

		% change from baseline, mean (SD)		
Time post bronchodilator (min)	**Parameter**	**Inspiromatic ($n = 29$)**	**Aerolizer ($n = 29$)**	***P*-value (paired *t*-test)**
15	FVC	4.34 (5.4)	5.48 (7)	0.663
	FEV_1	13.9 (6.3)	13 (6.9)	0.432
	FEF_{25-75}	23 (14.1)	24.97 (12.2)	0.088
30	FVC	6.03 (5.9)	6.38 (7)	0.251
	FEV_1	14.9 (6.3)	14 (6.6)	0.521
	FEF_{25-75}	46.34 (39.3)	28.8 (13)	0.297
60	FVC	6.48 (6.9)	7.83 (6.8)	0.802
	FEV_1	16.6 (7.1)	15.5 (7.5)	0.488
	FEF_{25-75}	28.34 (16.4)	31.55 (14.9)	0.235

TABLE 3 Blood pressure and heart rate 15, 30, and 60 min post Formoterol administration as marker of systemic response, compared between Inspiromatic versus Aerolizer devices

	Device delivering active drug		
Time post bronchodilator (minutes)	Inspiromatic (*n* = 29)	Aerolizer (*n* = 29)	*P*-value
Blood pressure, systolic- % of baseline, mean (SD)			
15	104.3 (11.1)	99.4 (25.7)	0.89
30	102.3 (10.5)	104 (10.9)	0.97
60	102.5 (11.8)	101.1 (27.0)	0.56
Blood pressure, diastolic- % of baseline, mean (SD)			
15	105.4 (15.0)	99.4 (25.7)	0.89
30	104.1 (19.5)	107.6 (12.0)	0.60
60	98.7 (16.8)	101.8 (26.0)	0.85
Heart rate- % of baseline, mean (SD)			
15	106.5 (14.8)	104.6 (17.3)	0.64
30	103.5 (13.2)	102.9 (16.0)	0.63
60	101.8 (14.7)	104.7 (19.9)	0.50

4 | DISCUSSION

In this phase I/II, randomized, double-blind cross over study we have demonstrated the safety, and efficacy of Formoterol delivery to asthmatic children via the Inspiromatic, an innovative device that actively suspends dry powder drugs in synchrony with the patient's inhalation. Moreover, we demonstrate its non-inferiority compared to the Aerolizer in terms of bronchodilation at all time points evaluated. Although the Inspiromatic scored higher in capsule emptying and comfort domains, due to the small sample size, this did not reach statistical significance, except for overall preference.

When using inhalers, children with asthma display peak inhalation flows, pressures, and acceleration rates that are inferior even to adults with severe emphysema. Variability is high and the true effective dose is difficult to ascertain.[19] Lung deposition may be optimized by applying inspiratory flows that are sufficiently high to achieve drug release and de-agglomeration of the API, but not too high, as to avoid oropharyngeal deposition.[20,21] The Inspiromatic may respond to this need. Once its sensor registers relatively low patient flow rates, the de-agglomeration process is triggered. As the release of the API from the carrier is effected by an inner pump rather than depending on the patient's inspiratory flow, reliable administration is expected to be achieved even with shallow inhalation, as may be expected in children and those with acute asthma exacerbation. Preclinical data show that this active mechanism enabled highly efficient drug dispersion. However, lung deposition beyond this initial dispersion would also depend on the patient's inhalation characteristics which in some cases may be a limiting factor.

Indeed, our cohort displayed rather low average flow rates of 21.3 L/min and achieved excellent bronchodilator response. Inspiromatic driven drug delivery resulted in more rapid bronchodilation in patients whose capsules were incompletely emptied, possibly implying more effective API de-agglomeration. In the current study, with older children in a stable condition, capsule emptying was sufficient to achieve bronchodilation in all cases. Delivered doses as low as 60% were shown to still achieve effective lung delivery.[17] The advantage in improved capsule emptying using the Inspiromatic may be more important in cases of transiently or chronically decreased inspiratory flows, such as in young children, neuromuscular patients, the elderly or during asthma[7] or COPD,[9] exacerbations. The scope of developing active DPIs that can reliably deliver stable effective drug doses is therefore broader than examined here and includes non traditional indications such as diabetes,[22] non small cell lung cancer,[23] and bacteriophages for antibiotic resistant respiratory infections.[24]

