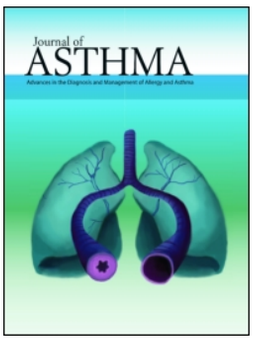

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ORIGINAL ARTICLE

Twelve- and 52-week safety of albuterol multidose dry powder inhaler in patients with persistent asthma

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Abstract

Objective: Evaluate the safety of albuterol multidose dry powder inhaler (MDPI), a novel, inhalation-driven device that does not require coordination of actuation with inhalation, in patients with persistent asthma. *Methods*: We report pooled safety data from two 12-week, multicenter, randomized, double-blind, repeat-dose, parallel-group studies and the 12-week double-blind phase of a 52-week multicenter safety study as well as safety data from the 40-week open-label phase of the 52-week safety study. In each study, eligible patients aged ≥12 years with persistent asthma received placebo MDPI or albuterol MDPI 180 μg (2 inhalations × 90 μg/inhalation) 4 times/day for 12 weeks. In the 40-week open-label phase of the 52-week safety study, patients received albuterol MDPI 180 μg (2 inhalations × 90 μg/inhalation) as needed (PRN). *Results*: During both 12-week studies and the 12-week double-blind phase of the 52-week study, adverse events were more common with placebo MDPI (50%; $n = 333$) than albuterol MDPI (40%; $n = 321$); most frequent were upper respiratory tract infection (placebo MDPI 11%, albuterol MDPI 10%), nasopharyngitis (6%, 5%), and headache (6%, 4%). Incidences of β_2-agonist-related events (excluding headache) during the pooled 12-week dosing periods were low (≤1%) in both groups. The safety profile with albuterol MDPI PRN during the 40-week open-label phase [most frequent adverse events: nasopharyngitis (12%), sinusitis (11%), upper respiratory tract infection (9%)] was similar to that observed during the 12-week pooled analysis. *Conclusions*: The safety profile of albuterol MDPI 180 μg in these studies was comparable with placebo MDPI and consistent with the well-characterized profile of albuterol in patients with asthma.

Keywords

Albuterol, asthma, dry powder inhaler, inhalation device, safety

History

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Introduction

A common challenge in the use of inhaler devices that deliver asthma medications is improper inhalation technique, which is associated with low lung distribution, poor adherence and poorly controlled asthma [1–4]. Achieving the correct synchronization of inhalation following actuation has been shown to be the main step that patients fail during inhaler technique assessment [4]. A novel, inhalation-driven, multidose dry powder inhaler (MDPI; Teva Pharmaceuticals, Inc., Frazer, PA) that does not require patient coordination of device actuation with inhalation has been developed with the goal of reducing administration errors associated with conventional metered-dose inhalers (MDIs).

Patients with asthma need quick-relief ''rescue'' medication, such as short-acting β_2-adrenergic agonists (SABAs; e.g. albuterol), that promptly reverses acute airflow obstruction and relieves bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, shortness of breath and wheezing [5]. Asthma treatment guidelines recommend the combination of controller medication along with quick-relief rescue medication for the treatment of persistent asthma [5]. Studies of long-term albuterol use in patients with asthma have indicated that regular use is well tolerated [6,7]. Studies have also demonstrated the efficacy and tolerability of albuterol/salbutamol delivered with either an MDI or earlier dry powder inhalers [8–10].

Long-term controller therapy for asthma is available in multiple MDIs and dry powder inhalers. While albuterol is currently available in multiple pressurized MDI and nebulized formulations, there is an unmet need for a dry powder inhaler rescue medication to complement the frequent usage of controller dry powder inhalers. Use of the same type of

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inhaler device for both rescue and controller medications requires that the patient master only one inhaler technique, which may improve overall asthma treatment outcomes [11].

Previous studies have shown albuterol MDPI to be effective in patients with persistent asthma and provide protection from exercise-induced bronchoconstriction [12,13]. Here, we present an integrated safety analysis of phase 3 studies of similar design investigating albuterol MDPI in adults and adolescents with persistent asthma: two 12-week pivotal asthma efficacy studies and the initial 12-week, double-blind portion of a 52-week safety study. Safety data from the 40-week open-label phase of the 52-week safety study are also reported.

