



Novel albuterol multidose dry powder inhaler in patients with exercise-induced bronchoconstriction: A single-dose, double-blind, randomized, 2-way crossover study

Nancy K. Ostrom ^{a,*}, Herminia Taveras ^b, Harald Iverson ^b, David S. Pearlman ^c

^a Allergy & Asthma Medical Group & Research Center, 5776 Ruffin Road, San Diego, CA 92123, USA

^b Teva Pharmaceuticals, 74 N.W. 176th Street, Miami, FL 33169, USA

^c Colorado Allergy & Asthma Centers, 125 Rampart Way, Suite 150, Denver, CO 80230, USA

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ABSTRACT

Background: A novel, inhalation-driven, multidose dry powder inhaler (MDPI) was developed that eliminates the need to coordinate device actuation with inhalation as is required with conventional metered-dose inhalers.

Objective: To evaluate albuterol MDPI efficacy and safety in patients with exercise-induced bronchoconstriction (EIB).

Methods: This single-dose, double-blind, 2-way crossover study randomized adolescents and adults with EIB ($\geq 20\%$ fall from pre-exercise challenge FEV_1) to treatment sequences of albuterol MDPI (180 μ g [2 inhalations of 90 μ g each])/placebo MDPI ($n = 19$) or the reverse sequence ($n = 19$). FEV_1 was measured 30 and 5 min predose, 30 min postdose (ie, 5 min before treadmill exercise challenge; baseline) and 5, 10, 15, 30, and 60 min after exercise challenge. The primary efficacy endpoint was maximum percentage fall from baseline in FEV_1 up to 60 min post-exercise challenge.

Results: Mean maximum percentage fall in FEV_1 within 60 min post-exercise challenge was $6.2 \pm 1.4\%$ for albuterol MDPI versus $22.4 \pm 1.4\%$ for placebo MDPI (between-treatment difference: -16.2% ; 95% CI: -20.2% to -12.1% ; $P < 0.0001$). A significantly higher percentage of albuterol MDPI-treated patients were protected against EIB ($< 10\%$ maximum FEV_1 fall post-exercise challenge) versus placebo MDPI (84.2% vs 15.8%; $P < 0.0001$). Protection with albuterol MDPI was evident within 5 min and maintained through 30 min; recovery was complete for both groups at 60 min. Treatment with a single dose of albuterol MDPI was generally well tolerated.

Conclusions: Albuterol MDPI provides clinically significant protection from EIB in adolescents and adults with EIB; no new safety issues were observed with short-term albuterol MDPI use. ClinicalTrials.gov identifier NCT01791972.

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1. Introduction

Exercise-induced bronchoconstriction (EIB) is a disorder characterized by airflow obstruction that usually occurs during or a few

List of abbreviations: AE, adverse event; ATS, American Thoracic Society; ECG, electrocardiogram; EIB, exercise-induced bronchoconstriction; FAS, full analysis set; ITT, intent-to-treat; MDI, metered-dose inhaler; MDPI, multidose dry powder inhaler; SABA, short-acting β_2 -adrenergic agonist; SV, screening visit; TV, treatment visit.

* Corresponding author.

E-mail addresses: nkostrom@aol.com (N.K. Ostrom), herminia.taveras@tevapharm.com (H. Taveras), harald.iverson@tevapharm.com (H. Iverson), ds.pearlman@coloradoallergy.com (D.S. Pearlman).

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minutes after vigorous exercise, peaks at 5–10 min after stopping physical exertion, and then resolves after another 20–30 min [1]. EIB has been reported in up to 90% of individuals with asthma, with higher rates in those with more severe or poorly controlled disease [2–4]. However, EIB also occurs in an estimated 5%–20% of individuals who do not have other symptoms of asthma [2,5]. Pre-treatment with an inhaled short-acting β_2 -adrenergic agonist (SABA), such as albuterol, is recommended for the prevention of EIB [1,5]. Inhaled SABAs are generally recognized as well tolerated and effective medications for short-term prevention of EIB [6].

