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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 (≥20% fall from pre-exercise challenge FEV_1) to treatment sequences of albuterol MDPI (180 μg [2 inhalations of 90 μg 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 ± 1.4% for albuterol MDPI versus 22.4 ± 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.

1. Introduction

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

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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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 ≥20% fall from the 5-min pre-exercise challenge absolute FEV_1, and a pre-exercise challenge best FEV_1 ≥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 FEV_1 not returning to within 20% of the pre-exercise FEV_1 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: FEV_1 ≥70% of predicted at 30 and 5 min before placebo MDPI, with the best value not exceeding ±15% of the best value measured at SV1; FEV_1 ≥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 FEV_1 ≥70% of predicted value for each predose, pre-exercise challenge determination; an FEV_1 ≥70% of predicted value for the postdose, pre-exercise challenge determination; a best predose, pre-exercise challenge FEV_1 that did not exceed ±15% of the best pre-exercise challenge FEV_1 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 FEV_1 that did not return to within 20% of their postdose, pre-exercise challenge FEV_1 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 ≥80% of the maximum rate for age (ie, 220 beats per minute minus age in years). The treadmill speed and

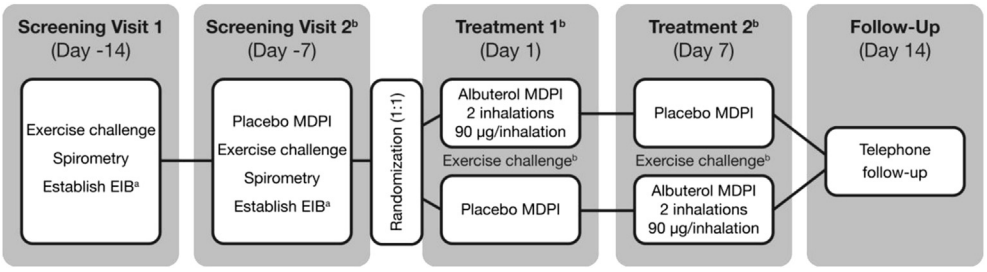

Fig. 1. Study design. The following visit windows were permitted: screening visit 1 (SV1) approximately 14 days before treatment 1 (T1); screening visit 2 (SV2) within 1–7 days after SV1; T1 within 2–7 days after SV2; treatment 2 (T2) within 2–7 days after T1; follow-up was required to be made at least 3 days after T2 but within14 days after T1. [a]EIB = ≥20% fall from the 5-min pre-exercise challenge absolute FEV_1; if criteria not met, exercise challenge was repeated once within 7 days. [b]Study 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.