Other approaches to increase fine particle dose have recently been proposed, for example, the use of an add on accessory device to the DPI, the "Axial Oscillating Sphere" (Respira Therapeutics Inc.), which uses a small spherical bead oscillating in a cylindrical chamber to promote powder dispersion.[25] Next to enhanced aerosol dispersion, it was shown in vitro to minimize flow rate dependency resulting in more consistent lung dosing. A further active DPI, developed by MicroDose Therapeutx, uses a piezoelectric system to de-aggregate and aerosolize drug and excipient from a foil dosing blister. Upon detection of an inhalation flow signal, synthetic jets are dispersed by the piezo vibrator to transport the aerosol through pierced holes in the blister, independent of inhalation velocity, and inhaler orientation.[26]

Advantageous features of the Inspiromatic, as an example of new generation active DPIs include: a) its use of easily loaded, commercially available drug capsules; b) live feedback to guide inspiratory flow intensity; and c) ability to download data on patient performance and compliance. The latter is of particularly high value in the "big data" era and has potential to inform future compliance and efficacy studies.

This study has a number of limitations. Other than small sample size and single center design, we included patients who had a normal FEV_1 at the time of clinic attendance, as long as their post exercise FEV_1 dropped to below 80% predicted. The performance of an exercise challenge might have caused release of broncho-constrictive

mediators, such as leukotrienes, tryptase, prostaglandin, and histamine, leading to a different pattern of bronchoconstriction from those attending the clinic with resting bronchoconstriction. It might be argued that bronchodilator "response" following exercise simply represented regression to the mean rather than true drug related reversibility. Nevertheless, a similar proportion of patients in each group were included following exercise, so that no bias was introduced. Due to small numbers, we did not perform sub-group analysis of the post-exercise group. Inspiratory flows could only be measured with the Inspiromatic device. Flows applied through the Aerolizer might have been higher or lower, even in the same subject on the same day, owing to its different mechanical properties and absence of traffic light feedback system. Any impact of this potential difference on the outcomes measured is speculative. Aerosolization of DPIs is highly dependent on the properties of the formulation,[27] and results from this study using Foradile™, containing 12 µg Formoterol fumarate and 20 g lactose, cannot automatically be extrapolated to other formulations. Our pre-clinical laboratory set-up did not include particle size measurements for Formoterol via the Inspiromatic. Although it uses an active release mechanism and as such is not entirely flow rate dependent, this might have shed some light on lung distribution in comparison to the Aerolizer. The Inspiromatic was developed as an experimental inhaler and the current study served as a proof of concept. In this initial study of safety and efficacy we evaluated older children, able to expire to residual volume and inspire to total lung capacity. In order to assess efficacy in young children unable to complete these maneuvers, a trial aimed at this younger age group would be important. Finally, the high cost of the Inspiromatic in its current format clearly exceeds that of the Aerolizer and similar devices currently on the market. Unless the price is markedly reduced, its use might be limited to those who stand to benefit most from its mechanism, that is, young children, elderly and others with reduced inspiratory flow.

In summary, we have shown that Formoterol inhalation via the Inspiromatic is safe and as efficacious as with the conventional Aerolizer DPI. The device is well accepted by asthmatic subjects. The benefits of this novel active mechanism must be substantiated in larger pediatric asthma populations that include younger subjects and applied to patients with additional indications, such as COPD and neuromuscular disease.

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CONFLICTS OF INTEREST

This study was managed and monitored by "Novo Trials" and funded by Inspiro Medical. Dr Steuer is one of the inventors of the Inspiromatic device. He was one of the owners of Inspiro Medical until June 2014, when it was acquired by OPKO. Currently, Dr Steuer holds stock in OPKO, but has no involvement in the company. The other authors have no conflict of interest to declare.

