

Pharmacokinetics and pharmacodynamics of albuterol multidose dry powder inhaler and albuterol hydrofluoroalkane in children with asthma

Anoshie Ratnayake, M.D., M.P.H.,¹ Herminia Taveras, Ph.D., M.P.H.,² Harald Iverson, Ph.D.,³ and Paul Shore, M.D., M.S.⁴

ABSTRACT

Background: Many children struggle with the use of albuterol hydrofluoroalkane (HFA) inhalers. Albuterol multidose dry powder inhaler (MDPI) may simplify rescue bronchodilator use in children.

Objective: To compare the pharmacokinetics (PK), pharmacodynamics (PD), and tolerability of albuterol MDPI and albuterol HFA after a single inhaled dose in children with asthma.

Methods: This single-center, open-label, two-period crossover study randomized children to albuterol MDPI or HFA 180 µg on two treatment days with a 4- to 14-day washout. Plasma albuterol concentrations were measured before the dose and up to 10 hours after the dose to determine the primary PK values of area under the plasma concentration-versus-time curve from time 0 to the last measurable concentration (AUC_{0-t}), maximum observed concentration (C_{max}), and AUC from time 0 extrapolated to infinity (AUC_{0-inf}). Heart rate and blood pressure before the dose and after the dose were monitored for PD effects, and adverse events (AE) were monitored for overall safety.

Results: Fifteen children, ages 6–11 years, were included (PK, $n = 13$ for time to C_{max} and terminal half-life of elimination; $n = 12$ for AUC and C_{max} due to incomplete data). AUC_{0-t} (geometric mean ratio [GMR] 1.056 [90% confidence interval {CI}, 0.88–1.268]) and AUC_{0-inf} (GMR 0.971 [90% CI, 0.821–1.147]) were comparable between treatments. C_{max} was larger for albuterol MDPI versus HFA (GMR 1.340 [90% CI, 1.098–1.636]). PD parameters between the treatments were comparable. No deaths, serious AEs, treatment-emergent AEs, or withdrawals due to AEs were reported for either treatment.

Conclusion: Albuterol MDPI and albuterol HFA had comparable PK and PD in children after a single 180-µg dose. ClinicalTrials.gov identifiers NCT01899144 and NCT02126839.

(Allergy Asthma Proc 37:370–375, 2016; doi: 10.2500/aap.2016.37.3985)

Albuterol, a short-acting β_2 -adrenergic agonist, promptly reverses acute airflow obstruction and relieves bronchoconstriction and accompanying acute asthma symptoms, such as cough, chest tightness, shortness of breath, and wheezing.¹ Inhaled short-acting β_2 -adrenergic agonists are recommended in the National Heart, Lung, and Blood Institute guidelines for the diagnosis and management of asthma as the

therapy of choice for the relief of acute asthma symptoms and the prevention of exercise-induced bronchospasm.¹ Studies of long-term albuterol use have not identified any safety concerns and have shown that albuterol is well tolerated in patients with asthma.^{2,3} Thus, albuterol is efficacious and safe for the treatment of asthma.^{2,3}

Albuterol is currently available in multiple metered-dose inhaler (MDI) formulations that require the patient to coordinate actuation with inspiration for proper drug delivery.⁴ Proper use of an MDI can be difficult for patients to learn, as demonstrated by the results of a study that found that, even after being shown how to use an MDI on three separate occasions, >65% of patients failed to use their MDI correctly.⁵ The technique can be especially difficult for pediatric patients, as found in a study in which more than half (55%) of the patients ages 6 to 10 years were identified as using MDIs improperly.⁶ An inability to coordinate manual actuation with inspiration may compromise drug delivery to the airways, which potentially results in suboptimal efficacy.⁴

A novel, inhalation-driven albuterol multidose dry powder inhaler (MDPI) (ProAir RespiClick; Teva Phar-

From ¹Allergy/Immunology and Respiratory Studies, WCCT Global, Costa Mesa, California, ²Clinical Research and Development, ³Statistics Department, and ⁴Clinical Research and Development, Teva Pharmaceuticals, Frazer, Pennsylvania