Methods

Safety data were pooled from two 12-week, multicenter, randomized, double-blind, placebo-controlled, repeat-dose, parallel-group studies (NCT01424813 and NCT01747629) conducted between December 2012 and November 2013 at multiple study centers (a total of 55 sites) located throughout the USA. Efficacy data will be reported elsewhere. Data from the initial 12-week, randomized, double-blind, placebo-controlled, parallel-group period of a separate 52-week safety study (NCT01698320) conducted from October 2012 to December 2013 at 30 US study centers were also included in the pooled analysis. In this 52-week study, the initial 12-week period was followed by a 40-week open-label phase during which all patients received albuterol MDPI as needed (PRN). All studies were conducted in full accordance with Good Clinical Practice: Consolidated Guideline (E6) and any applicable national and local laws and regulations. All protocols were approved by the appropriate institutional review board, and written informed consent was obtained from each patient before screening.

Clinical trial registry information

All three trials mentioned herein are registered at www.clinicaltrials.gov: NCT01424813, NCT01747629 and NCT01698320.

Patients

Each of the three studies enrolled male or female patients aged 12 years or older with a diagnosis of persistent asthma in accordance with the National Asthma Education and Prevention Program Guidelines Expert Panel Report 3 [5]. Inclusion criteria specific to the two pivotal efficacy studies required that patients have persistent asthma for a minimum of 3 months that was stable for at least 4 weeks before screening; forced expiratory volume in 1 second (FEV_1) 50–80% (50–85% for adolescents 12–17 years of age) predicted for age, height, gender, and race per National Health and Nutrition Examination Survey (NHANES) III reference values [14]; use of a stable inhaled corticosteroid (ICS) dose equivalent to $\leq$500 µg fluticasone propionate per day for at least 4 weeks (patients remained on the same dose of ICSs for the duration of the study); reversible bronchoconstriction ($\geq$15% increase from baseline FEV_1 within 30 min after albuterol hydrofluoroalkane [HFA] MDI, 2 inhalations × 90 µg/inhalation) demonstrated via spirometry at the screening visit; and the ability to withhold ICS and rescue medication for 6 h before spirometry. Eligibility criteria specific to the 52-week safety study required current use of an MDI containing any SABA (e.g. albuterol and levalbuterol) on average of at least once/week over the 4 weeks before screening.

Exclusion criteria were matched across all three studies. Patients were excluded if they had known hypersensitivity to albuterol, any of the excipients in the formulations, or severe milk protein allergy; history of an upper or lower respiratory tract infection or disorder ($\leq$1 week); history of alcohol or drug abuse ($\leq$2 years); use of any prohibited concomitant medications (e.g. oral β_2-adrenergic agonists for asthma, β-blocking antihypertensive products, monoamine oxidase inhibitors and tricyclic antidepressants); history of a life-threatening asthma episode requiring intubation and/or associated with hypercapnia, respiratory arrest or hypoxic seizures; asthma exacerbation requiring oral or systemic corticosteroids ($\leq$3 months) or hospitalization for asthma ($\leq$6 months). Patients were not enrolled if they had any clinically significant endocrine, hematologic, hepatic, renal, gastrointestinal, neurological, cardiac, metabolic, or immunological disorder, or any nonasthmatic acute or chronic pulmonary condition. Pregnant or lactating women were not included, and all women of childbearing potential were required to use effective contraception throughout the study.

Study design

Study designs through the 12-week double-blind phases (Figure 1) were similar in all three studies. After an initial screening visit, eligible patients entered a 2-week run-in period during which they self-administered single-blind placebo MDPI 4 times/day (QID; at approximately 7 am, 12 noon, 5 pm and bedtime). Patients were required to record the following information in daily diaries during the run-in period and throughout the study: study medication use (time and number of inhalations), daily asthma symptom scores, rescue medication use and peak expiratory flow rate measured each morning after assessment of asthma symptoms. At the end of the run-in period, compliance with the schedule of study drug administration and daily diary completion was assessed. In the 12-week efficacy studies, noncompliance was defined as missing any diary entries or study dose administrations on at least 4 days or missing all scheduled dose administrations on any single day during the last 7 days of the run-in period; in the 52-week safety study, noncompliance was defined as being less than 80% compliant with scheduled inhaler use and diary card completion for the last 5 days of the run-in period. Patients who met compliance criteria and continued to meet eligibility criteria during the run-in period were randomized in a 1:1 ratio to albuterol MDPI 90 µg/inhalation × 2 inhalations (180 µg total) QID or placebo MDPI 2 inhalations QID at approximately 7 am, 12 noon, 5 pm, and bedtime for the 12-week, double-blind period. The assigned treatment for each patient was defined by a randomization code number via a central interactive voice response system/interactive web response system. Patients returned at day 8, day 22 and for routine visits every 21 days thereafter for a total of six visits across 12 weeks. During the open-label portion of the