A novel, inhalation-driven, multidose dry powder inhaler (MDPI; Teva Pharmaceuticals, Inc., Frazer, PA) has been developed

that eliminates the need for patients to coordinate device actuation with inhalation. This device may reduce drug delivery errors that have been noted with conventional metered-dose inhalers (MDIs), the predominant device used for delivery of SABAs in EIB [7,8]. The present study was designed to evaluate the efficacy and safety of a single dose of albuterol administered with the inhalation-driven MDPI versus a placebo MDPI in adult and adolescent patients with EIB.

2. Methods

2.1. Study design

This single-dose, randomized, double-blind, placebo-controlled, 2-treatment, 2-sequence, 2-way crossover study was conducted at 6 centers throughout the United States from March to June 2013. The study consisted of 2 screening visits (SV1 and SV2), 2 treatment visits (TV1 and TV2), and a follow-up telephone call (Fig. 1). At each visit, spirometry assessments were made before and after treadmill exercise challenge. The timing of the first pre-exercise spirometry measurement was to be consistent across each study visit (ie, within 1 h of the timing at SV1).

Patients were randomized 1:1 via an interactive response system to receive double-blind treatment with a single dose of albuterol MDPI (total dose of 180 µg [2 inhalations of 90 µg each]) followed approximately 6 days later by a single dose of matching placebo MDPI (2 inhalations), or placebo MDPI followed approximately 6 days later by albuterol MDPI. Patients and investigators remained blinded to treatment assignment after randomization. The exercise challenge test with spirometric measurement was performed after each dose.

The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Consolidated E6 Guidelines and all applicable regulatory guidelines. The protocol was approved by an Independent Ethics Committee/Institutional Review Board for each site. Written informed consent was obtained from each adult patient and from the parent/legal guardian of each adolescent patient, with the adolescent providing written assent, before conducting any study-related procedures.

2.2. Patients

Male or female patients aged 12–50 years inclusive were eligible if they had a documented history of EIB with or without underlying asthma, evidence of EIB at SV1 as demonstrated by a $\geq 20\%$ fall from the 5-min pre-exercise challenge absolute FEV₁, and a pre-exercise challenge best FEV₁ $\geq 70\%$ of predicted for age, height, gender, and race [9]. Patients with underlying asthma had to

be well controlled in the investigator's judgment per National Asthma Education and Prevention Program guidelines [1]; those requiring an inhaled corticosteroid had to be taking stable low to moderate doses (equivalent to fluticasone propionate ≤ 500 µg/day) for at least 4 weeks before SV1.

Exclusion criteria included: need for a rescue bronchodilator after exercise challenge at SV1 with the resulting FEV₁ not returning to within 20% of the pre-exercise FEV₁ within 30 min after administration of the rescue medication, current continuous treatment with β_2 -adrenergic antagonists or nonselective β -receptor antagonists, use of a long-acting β_2 -adrenergic agonist within 2 weeks preceding SV1, asthma exacerbation requiring oral corticosteroid within 3 months preceding SV1, hospitalization for asthma within 6 months preceding SV1, history of life-threatening asthma, unresolved respiratory infection or disorder within 2 weeks, or any clinically significant non-asthmatic acute or chronic condition that in the investigator's opinion would pose a safety risk for the patient or affect measurement of study endpoints.

At SV2, patients received placebo MDPI and were required to have: FEV₁ $\geq 70\%$ of predicted at 30 and 5 min before placebo MDPI, with the best value not exceeding $\pm 15\%$ of the best value measured at SV1; FEV₁ $\geq 70\%$ of predicted at 30 min after placebo MDPI (ie, 5 min before exercise challenge); demonstration of EIB (at both SV1 and SV2); and no respiratory tract infection or asthma exacerbation between SV1 and SV2. If any of the spirometry criteria were not met at SV1 or SV2, the exercise challenge was repeated once within the next 7 days of the respective visit.