H. Taveras and H. Iverson are employees of Teva Pharmaceuticals, Miami, Florida. P. Shore was an employee of Teva Pharmaceuticals, Frazer, Pennsylvania, at the time of manuscript preparation. A. Ratnayake has no conflicts of interest pertaining to this article

This study was sponsored by Teva Branded Pharmaceutical Products R&D, Inc. Medical writing assistance was provided by Lisa Feder, Ph.D., Peloton Advantage, and was funded by Teva Branded Pharmaceutical Products R&D, Inc. Teva provided a full review of the article

Presented in poster format at the American College of Allergy, Asthma & Immunology annual scientific meeting, San Antonio, Texas, November 5–9, 2015

Address correspondence to Anoshie Ratnayake, M.D., WCCT Global, 3545 Howard Way, Costa Mesa, CA 92626

E-mail address: anoshie@gmail.com

Published online August 12, 2016

Copyright © 2016, OceanSide Publications, Inc., U.S.A.

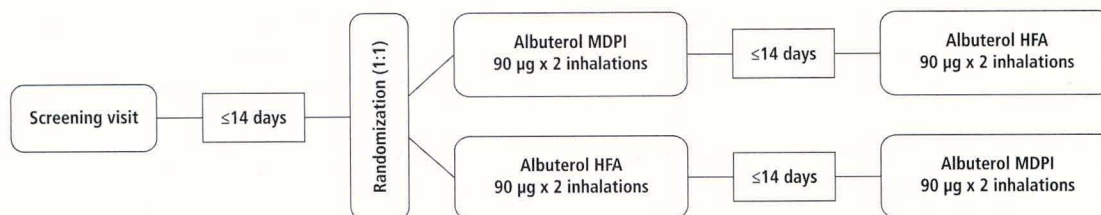


Figure 1. Study design. HFA = Hydrofluoroalkane; MDPI = multidose dry powder inhaler.

maceuticals, Inc., Frazer, PA) that does not require patient coordination of actuation with inhalation has been developed with the goal of reducing administration errors associated with conventional MDIs. The safety and efficacy of albuterol MDPI in adolescents and adults have been shown to be comparable with those of an available albuterol hydrofluoroalkane (HFA) inhaler (ProAir HFA Inhalation Aerosol; Teva Respiratory LLC, Horsham, PA). Albuterol MDPI was approved in March 2015 by the U.S. Food and Drug Administration for the treatment or prevention of bronchospasm in patients ages ≥ 12 years with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients ages ≥ 12 years.⁷

Albuterol MDPI demonstrated safety comparable with that of a placebo MDPI in an integrated safety analysis of phase III studies of patients ages ≥ 12 years with persistent asthma,⁸ as well as efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) profiles comparable with those of albuterol HFA in studies of adults and children ages ≥ 12 years.⁹

The objective of the present study, which was part of the pediatric development program for albuterol MDPI and led to the U.S. Food and Drug Administration approval of the expanded indication for treatment of patients ≥ 4 years of age, was to compare the PK, PD, and safety profiles of albuterol MDPI and albuterol HFA after administration of a single inhaled dose to pediatric patients with persistent asthma.⁷

METHODS

Patients

Male and premenarchal female patients were eligible for the study if they were ages 4 to 11 years (inclusive) with a physician diagnosis of persistent asthma of at least 3 months' duration and stable for at least 4 weeks before screening. Patients were required to have a forced expiratory volume in 1 second (FEV₁) of $\geq 80\%$ predicted for age, height, sex, and race based on the pediatric population standards. If patients were receiving inhaled corticosteroids, they were required to be on a stable low-dose regimen (≤ 200 µg fluticasone propionate per day or equivalent) for ≥ 4 weeks before screening and that regimen was expected to be maintained for the duration of the study. In addition, eligi-

ble patients required <4 inhalations per week, on average, of a rescue bronchodilator for the 4 weeks before the screening visit, were able to demonstrate an acceptable and reproducible inhalation technique with the albuterol MDPI and albuterol HFA devices, and were able to maintain a peak inspiratory flow rate of at least 30 L/min on the In-Check DIAL (Alliance Tech Medical, Inc., Granbury, TX) inhaler training device, with the device-resistance setting that corresponded to that of the Turbuhaler (AstraZeneca LP, Wilmington, DE) MDPI because it has a similar resistance to the albuterol MDPI device.