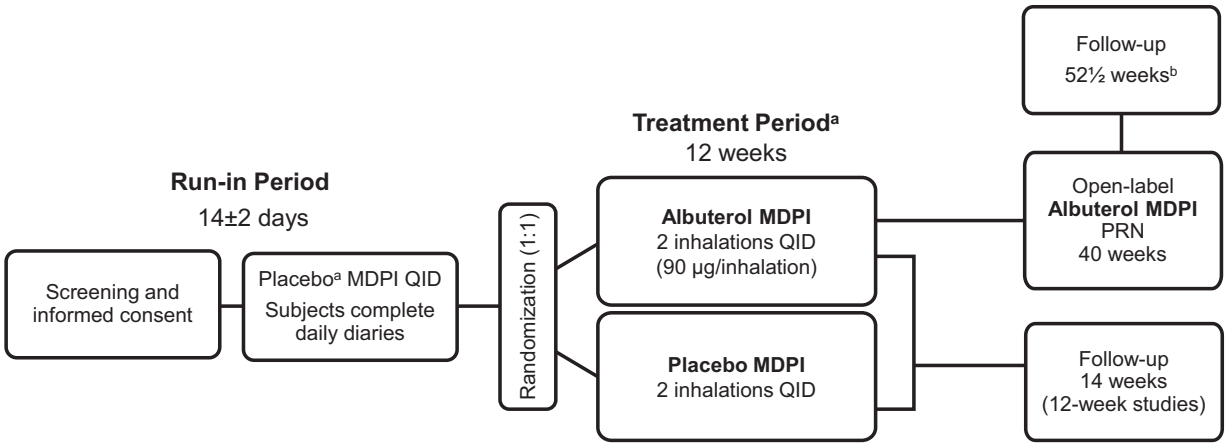

Figure 1. Study design of three pivotal phase three studies (ABS-AS-301, ABS-AS-304 and ABS-AS-307). HFA, hydrofluoroalkane; MDI, metered-dose inhaler; MDPI, multidose dry powder inhaler; PRN, as needed; QID, four times a day. [a]All patients were provided with an albuterol HFA MDI to use as needed for breakthrough asthma symptoms. [b]Final follow-up of adverse events was conducted 3 (±1) days after the last treatment visit.

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52-week safety study (weeks 13–52), all patients were provided with open-label albuterol MDPI 90 µg administered as two inhalations every 4–6 h PRN for the relief of asthma symptoms and, if applicable, two inhalations 15–30 min before sports/exercise. In all three studies, patients were provided with a rescue albuterol HFA MDI inhaler to use as needed for relief of asthma symptoms. During the double-blind period, the investigators, the sponsor, and any personnel involved in patient assessment, monitoring, analysis, and data management (excluding the designated clinical supplies unit personnel) were blinded to the patient's treatment assignment. To ensure blinding, patients were also dispensed a single MDPI inhaler, containing either placebo or albuterol.

Safety assessments

Safety data for the albuterol MDPI and placebo MDPI groups from the two 12-week studies along with the first 12 weeks of the 52-week safety study were combined for this analysis. Adverse events, physical examinations and vital signs were assessed in all studies. Electrocardiogram (ECG), hematology, clinical chemistry and urinalysis evaluations were not performed in the two 12-week efficacy studies; in the 52-week safety study, blood samples were collected for laboratory evaluations and ECGs were conducted at the screening visit, week 12 and week 52 or early termination/discontinuation.

Statistical analysis

The integrated safety population included all patients who received at least one dose of study drug in the three pivotal studies. The incidences of death, discontinuations, adverse events and serious adverse events during the 12-week phases of all three studies were assessed. To assess the incidence of adverse events potentially related to β_2-adrenergic agonists, known possible events associated with the use of β_2-adrenergic agonists [e.g. cardiovascular, metabolic (low potassium levels, elevated glucose levels) and central nervous system effects] were reviewed separately. For the 52-week safety study, adverse events that occurred during the 40-week open-label phase in patients treated with albuterol MDPI during the 12-week double-blind period and who continued on albuterol MDPI PRN during the open-label phase are presented.