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REFERENCES

1. Martin AR, Finlay WH. Nebulizers for drug delivery to the lungs. *Expert Opin Drug Deliv*. 2015;12:889–900.
2. Winkler J, Hochhaus G, Derendorf H. How the lung handles drugs: pharmacokinetics and pharmacodynamics of inhaled corticosteroids. *Proc Am Thorac Soc*. 2004;1:356–363.
3. Erzinger S, Schueepp KG, Brooks-Wildhaber J, Devadason SG, Wildhaber JH. Facemasks and aerosol delivery in vivo. *J Aerosol Med*. 2007;20:S78–83; discussion S83-74.
4. Thorsson L, Edsbacker S, Conradson TB. Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler P-MDI. *Eur Respir J*. 1994;7:1839–1844.
5. Pirozynski M, Sosnowski TR. Inhalation devices: from basic science to practical use, innovative vs generic products. *Expert Opin Drug Deliv*. 2016;13:1559–1571.
6. Everard ML, Devadason SG, Le Souef PN. Flow early in the inspiratory manoeuvre affects the aerosol particle size distribution from a Turbuhaler. *Respir Med*. 1997;91:624–628.
7. Newman SP, Busse WW. Evolution of dry powder inhaler design, formulation, and performance. *Respir Med*. 2002;96:293–304.
8. Chrystyn H, Price D. Not all asthma inhalers are the same: factors to consider when prescribing an inhaler. *Prim Care Respir J*. 2009;18:243–249.
9. Mahler DA, Waterman LA, Ward J, Gifford AH. Comparison of dry powder versus nebulized beta-agonist in patients with COPD who have suboptimal peak inspiratory flow rate. *J Aerosol Med Pulm Drug Deliv*. 2014;27:103–109.
10. Weers J, Clark A. The impact of inspiratory flow rate on drug delivery to the lungs with dry powder inhalers. *Pharm Res*. 2017;34:507–528.
11. Hoppentocht M, Hagedoorn P, Frijlink HW, de Boer AH. Technological and practical challenges of dry powder inhalers and formulations. *Adv Drug Deliv Rev*. 2014;75:18–31.
12. Clark AR. The role of inspiratory pressures in determining the flow rates though dry powder inhalers; a review. *Curr Pharm Des*. 2015;21:3974–3983.
13. Polgar G. Pulmonary function tests in children. *J Pediatr*. 1979;95:168–170.
14. Sterk PJ, Fabbri LM, Quanjer PH, et al. Airway responsiveness. standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. report working party standardization of lung function tests, european community for steel and coal. official statement of the european respiratory society. *Eur Respir J Suppl*. 1993;16:53–83.
15. Weuthen T, Roeder S, Brand P, Mullinger B, Scheuch G. In vitro testing of two formoterol dry powder inhalers at different flow rates. *J Aerosol Med*. 2002;15:297–303.
16. Nielsen KG, Skov M, Klug B, Ifversen M, Bisgaard H. Flow-dependent effect of formoterol dry-powder inhaled from the Aerolizer. *Eur Respir J*. 1997;10:2105–2109.
17. Meyer T, Brand P, Ehlich H, et al. Deposition of Foradil P in human lungs: comparison of in vitro and in vivo data. *J Aerosol Med*. 2004;17:43–49.

18. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. *Eur Respir J*. 2005;26:153–161.
19. Azouz W, Chetcuti P, Hosker H, Saralaya D, Chrystyn H. Inhalation characteristics of asthma patients, COPD patients and healthy volunteers with the Spiromax(R) and Turbuhaler(R) devices: a randomised, cross-over study. *BMC Pulm Med*. 2015;15:47.
20. Frijlink HW, de Boer AH. Trends in the technology-driven development of new inhalation devices. *Drug Discov Today Technol*. 2005;2:47–57.
21. Heyder J. Deposition of inhaled particles in the human respiratory tract and consequences for regional targeting in respiratory drug delivery. *Proc Am Thorac Soc*. 2004;1:315–320.
22. Mikhail N. Place of technosphere inhaled insulin in treatment of diabetes. *World J Diabetes*. 2016;7:599–604.
23. Bakhtiary Z, Barar J, Aghanejad A, Saei AA, Nemati E. Ezzati Nazhad Dolatabadi J, Omidi Y. Microparticles containing erlotinib-loaded solid lipid nanoparticles for treatment of non-small cell lung cancer. *Drug Dev Ind Pharm*. 2017:1–30.
24. Bodier-Montagutelli E, Morello E, L'Hostis G, et al. Inhaled phage therapy: a promising and challenging approach to treat bacterial respiratory infections. *Expert Opin Drug Deliv*. 2017;14:959–972.
25. Buttini F, Hannon J, Saavedra K, et al. Accessorized DPI: a shortcut towards flexibility and patient adaptability in dry powder inhalation. *Pharm Res*. 2016;33:3012–3020.
26. Corcoran TE, Venkataramanan R, Hoffman RM, et al. Systemic delivery of atropine sulfate by the MicroDose Dry-Powder Inhaler. *J Aerosol Med Pulm Drug Deliv*. 2013;26:46–55.
27. Lu D, Lee SL, Lionberger RA, et al. International guidelines for bioequivalence of locally acting orally inhaled drug products: similarities and differences. *AAPS J*. 2015;17:546–557.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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