Patients were excluded if they had a known hypersensitivity to albuterol or any of the excipients in the inhaler formulations, including severe milk protein allergy, or if they had a history of life-threatening asthma (which required intubation and/or was associated with hypercapnia, respiratory arrest, or hypoxic seizures); any asthma exacerbation that required systemic corticosteroids within 3 months of the screening visit or any hospitalization for asthma within 6 months before the screening visit; proneness to orthostatic dysregulation, syncope, or blackouts; a history of a respiratory infection or disorder that had not resolved within 2 weeks of the screening visit; and the presence of a nonasthmatic acute or chronic condition, clinically significant cardiovascular disease, or clinically significant hepatic, renal, or endocrine dysfunction, stroke, uncontrolled diabetes mellitus, hyperthyroidism, convulsive disorder, and malignancy other than basal cell carcinoma. Patients were also excluded from the study if they had previously participated in an albuterol MDPI study. Signed written informed consent was obtained from the parents or guardians of all the patients and assent from the patients themselves when applicable.

Study Design

This was a phase I, single center, randomized, open-label, single-dose, two-period crossover study (Fig. 1). It consisted of a screening visit and, up to 14 days later, two treatment visits that were separated by a 4- to 14-day washout period. Eligible patients were housed overnight before each treatment visit. The treatment order was defined by a two-sequence randomization code. During the first treatment visit, eligible patients

were assigned to the next available randomization number in ascending order, with the assigned number determining the treatment sequence. Patients were randomized (1:1) to receive one of two treatment sequences: (1) albuterol MDPI 180 μg (90 μg , two inhalations), followed by the 4- to 14-day washout period, followed by albuterol HFA 180 μg (90 μg , two inhalations), or (2) albuterol HFA 180 μg (90 μg , two inhalations), followed by the 4- to 14-day washout period, followed by albuterol MDPI 180 μg (90 μg , two inhalations).

For patients to be randomized at the first treatment visit and continue in the study, they had to remain in good health; could not experience an adverse event (AE) that resulted in failure to meet selection criteria; could not use prohibited concomitant medications during the previous period; could not receive rescue albuterol for at least 72 hours before the treatment visit; could not have an asthma exacerbation, upper respiratory tract infection, or any additional treatment for asthma; and had to continue to have FEV₁ of $\geq 80\%$ of the predicted value, demonstrate correct use of each device, and have peak inspiratory flow rates of at least 30 L/min on the In-Check DIAL device.

The protocol was approved by the institutional review board of Quorum Review IRB, Seattle, Washington, and the study was conducted in full accordance with the International Council for Harmonisation Good Clinical Practice Consolidated Guideline (E6) and any applicable national and local laws and regulations. The clinical trial registration identifier is NCT01844401.

PK Assessments

At each treatment visit, blood samples were collected 5 minutes before the dose and 30, 60, 120, 360, and 600 minutes after the dose to determine the plasma albuterol concentration. The plasma albuterol concentration was measured using a validated liquid chromatography–tandem mass spectrometric method, carried out at the analytical testing facility (XenoBiotic Laboratories, Inc., Plainsboro, NJ). The lower limit of quantitation of the albuterol assay was 2 pg/mL, with linearity demonstrated between 2 and 600 pg/mL. The primary PK variables were area under the plasma concentration–versus–time curve from time 0 to the last measurable concentration up to 600 minutes after dosing (AUC_{0-t}) and maximum observed plasma albuterol concentration (C_{max}). Other PK variables of interest included AUC from time 0 extrapolated to infinity ($\text{AUC}_{0-\text{inf}}$), time to C_{max} (t_{max}), and terminal half-life of elimination ($t_{1/2}$).

PD Assessments

Sitting vital signs (blood pressure and heart rate) were recorded 10 minutes before the predose and after

the dose at the 30-, 60-, 120-, and 360-minute blood sample collections. The PD end point was the treatment effect on these vital signs over 6 hours after the dose.