Results

Patient disposition and baseline characteristics

A total of 1142 patients were screened and 711 were enrolled in the run-in periods of the three pivotal studies; of these, 655 patients were randomized and 653 received at least one dose of study drug or placebo and comprised the safety population for the 12-week integrated analysis (Figure 2). The majority of patients (≥94%) in both treatment groups in the safety population completed the study. The most common reasons for withdrawal in the albuterol MDPI group were withdrawal by patient (1%) and loss to follow-up (1%). Demographic characteristics were well balanced across treatment groups (Table 1). The mean age was 37.6 years and adolescent patients (12–17 years) represented 16% of the population. Most patients were white (75%), an appreciable minority (21%) was black and 11% were Hispanic or Latino. The mean body mass index was 28.6 kg/m^2 (range: 14.6–57.9 kg/m^2). All patients enrolled in the two 12-week studies continued to receive concomitant medications with an indication for asthma throughout the study. Of the 168 patients treated with albuterol MDPI in the 52-week safety study, 100 (60%) were receiving concomitant asthma medications.

Safety

Twelve-week double-blind treatment periods

There were no deaths during the pooled 12-week treatment periods. A total of five patients (three in the albuterol MDPI group and two in the placebo MDPI group) experienced an adverse event resulting in study drug withdrawal during the 12-week treatment period. In the albuterol MDPI group, the adverse events resulting in discontinuation were pharyngeal abscess ($n = 1$); migraine ($n = 1$) and enterocolitis, increased blood pressure, oral herpes simplex, hypokalemia, hypomagnesemia and hyponatremia ($n = 1$). In the placebo MDPI group, adverse events resulting in discontinuation were asthma ($n = 1$); and dysphonia and oropharyngeal pain ($n = 1$).

Three patients experienced serious adverse events: two (0.6%) patients in the albuterol MDPI group (one with

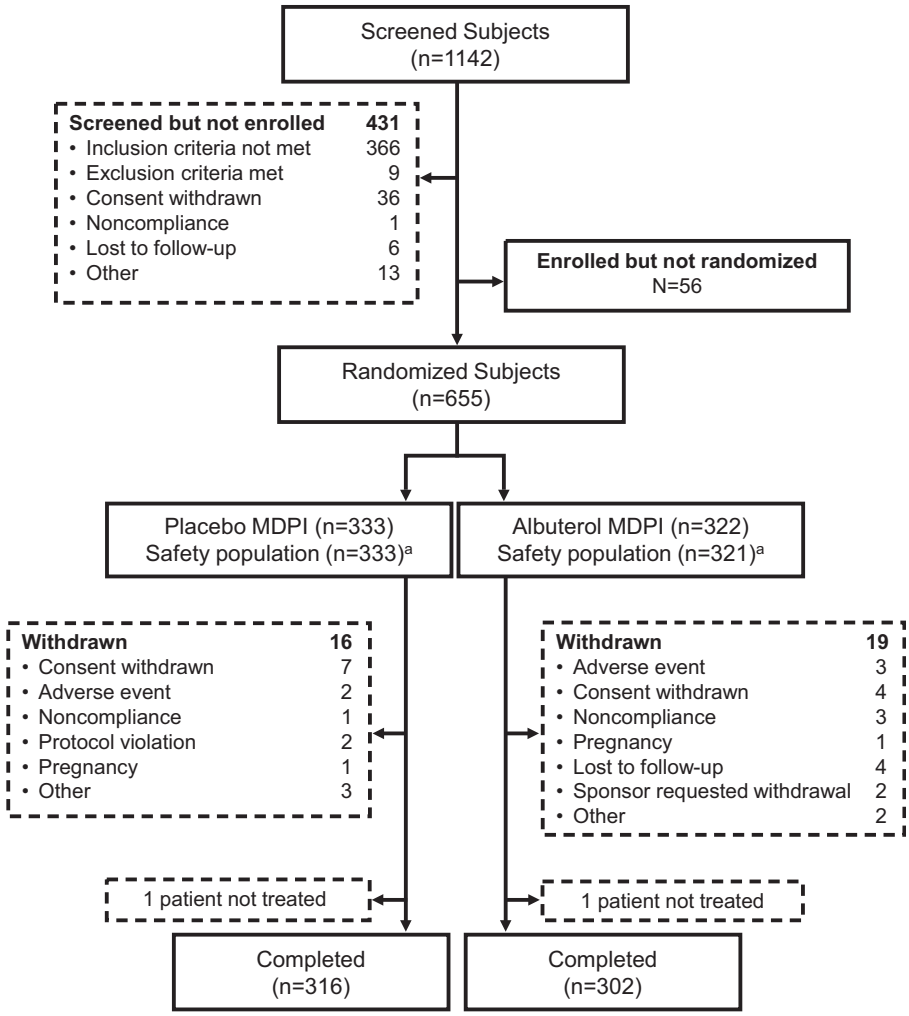

Figure 2. Patient disposition for the integrated safety population. MDPI, multidose dry powder inhaler; QID, four times a day. [a]One patient in one of the 12-week double-blind studies took both albuterol MDPI and placebo MDPI in error and was therefore included in both treatment groups of the safety population. Thus, 321 patients were treated with albuterol MDPI 180 µg QID and 333 patients were treated with placebo MDPI.