Patients were randomized to treatment if they met the above criteria and demonstrated at TV1 an FEV₁ $\geq 70\%$ of predicted value for each predose, pre-exercise challenge determination; an FEV₁ $\geq 70\%$ of predicted value for the postdose, pre-exercise challenge determination; a best predose, pre-exercise challenge FEV₁ that did not exceed $\pm 15\%$ of the best pre-exercise challenge FEV₁ at SV1; and had no respiratory infection or asthma exacerbation between SV2 and TV1. Patients could continue participating in the study if they met the above criteria in addition to not requiring a rescue bronchodilator after the exercise challenge at TV1 or TV2 for a fall in FEV₁ that did not return to within 20% of their postdose, pre-exercise challenge FEV₁ within 30 min after administration of the rescue medication.

2.3. Exercise challenge and spirometry

The exercise challenge test was conducted according to American Thoracic Society (ATS) guidelines [10]. Each patient ran on a motor-driven treadmill that was set at a speed and incline sufficient to increase heart rate to $\geq 80\%$ of the maximum rate for age (ie, 220 beats per minute minus age in years). The treadmill speed and

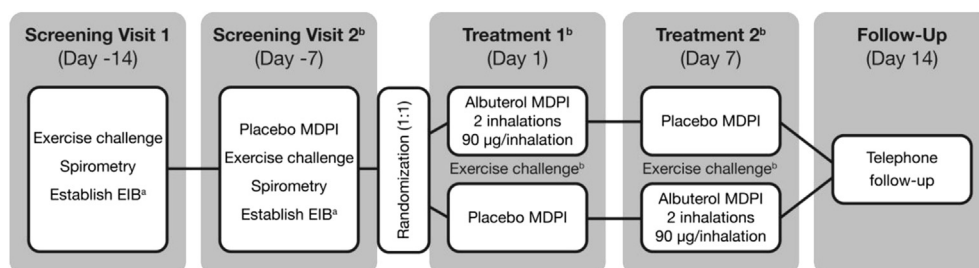


Fig. 1. Study design. The following visit windows were permitted: screening visit 1 (SV1) approximately 14 days before treatment 1 (T1); screening visit 2 (SV2) within 1–7 days after SV1; T1 within 2–7 days after SV2; treatment 2 (T2) within 2–7 days after T1; follow-up was required to be made at least 3 days after T2 but within 14 days after T1. ^aEIB = $\geq 20\%$ fall from the 5-min pre-exercise challenge absolute FEV₁; if criteria not met, exercise challenge was repeated once within 7 days. ^bStudy medication administered ~ 30 min before exercise challenge; spirometry assessments conducted ~ 30 (± 5) and 5 min before study drug administration, 30 min postdose (5 min before the exercise challenge [baseline]), and 5, 10, 15, 30, and 60 min after the exercise challenge. EIB, exercise-induced bronchoconstriction; MDPI, multidose dry powder inhaler.

incline needed to achieve and maintain the specified heart rate over a period of 6–8 min was determined at SV1 using a stepped-exercise protocol in accordance with ATS guidelines, and then these settings were used for all subsequent exercise challenges, with adjustments allowed only if there was evidence of a training effect. Heart rate was monitored continuously during the exercise challenge until 60 min after exercise challenge completion. FEV₁ was determined by standard spirometric techniques at approximately 30 and 5 min before exercise challenge at SV1, and at approximately 30 and 5 min before dosing and at 30 min after dosing (5 min before the exercise challenge [baseline]) at the other visits. During all exercise challenges (SV1, SV2, TV1, and TV2), the patient inhaled compressed air via an appropriate balloon reservoir at a fixed flow rate. The temperature of the room in which the exercise challenges were conducted was maintained between 20 °C and 25 °C. Spirometric FEV₁ determinations were made 5, 10, 15, 30, and 60 min after completion of the exercise challenge. For each predose and pre-exercise challenge spirometry, a maximum of 8 maneuvers was performed, and the highest value obtained from 3 acceptable and 2 repeatable spirometric maneuvers was used [11]. For each post-exercise challenge spirometry, the highest value of 2 acceptable spirometry data collection system incorporating a quality control program (Biomedical Systems, Inc., St. Louis, MO) was used to reduce FEV₁ variability between and within patients and between study sites.