Safety

Safety was assessed based on medical history, AEs, 12-lead electrocardiograms, clinical laboratory evaluations, vital signs, physical examinations, spirometry, peak expiratory flow, and concomitant medication usage. Each AE was encoded through use of the Medical Dictionary for Regulatory Activities (MedDRA; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, McLean, VA). Asthma exacerbations were defined as any worsening of asthma that required any treatment other than rescue albuterol and/or regular inhaled corticosteroid use. This included requiring the use of systemic corticosteroids and/or emergency department visits or hospitalization, a change in the patient's regular inhaled corticosteroid dose, or the addition of other asthma medications. Asthma exacerbations were not considered AEs unless they met the criteria for serious AEs. Asthma exacerbations that were not serious AEs were reported separately from AEs.

Statistical Analyses

The PK analysis set included all randomized patients who received at least one dose of study medication with sufficient data to calculate the PK parameters AUC_{0-t} and C_{max} from any treatment period before experiencing a major protocol violation. The safety population included all randomized patients who received at least one dose of study medication. Patient data were summarized with descriptive statistics. Continuous variables included number, mean (standard deviation), median, and minimum and maximum; categorical variables included patient counts and percentages.

Comparisons between treatment groups for the primary end points were carried out with an analysis of variance model that included sequence, period, and treatment group (device) as fixed effects and patient nested within sequence as a random effect. The geometric least square mean ratio among treatment groups was estimated, and the 90% confidence interval (CI) was computed. Because of the small sample size, no formal comparative analysis was planned for the purpose of assessing clinical comparability based on preset statistical criteria.

The model used for the primary PK analysis was also used to obtain point estimates of geometric means by treatment and the 90% CI for the treatment geometric mean ratio (GMR) of $\text{AUC}_{0-\text{inf}}$. Summary statistics by

treatment were calculated for AUC_{0-inf} , t_{max} , and $t_{1/2}$. For PD parameters, the maximum increase from baseline in systolic blood pressure, the maximum decrease from baseline in diastolic blood pressure, and the maximum increase from baseline in heart rate were calculated. All data were processed and summarized with SAS software, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patients

Of 24 patients screened for enrollment, 15 children ages 6 to 11 years were included in the study. There were twice as many girls as boys and equal numbers of white and black patients. All 15 patients received at least one previous medication; all received previous albuterol or albuterol sulfate; eight received previous beclomethasone dipropionate; and single patients received previous fluticasone propionate, loratadine, ibuprofen, naproxen sodium, and amoxicillin. Patient demographics and baseline clinical characteristics are summarized in Table 1.

The PK population contained 14 patients, which provided data for 13 patients per treatment group. Only the 12 patients who received both treatments were included in the comparative PK analysis. PK data from one patient were excluded for both treatment periods due to a protocol violation and predose albuterol plasma concentrations that exceeded 5% of C_{max} during the albuterol MDPI treatment period. PK data were excluded from two additional patients for one period because their albuterol plasma concentrations also exceeded 5% of C_{max} before dosing. Therefore, the PK analysis set consisted of complete data from 12 patients plus data for the albuterol MDPI treatment period from one patient and data for the albuterol HFA treatment period from another patient.

PK Analysis

The mean plasma concentration versus time profile for each treatment is shown in Fig. 2. As shown in Table 2, the mean AUC_{0-t} and AUC_{0-inf} were comparable for both treatments up to 10 hours after dosing. C_{max} was larger for albuterol MDPI compared with albuterol HFA. Median t_{max} and mean $t_{1/2}$ were shorter for albuterol MDPI compared with albuterol HFA.

PD Analysis

There were no differences between the two treatments with regard to heart rate or blood pressure at any time after dosing, as shown in Table 3.