Table 1. Demographic characteristics (12-week integrated safety population).

Characteristic	Albuterol MDPI 180 µg (2 inhalations × 90 µg/inhalation) ($n = 321$)	Placebo MDPI ($n = 333$)	Total ($n = 653$)[a]
Age, years			
Mean (SD)	37.5 (16.3)	37.7 (15.8)	37.6 (16.0)
12–17, *n* (%)	55 (17)	50 (15)	105 (16)
18–64, *n* (%)	252 (79)	273 (82)	524 (80)
≥65, *n* (%)	14 (4)	10 (3)	24 (4)
Sex, *n* (%)			
Male	139 (43)	130 (39)	268 (41)
Female	182 (57)	203 (61)	385 (59)
Race, *n* (%)			
White	238 (74)	254 (76)	491 (75)
Black	70 (22)	70 (21)	140 (21)
Other[b]	13 (4)	9 (3)	22 (3)
Ethnicity, *n* (%)			
Hispanic or Latino	39 (12)	37 (11)	75 (11)
Not Hispanic or Latino	282 (88)	296 (89)	578 (89)
BMI, mean (SD), kg/m^2	28.4 (7.0)	28.8 (6.8)	28.6 (6.9)

BMI, body mass index; MDPI, multidose dry powder inhaler; SD, standard deviation.
[a]One patient randomized to albuterol MDPI in the 52-week safety study was assigned an incorrect medication kit and was also treated with placebo MDPI. This patient is included in each treatment group but is counted only once for the overall total.
[b]Other includes Asian, American Indian, Alaskan Native and Pacific Islander.

enterocolitis and one with pharyngeal abscess) and one (0.3%) patient in the placebo MDPI group (spontaneous abortion during the first trimester that resolved and was not related to study drug). All serious adverse events were resolved. The patients with enterocolitis and pharyngeal abscess were withdrawn from the study.

The most common (≥5%) adverse events were upper respiratory tract infection, nasopharyngitis and headache

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Table 2. Adverse events (12-week integrated safety population).

Event	Number (%) of patients: Albuterol MDPI 180 µg (2 inhalations × 90 µg/inhalation) ($n = 321$)	Placebo MDPI ($n = 333$)
≥1 Adverse event	128 (40)	166 (50)
≥1 Adverse event leading to withdrawal from study	3 (<1)	2 (<1)
≥1 Serious adverse event	2 (<1)	1 (<1)
Adverse events in >2% of patients in either treatment group (preferred term)		
Upper respiratory tract infection	31 (10)	38 (11)
Nasopharyngitis	17 (5)	21 (6)
Headache	13 (4)	19 (6)
Oropharyngeal pain	11 (3)	13 (4)
Cough	10 (3)	13 (4)
Sinusitis	8 (2)	14 (4)
Influenza	5 (2)	13 (4)
Bronchitis	3 (<1)	11 (3)

MDPI, multidose dry powder inhaler.

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(Table 2). The incidence of adverse events most likely related to β_2-adrenergic agonists was low and only headache and sinus headache were reported in at least 1% of patients in the albuterol group (Table 3). Headache was reported less frequently with albuterol MDPI (4%) than with placebo MDPI (6%) and the incidence of sinus headache was similar in the two groups (1% and <1%, respectively).

The majority of physical examination findings were normal at baseline and at week 12; there were no clinically meaningful trends in mean changes from baseline for any vital signs.

Fifty-two-week safety study

Of the 168 patients treated with albuterol MDPI during the 12-week double-blind phase, 156 continued in the 40-week open-label albuterol MDPI phase. There were no deaths during the open-label phase. A total of two patients experienced an adverse event that caused study drug withdrawal (one patient with pancreatic carcinoma and one with gastrointestinal carcinoma). Of the 156 patients who were treated with albuterol MDPI during the 12-week double-blind phase and continued on albuterol MDPI during the 40-week open-label phase, four experienced serious adverse events during the 40-week open-label phase. Of these four patients, one experienced cellulitis and one experienced atrial fibrillation, each of which resolved; one experienced pancreatic carcinoma and one experienced gastrointestinal carcinoma, neither of which resolved.

The most frequent adverse events during the open-label phase were nasopharyngitis (12%), sinusitis (11%), and upper respiratory tract infection (9%; Table 4). There were no clinically meaningful trends in changes in clinical laboratory variables and vital signs from screening to week 52 in patients who continued to receive albuterol MDPI during the open-label phase. There were no clinically relevant ECG findings in albuterol MDPI-treated patients at any time point in the 52-week safety study; no patient had a QTc interval length (Bazett or Fridericia) longer than 500 ms at any time point.