2.4. Endpoints

The primary efficacy endpoint was the maximum percentage fall from baseline in FEV₁ observed up to 60 min post-exercise challenge [12]. The secondary efficacy endpoint was the percentage of patients who were fully “protected” (maximum FEV₁ post-exercise challenge fall <10%) [12]. Additional endpoints included percentage of patients partially protected (10%–20% fall) and “unprotected” (>20% fall), as well as the time to recovery, defined as the time from completion of the exercise challenge to the first measured post-exercise challenge FEV₁ value within 10% of the pre-exercise challenge baseline FEV₁ [12]. Safety was monitored by reported adverse events (AEs), vital signs measurements, 12-lead electrocardiogram (ECG) findings, and physical examination findings.

2.5. Statistics

Based on a previous randomized, double-blind, crossover study comparing albuterol MDPI with breath-actuated albuterol and placebo, the residual root mean square error in the crossover model was assumed to have a value of 11.25%, indicating that a total of 30 patients would be required to provide 90% power to detect a difference of 10%, with the model-based *t*-test performed at the 0.05 level of significance. Therefore, approximately 36 patients were to be randomized to ensure that 30 patients completed the study. Efficacy assessments were made in the full analysis set, which consisted of all randomized patients who received at least 1 dose of albuterol MDPI or placebo MDPI and had at least 1 post-baseline primary endpoint assessment. Safety assessments were made in all randomized patients who received at least 1 dose of study treatment. The primary efficacy endpoint was analyzed using a mixed-effect analysis of covariance with fixed effects of sequence, treatment group, period, and center, within-period baseline FEV₁ as a covariate, and random effect for patient within sequence. The secondary efficacy endpoint was analyzed using a logistic regression model with terms for treatment and period, computed with the generalized estimating equations algorithm, which adjusts estimates for potential correlation between measurements on the

same patient. The time to recovery was analyzed with a gamma frailty proportional hazards model, with a piecewise constant baseline hazard, and terms for treatment, period, and sequence, and a random frailty term for each patient. The statistical tests were performed at a significance level of 0.05. Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (version 15.1). Safety parameters were summarized using descriptive statistics.

3. Results

3.1. Patient disposition and baseline characteristics

A total of 64 patients with EIB were screened; of these, 21 did not meet inclusion criteria, 2 met exclusion criteria, 2 withdrew consent, and 1 was withdrawn for other reasons (Fig. 2). The remaining 38 patients were enrolled and randomized: 19 to the albuterol MDPI/placebo MDPI treatment sequence and 19 to the placebo MDPI/albuterol MDPI treatment sequence. All 38 patients completed the study and were included in the efficacy and safety analyses. Patients in the 2 treatment sequences were well matched with respect to demographics and baseline FEV₁ (Table 1). The mean age of the study cohort was 31.8 years; except for 2 patients, all were >18 years of age. All patients enrolled in the study had a history of asthma. Prior to exercise challenge at SV1 and SV2, the mean FEV₁ ranged from 86% to 87% of predicted, and the maximum fall in FEV₁ after the exercise challenge was 26.1% at SV1 and 23.5% at SV2. No patient discontinued the study due to the need for a rescue bronchodilator after the exercise challenge at TV1 or TV2 for a fall in FEV₁ that did not return to within 20% of their postdose, pre-exercise challenge FEV₁ within 30 min after administration of rescue medication.