Safety Analysis

There were no deaths, no serious AEs, no withdrawals due to AEs, and no treatment-emergent AEs during

Table 1 Patient demographics and baseline clinical characteristics

Parameter	Patients (N = 15)
Age, y	
Mean $\pm$ SD	8.6 $\pm$ 1.9
Range	6–11
Sex, no. (%)	
Boys	5 (33)
Girls	10 (67)
Race, no. (%)	
White	7 (47)
Black	7 (47)
Other	1 (6)
Weight, kg	
Mean $\pm$ SD	36.3 $\pm$ 10.5
Range	19.3–53.1
Height, cm	
Mean $\pm$ SD	137.6 $\pm$ 14.2
Range	116.4–157.9
BMI, kg/m ²	
Mean $\pm$ SD	18.7 $\pm$ 2.6
Range	14.2–22.8
FVC, L	
Mean $\pm$ SD	2.0 $\pm$ 0.5
Range	1.2–2.8
FEV ₁ , L	
Mean $\pm$ SD	1.7 $\pm$ 0.4
Range	1.1–2.4
Predicted FEV ₁ , L	
Mean $\pm$ SD	1.9 $\pm$ 0.5
Range	1.3–2.7
Predicted FEV ₁ , %	
Mean $\pm$ SD	86.9 $\pm$ 5.3
Range	80.0–96.4
FEV ₁ :FVC, %	
Mean $\pm$ SD	84.9 $\pm$ 6.5
Range	73.8–97.5
Peak expiratory flow rate, L/s	
Mean $\pm$ SD	3.8 $\pm$ 0.9
Range	2.4–5.5

SD = Standard deviation; BMI = body mass index; FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 second.

the study. No asthma exacerbations were reported during the study. No clinically significant changes were observed in laboratory parameters, physical examination findings, vital signs, or electrocardiograms during the study (data not shown).

DISCUSSION

In the present randomized, open-label, two-period crossover study, AUC_{0-t} and AUC_{0-inf} were compara-

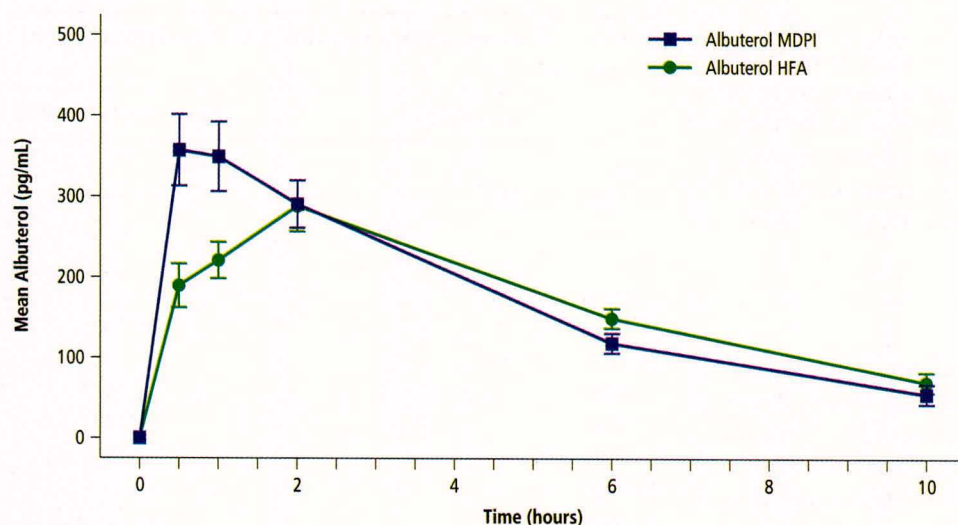


Figure 2. Plasma albuterol concentration (mean $\pm$ standard error) versus time in pediatric patients. HFA = Hydrofluoroalkane; MDPI = multidose dry powder inhaler.