Table 3. Adverse events related to β_2-adrenergic agonists (12-week integrated safety population).

Preferred term	Number (%) of patients: Albuterol MDPI 180 µg (2 inhalations × 90 µg/inhalation) ($n = 321$)	Placebo MDPI ($n = 333$)
Headache	13 (4)	19 (6)
Sinus headache	4 (1)	3 (<1)
Migraine	2 (<1)	3 (<1)
Anxiety	2 (<1)	0
Feeling jittery	2 (<1)	0
Tremor	2 (<1)	0
Arthralgia	1 (<1)	4 (1)
Myalgia	1 (<1)	3 (<1)
Hypertension	1 (<1)	2 (<1)
Increased blood pressure	1 (<1)	1 (<1)
Muscle spasms	1 (<1)	1 (<1)
Angina pectoris	1 (<1)	0
Hot flush	1 (<1)	0
Hypokalemia	1 (<1)	0
Insomnia	1 (<1)	0
Palpitations	1 (<1)	0
Paresthesia	1 (<1)	0
Peripheral edema	1 (<1)	0
Dizziness	0	2 (<1)
Nerve compression	0	1 (<1)
Orthostatic intolerance	0	1 (<1)
Syncope	0	1 (<1)
Tension headache	0	1 (<1)

MDPI, multidose dry powder inhaler.

Discussion

In this integrated safety analysis of three randomized, placebo-controlled studies in patients with asthma, QID dosing of albuterol MDPI over 12 weeks was generally well tolerated. The safety profile of albuterol MDPI was generally consistent with that of the well-characterized profile of inhaled albuterol in adults and adolescents with asthma [6,7,15–17]. A previous 12-week safety study by Tinkelman et al. [7] reported serious adverse events in 2.6% of patients in the albuterol HFA MDI group and 0.5% of patients in the albuterol chlorofluorocarbon (CFC) MDI group, percentages

Table 4. Adverse events occurring in >2% of patients treated with albuterol MDPI PRN during the open-label phase of the 52-week safety study.

Preferred term	Albuterol MDPI 180 µg (2 inhalations × 90 µg/inhalation) Open-label phase Weeks 13–52 $n = 168$[a] Number (%) of patients
Nasopharyngitis	20 (12)
Sinusitis	19 (11)
Upper respiratory tract infection	15 (9)
Cough	11 (7)
Oropharyngeal pain	10 (6)
Headache	10 (6)
Pyrexia	7 (4)
Bronchitis	6 (4)
Abdominal pain upper	6 (4)
Arthralgia	5 (3)

MDPI, multidose dry powder inhaler; PRN, as needed; QID, four times daily.

[a]Patients enrolled in the albuterol MDPI QID arm during the 12-week double-blind phase ($n = 168$); 156 of those patients continued in the open-label phase of the study and received albuterol MDPI PRN.

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similar to the present study (0.6% during the 12-week double-blind pooled treatment periods and 2.6% during the 40-week open-label phase). Tinkelman et al. also reported a low incidence of adverse events typically associated with β_2-adrenergic agonists, including palpitations (2% in both albuterol HFA and CFC MDI groups) and nausea (10%, albuterol HFA MDI group; 9%, albuterol CFC MDI group). The present study also reported low rates of adverse events potentially related to β_2-adrenergic agonists, with only headache (4%) and sinus headache (1%) being reported in at least 1% of patients in the albuterol group in the 12-week double-blind pooled treatment periods. In a study in which patients used an albuterol CFC MDI and then switched to an albuterol HFA MDI, the incidence of headache was 13% for the 3 weeks that patients continued on the albuterol CFC MDI and 5% for the first 3 weeks following the switch to the albuterol HFA MDI [18], further suggesting that the results of this study are consistent with the well-characterized profile of albuterol.

Evaluation of the 52-week MDPI safety study indicated no evidence of a change in the reporting pattern of adverse events. The incidence of serious adverse events was low and occurred in only 4 of the 156 patients (2.5%) who continued on albuterol MDPI during the 40-week open-label phase. In a similarly conducted study, Ramsdell et al. evaluated the safety of albuterol HFA in patients with asthma administered twice daily over 1 year [6]. Serious adverse events were reported in 3% of patients receiving albuterol HFA, consistent with the safety profile reported in the present study. Additionally, a study conducted by Hamilos et al. evaluated the long-term safety of levalbuterol HFA in comparison to racemic albuterol HFA administered to patients with stable asthma over 12 months. The incidence of serious adverse events was similar between the two treatment groups (3.6% for levalbuterol and 5.2% for racemic albuterol) and consistent with the current study [19].