3.2. Efficacy

In the primary efficacy analysis, the mean maximum percentage fall in FEV₁ up to 60 min post-exercise challenge was 6.2% following treatment with albuterol MDPI compared with 22.4% following treatment with placebo MDPI (Fig. 3). The difference between treatments (albuterol MDPI – placebo MDPI) was –16.2% (95% CI: –20.2% to –12.1%; *P* < 0.0001). A significant between-treatment difference in percentage fall from baseline in FEV₁ was observed by 5 min and was maintained through 30 min following the exercise challenge (*P* < 0.0001) (Fig. 4).

The percentages of patients whose maximum fall from the baseline FEV₁ after exercise challenge was <10% (fully protected), 10%–20% (partially protected), and >20% (unprotected) are shown in Fig. 5. A significantly higher percentage of patients were protected from EIB with albuterol MDPI compared with placebo MDPI (84.2% vs 15.8%; *P* < 0.0001). The odds ratio for protection against EIB with albuterol MDPI compared with placebo MDPI was 28.4 (95% CI: 9.4 to 86.4). Treatment of the 38 patients with albuterol MDPI resulted in 32 being fully protected, 5 being partially protected, and 1 being unprotected following exercise challenge (Fig. 6). Six patients receiving placebo were protected, 10 partially protected, and 22 were unprotected following exercise challenge (Fig. 6).

Recovery from EIB, defined as the time from completion of the exercise challenge to the first measured post-exercise challenge FEV₁ within 10% of the pre-exercise baseline value, was not achieved within 60 min in 1 patient (3%) following use of albuterol MDPI compared with 6 patients (16%) following use of placebo MDPI. Recovery was observed in a median of 5.1 min for patients using albuterol MDPI compared with 30.1 min for patients using placebo MDPI (*P* < 0.0001).

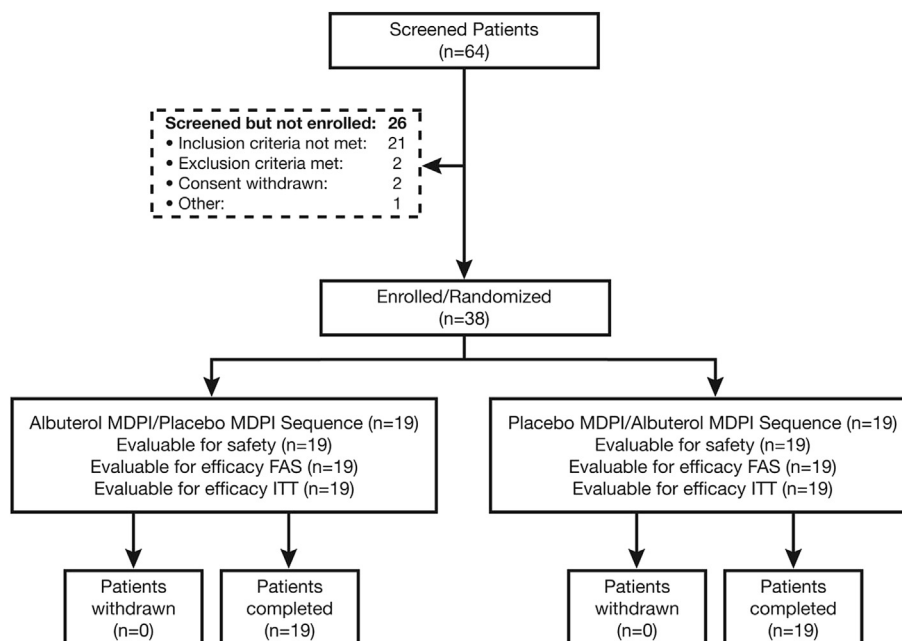


Fig. 2. Patient disposition.