In the present study, albuterol was delivered via a new MDPI, which is distinct from available albuterol delivery systems and represents a novel approach for the effective delivery of rescue medication for patients with asthma. Delivery via this MDPI eliminates the need for the patient to coordinate actuation with inhalation, a maneuver that may be difficult for patients to manage, particularly the elderly and young children. Prior to the development of the albuterol MDPI, inhaled albuterol was most commonly delivered via an MDI, which requires the patient's coordination of actuation at the beginning of inspiration [20]. The act of synchronizing (achieving the correct inhalation following actuation) has been one of the main steps that patients fail upon assessment of their inhaler technique [4]. Poor inhaler technique has been associated with uncontrolled asthma [3,4,21–27]; therefore, devices that simplify the delivery of inhaled asthma medications may lead to improved asthma control.

Previous studies have demonstrated similar efficacy and safety of albuterol/salbutamol delivered via MDI or dry powder inhaler devices [8–10]. The incidence and type of adverse events as well as effects on cardiac measures, blood pressure and heart rate were independent of the delivery device used to administer albuterol/salbutamol [8,10]. Similarly, in the present study, there were no effects evident on ECG or QTc intervals with administration of albuterol MDPI over 52 weeks. The development of this MDPI for the delivery of albuterol and ICSs provides an alternative to currently available MDIs and allows patients to use similar devices for the delivery of both controller and rescue medication for asthma control, which may mitigate drug administration issues seen with pressurized MDI devices.

While this study represents a large aggregate database of placebo-controlled safety evaluations of albuterol MDPI versus placebo, a potential limitation is the lack of a direct active comparator. However, results in this assessment are generally consistent with prior evaluations of inhaled albuterol formulations. An additional limitation of this study is the restriction to patients with asthma and patients aged 12 years or older, recognizing that bronchodilator medications are utilized in other disease states such as chronic obstructive pulmonary disease and in pediatric age groups not considered in this study.

Conclusions

An integrated safety analysis of three phase three trials demonstrated that albuterol 180 µg (2 inhalations × 90 µg/inhalation) administered QID for 12 weeks from a novel MDPI is well-tolerated, with a safety profile comparable to placebo MDPI. Open-label treatment with albuterol MDPI PRN, which is consistent with rescue inhaler use in the real-world setting, demonstrated a safety profile consistent with the extensively characterized safety profile of currently available albuterol products delivered via MDIs in patients with asthma. These studies show that albuterol delivered by the novel MDPI under evaluation is a generally well-tolerated rescue treatment for asthma. The MDPI represents an option for adults and adolescents with persistent asthma and may help address administration errors associated with conventional MDIs.

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Declaration of interest

These studies were sponsored by Teva Branded Pharmaceutical Products R&D, Inc. Medical writing assistance was provided by Lisa Feder, PhD of Peloton Advantage and was funded by Teva Branded Pharmaceutical Products R&D, Inc. Teva provided a full review of the article. Gordon Raphael has no declaration of interest to report. Herminia Taveras and Harald Iverson are employees of Teva Pharmaceuticals, Miami, FL. Christopher O'Brien is a former employee of Teva Pharmaceuticals, Frazer, PA. David Miller is employed by Northeast Medical Research Associates, which has received research grants from Teva Pharmaceuticals.