3.3. Safety

There were no deaths, discontinuations due to AEs, or serious AEs during the study. Two patients reported AEs following randomization: 1 patient (3%) in the placebo MDPI group had a severe migraine and 1 (3%) patient in the albuterol MDPI group had moderate sinus bradycardia; neither was judged related to

treatment by the investigators. There was no evidence of paradoxical bronchospasms or clinical symptoms suggestive of local irritation. There were no apparent effects on vital signs during the study beyond the effect of exercise on heart rate. No clinically significant ECG findings were reported, except for 1 patient randomized to placebo MDPI who showed marked sinus bradycardia, atrial premature beats, and left axis deviation when measured at

Table 1
Demographics and baseline characteristics (randomized patients).

Characteristic	Albuterol MDPI/Placebo MDPI (n = 19)	Placebo MDPI/Albuterol MDPI (n = 19)	Total (N = 38)
Age			
Mean (SD), years	31.7 (7.1)	31.9 (8.9)	31.8 (7.9)
<18 years, n (%)	1 (5)	1 (5)	2 (5)
≥18 years, n (%)	18 (95)	18 (95)	36 (95)
Age range, years	16–43	16–50	16–50
Gender, n (%)			
Male	10 (53)	9 (47)	19 (50)
Female	9 (47)	10 (53)	19 (50)
Race, n (%)			
White	14 (74)	16 (84)	30 (79)
Black	4 (21)	2 (11)	6 (16)
Asian	0 (0)	1 (5)	1 (3)
Other	1 (5)	0 (0)	1 (3)
Ethnicity, n (%)			
Hispanic/Latino	2 (11)	2 (11)	4 (11)
Not Hispanic/Latino	17 (89)	17 (89)	34 (89)
BMI, mean (SD), kg/m ²	28.1 (4.0)	25.3 (4.6)	26.7 (4.5)
Previous history of asthma, n (%)	19 (100)	19 (100)	38 (100)
5–10 years	0	2	2
10–15 years	2	1	3
≥15 years	17	16	33
Baseline FEV ₁ , mean (SD)			
Pre-exercise challenge FEV ₁ at SV1, % predicted	84.6 (9.4)	88.2 (9.4)	86.4 (9.4)
Maximum % fall in FEV ₁ post-exercise challenge at SV1 ^a	26.1 (11.8)	26.0 (7.5)	26.1 (9.8)
Pre-dose and pre-exercise challenge FEV ₁ at SV2, % predicted	84.8 (7.5)	88.2 (8.1)	86.5 (7.9)
Postdose and pre-exercise challenge FEV ₁ at SV2, % predicted	85.2 (6.6)	88.9 (9.8)	87.0 (8.5)
Maximum % fall in FEV ₁ post-exercise challenge at SV2	23.6 (11.1)	23.4 (7.9)	23.5 (9.5)

BMI, body-mass index; SD, standard deviation; SV1, screening visit 1; SV2, screening visit 2.

^a Data for 18 patients in each treatment sequence.

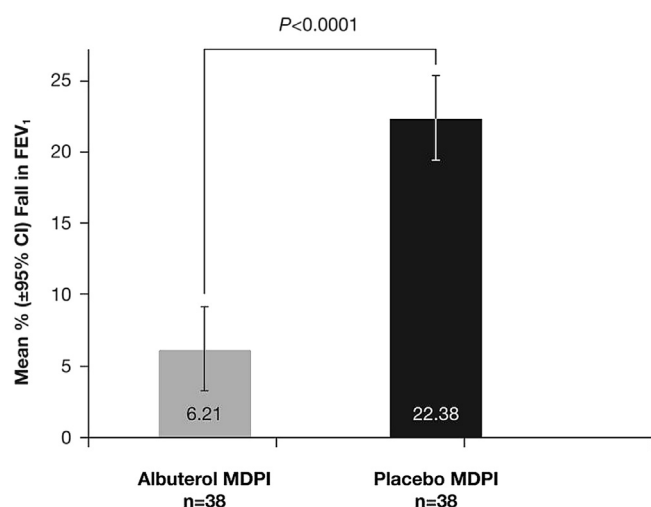


Fig. 3. Maximum percentage fall from baseline in FEV₁ observed up to 60 min after exercise challenge (full analysis set). CI, confidence interval; MDPI, multidose dry powder inhaler.