References

1. Robinson CA, Tsourounis C. Inhaled corticosteroid metered-dose inhalers: how do variations in technique for solutions versus suspensions affect drug distribution? Ann Pharmacother 2013;47:416–420.
2. Leach C. Effect of formulation parameters on hydrofluoroalkane-beclomethasone dipropionate drug deposition in humans. J Allergy Clin Immunol 1999;104:S250–S252.
3. Baddar S, Jayakrishnan B, Al-Rawas OA. Asthma control: importance of compliance and inhaler technique assessments. J Asthma 2014;51:429–434.
4. Levy ML, Hardwell A, McKnight E, Holmes J. Asthma patients' inability to use a pressurised metered-dose inhaler (pMDI) correctly correlates with poor asthma control as defined by the Global Initiative for Asthma (GINA) strategy: a retrospective analysis. Prim Care Respir J 2013;22:406–411.
5. Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, US Department of Health and Human Services; 2007. Available from: http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report [last accessed 18 August 2015].
6. Ramsdell JW, Klinger NM, Ekholm BP, Colice GL. Safety of long-term treatment with HFA albuterol. Chest 1999;115:945–951.
7. Tinkelman DG, Bleecker ER, Ramsdell J, Ekholm BP, Klinger NM, Colice GL, Slade HB. Proventil HFA and ventolin have similar safety profiles during regular use. Chest 1998;113:290–296.
8. Bondesson E, Friberg K, Soliman S, Lofdahl CG. Safety and efficacy of a high cumulative dose of salbutamol inhaled via Turbuhaler or via a pressurized metered-dose inhaler in patients with asthma. Respir Med 1998;92:325–330.
9. Golish J, Curtis-McCarthy P, McCarthy K, Kavuru M, Wagner W, Beck G, Eng P. Albuterol delivered by metered-dose inhaler (MDI), MDI with spacer, and Rotahaler device – a comparison of efficacy and safety. J Asthma 1998;35:373–379.
10. Geoffroy P, Lalonde RL, Ahrens R, Clarke W, Hill MR, Vaughan LM, Grossman J. Clinical comparability of albuterol delivered by the breath-actuated inhaler (Spiros) and albuterol by MDI in patients with asthma. Ann Allergy Asthma Immunol 1999;82:377–382.
11. Price D, Chrystyn H, Kaplan A, Haughney J, Roman-Rodriguez M, Burden A, Chisholm A, et al. Effectiveness of same versus mixed asthma inhaler devices: a retrospective observational study in primary care. Allergy Asthma Immunol Res 2012;4:184–191.
12. Ostrom NK, Taveras H, Iverson H, Pearlman DS. A novel albuterol multidose dry powder inhaler in adult and adolescent patients with exercise-induced bronchoconstriction: a single-dose study [abstract]. Presented at: Annual Scientific Meeting of the American College of Allergy, Asthma and Immunology; 2014 Nov 6–10; Atlanta, GA.
13. Raphael G, Taveras H, Iverson H, O'Brien C, Miller D. Efficacy of albuterol multidose dry powder inhaler versus placebo in subjects 12 years of age and older with persistent asthma [poster P74]. Presented at: Annual Scientific Meeting of the American College of Allergy, Asthma and Immunology; 2014 Nov 6–10; Atlanta, GA.
14. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179–187.
15. Gross G, Cohen RM, Guy H. Efficacy response of inhaled HFA-albuterol delivered via the breath-actuated Autohaler inhalation device is comparable to dose in patients with asthma. J Asthma 2003;40:487–495.
16. Ventolin HFA [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2012.
17. Proair HFA [package insert]. Horsham, PA: Teva Respiratory, LLC; 2012.
18. Lumry W, Noveck R, Weinstein S, Barnhart F, Vandermeer A, Murray A, Reisner C. Switching from Ventolin CFC to Ventolin HFA is well tolerated and effective in patients with asthma. Ann Allergy Asthma Immunol 2001;86:297–303.
19. Hamilos DL, D'Urzo A, Levy RJ, Marcus M, Tripp K, Parsey M, Baumgartner RA, et al. Long-term safety study of levalbuterol administered via metered-dose inhaler in patients with asthma. Ann Allergy Asthma Immunol 2007;99:540–548.
20. Fink JB, Rubin BK. Problems with inhaler use: a call for improved clinician and patient education. Respir Care 2005;50:1360–1374.
21. Al-Jahdali H, Ahmed A, Al-Harbi A, Khan M, Baharoon S, Bin SS, Halwani R, et al. Improper inhaler technique is associated with poor asthma control and frequent emergency department visits. Allergy Asthma Clin Immunol 2013;9:8.
22. Dalcin PT, Grutcki DM, Laporte PP, Lima PB, Menegotto SM, Pereira RP. Factors related to the incorrect use of inhalers by asthma patients. J Bras Pneumol 2014;40:13–20.
23. Giraud V, Allaert FA, Roche N. Inhaler technique and asthma: feasability and acceptability of training by pharmacists. Respir Med 2011;105:1815–1822.
24. Onyedum C, Desalu O, Nwosu N, Chukwuka C, Ukwaja K, Ezeudo C. Evaluation of inhaler techniques among asthma patients seen in Nigeria: an observational cross sectional study. Ann Med Health Sci Res 2014;4:67–73.
25. Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, Serra M, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med 2011;105:930–938.
26. Reznik M, Silver EJ, Cao Y. Evaluation of MDI-spacer utilization and technique in caregivers of urban minority children with persistent asthma. J Asthma 2014;51:149–154.
27. Ottenbros S, Teichert M, de Groot R, Griens F, Sodihardjo F, Wensing M, de Gier JJ. Pharmacist-led intervention study to improve drug therapy in asthma and COPD patients. Int J Clin Pharm 2014;36:336–344.