30 min before dosing at TV1. ECG findings in this patient were not clinically significant at 30 min post-exercise challenge.

4. Discussion

The results of this study demonstrate that albuterol administered via a novel inhalation-driven MDPI provides clinically significant protection ($\geq 50\%$ protection compared with placebo or $<10\%$ decrease in FEV₁ after exercise, per published guidelines) [4] from EIB in patients aged 12–50 years. Efficacy was evidenced by the significant attenuation of the maximum percentage fall in FEV₁ following the treadmill exercise challenge, and by the significantly higher proportion of patients who were fully protected against EIB (as defined by a $<10\%$ decline in FEV₁ post-exercise challenge) following treatment with albuterol MDPI compared with placebo MDPI. The criterion of $<10\%$ FEV₁ decline post-exercise challenge is considered clinically to reflect complete protection from EIB as

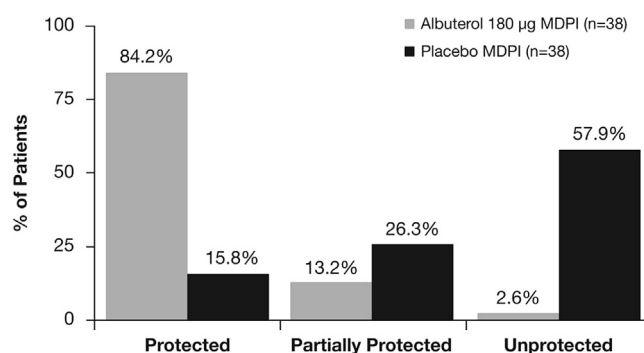


Fig. 5. Percentage of patients who were protected, partially protected, or unprotected by study treatment (full analysis set). ^aPatients were classified as protected ($<10\%$ fall), partially protected ($10\text{--}20\%$ fall), and unprotected ($>20\%$ fall) based on maximum percentage change in FEV₁ post-exercise challenge. MDPI, multidose dry powder inhaler.

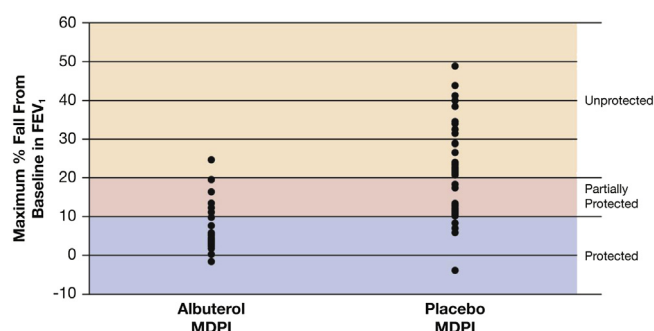


Fig. 6. Maximum percentage fall from baseline in FEV₁ in patients treated with albuterol MDPI or placebo following exercise challenge. MDPI, multidose dry powder inhaler.

defined by Weiler and colleagues [4]. The estimated mean percentage fall in FEV₁ was 6.2% in patients treated with albuterol MDPI and 22.4% in patients treated with placebo MDPI.

In the present study, the treadmill exercise challenge was

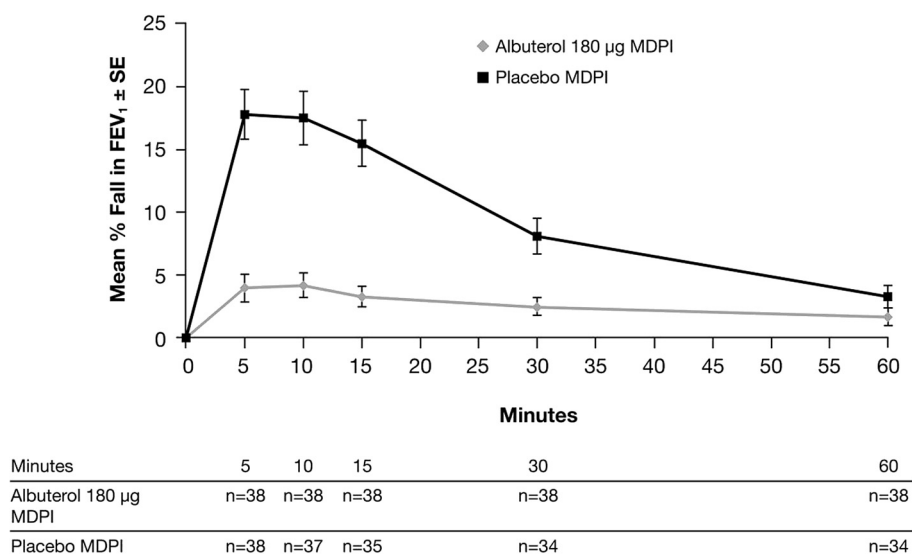


Fig. 4. Mean percentage fall from baseline in FEV₁ at each time point within 60 min post-exercise challenge (full analysis set). Four patients in the placebo group required rescue medication following the exercise challenge, after which FEV₁ values were no longer recorded. MDPI, multidose dry powder inhaler; SE, standard error.

started approximately 30 min after dosing, and protection from EIB was evident starting with the first FEV₁ assessment made 5 min post-exercise challenge. The magnitude of the protection from EIB following treatment with albuterol MDPI was consistent with studies of other albuterol formulations in patients with EIB [13,14].

Current clinical practice guidelines from the American Thoracic Society indicate that patients with EIB should receive a SABA, such as albuterol, shortly before exercise [5]. This prophylactic use of SABA is designed to minimize or prevent symptoms of EIB. As shown in this study, albuterol MDPI administered approximately 30 min before the exercise challenge attenuated the exercise-induced FEV₁ decline and protected nearly 85% of the patients from EIB.

There were no new safety issues with the single doses of albuterol MDPI used in the present study. It should be noted that this study was designed primarily to assess treatment efficacy in EIB and not to assess the long-term safety of this albuterol formulation. The safety of long-term treatment with albuterol MDPI will be assessed in other studies of this formulation in patients with asthma.

The MDI is the predominant device for delivery of inhaled medications. The effectiveness of the conventional “press-and-breathe” MDI depends on the patient’s ability to coordinate actuation of the MDI with inhalation. Inability to coordinate manual actuation and inhalation may compromise delivery of the active drug to the airways [7]. The novel inhalation-driven MDPI used in the present study eliminates the necessity for the patient to coordinate actuation with inhalation. Devices that use breath actuation have been found to reduce administration errors compared with conventional MDIs [8]. In a recent study conducted in 317 patients with asthma or chronic obstructive pulmonary disease, ease-of-use and patient satisfaction with the albuterol MDPI were assessed using a questionnaire in which responses were rated on a 7-point scale [15]. The majority (83%) of patients were somewhat to very satisfied with the albuterol MDPI inhaler. More than 90% of patients were satisfied with ease of holding and handling, using/taking, and inhaling a dose from the device.

In summary, the albuterol MDPI was statistically and clinically significant compared with placebo MDPI in protecting patients from EIB, and represents a viable option for use by patients with a history of EIB.

5. Disclosures

Nancy K. Ostrom serves as a remunerated consultant to and/or advisory board member for Novartis, Teva, Allergan, Meda, AstraZeneca, and Merck; as a remunerated speaker for Teva, Sunovion, Meda, AstraZeneca, Merck, GlaxoSmithKline, and Novartis; and has received research grants from AstraZeneca, Merck, GlaxoSmithKline, Mylan, Novartis, Schering-Plough, Sunovion, Teva, Apotex, Boehringer-Ingelheim, Cephalon, Cytos, Genentech, Johnson & Johnson, MedImmune, Nestle, Rigal, Watson, Alcon, Amgen, HRA, and Proctor & Gamble.

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