Table 2 Pharmacokinetic profile of albuterol MDPI and albuterol HFA in pediatric patients

	Albuterol MDPI 180 μ g	Albuterol HFA 180 μ g
AUC_{0-t} pg $\cdot$ hr/mL		
Mean $\pm$ SD	1752.3 $\pm$ 590.2	1719.5 $\pm$ 519.0
Geometric mean $\pm$ SE	1662.8 $\pm$ 157.1	1651.0 $\pm$ 136.3
Geometric mean ratio	—	1.056
90% CI	—	0.880–1.268
C_{max} pg/mL		
Mean $\pm$ SD	379.6 $\pm$ 157.0	294.9 $\pm$ 110.6
Geometric mean $\pm$ SE	352.8 $\pm$ 38.8	278.0 $\pm$ 27.2
Geometric mean ratio	—	1.340
90% CI	—	1.098–1.636
AUC_{0-inf} pg $\cdot$ hr/mL		
Mean $\pm$ SD	2045.0 $\pm$ 631.7	2166.7 $\pm$ 545.2
Geometric mean $\pm$ SE	1953.1 $\pm$ 173.9	2103.4 $\pm$ 149.5
Geometric mean ratio	—	0.971
90% CI	—	0.821–1.147
t_{max} hr		
Mean $\pm$ SD	1.01 $\pm$ 0.6	1.77 $\pm$ 0.4
Geometric mean $\pm$ SE	0.9 $\pm$ 0.14	1.7 $\pm$ 0.14
Median	1.0	2.0
$t_{1/2}$ hr		
Mean $\pm$ SD	3.6 $\pm$ 0.9	4.3 $\pm$ 1.2
Geometric mean $\pm$ SE	3.5 $\pm$ 0.2	4.2 $\pm$ 0.3
Median	3.2	4.3

MDPI = Multidose dry powder inhaler; HFA = hydrofluoroalkane; AUC_{0-t} = area under the plasma albuterol concentration–time curve from time 0 to the time of the last detectable plasma albuterol concentration measured up to 10 hr; SD = standard deviation; SE = standard error; CI = confidence interval; C_{max} = maximum observed plasma albuterol concentration; AUC_{0-inf} = area under the albuterol plasma concentration–time curve from time 0 extrapolated to infinity; t_{max} = time to maximum plasma albuterol concentration; $t_{1/2}$ = terminal half-life of elimination.

ble between albuterol MDPI and albuterol HFA after a single dose of 180 μ g administered as two inhalations of 90 μ g to pediatric patients with asthma. Although C_{max} was larger and median t_{max} and mean $t_{1/2}$ were slightly shorter for albuterol MDPI compared with

those of albuterol HFA, high variability was present in these parameters, with coefficients of variation of 41.4 and 37.5%, respectively, for C_{max} ; 60.8 and 24.8%, respectively, for t_{max} ; and 25.0 and 27.9%, respectively, for $t_{1/2}$. There were no differences between treatments

Table 3 Pharmacodynamic end points with albuterol MDPI and albuterol HFA in pediatric patients

	Albuterol MDPI 180 µg	Albuterol HFA 180 µg
Maximum increase from baseline in SBP, mean ± SD, mm Hg	3.9 ± 7.76	4.6 ± 8.26
Maximum decrease from baseline in DBP, mean ± SD, mm Hg	6.7 ± 5.06	5.2 ± 6.43
Maximum increase in heart rate, mean ± SD, beats/min	10.5 ± 5.55	11.2 ± 7.49

MDPI = Multidose dry powder inhaler; HFA = hydrofluoroalkane; SBP = systolic blood pressure; SD = standard deviation; DBP = diastolic blood pressure.

with regard to PD parameters; no deaths, serious AEs, withdrawals due to AEs, or treatment-emergent AEs were reported during this study.

In a study conducted in adult patients with asthma, the PKs of albuterol MDPI and albuterol HFA were evaluated after cumulative doses of 90, 180, 360, 720, and 1440 µg.⁹ Similar to the present study, systemic exposure was comparable between the two treatments, whereas C_{max} was numerically higher and the mean t_{max} was numerically earlier with albuterol MDPI. No safety signals with albuterol MDPI were identified in phase II and III studies conducted to date or in an integrated safety analysis of phase III studies.⁸

Limitations of this study included its open-label design, single-dose administration protocol, and the small number of patients, and that the study was conducted at a single site. In addition, the need to limit the number of blood samples drawn from the pediatric patients may have limited the precise assessment of PK parameters. The study was not designed to evaluate the efficacy of the two treatments in these patients; therefore, it does not allow comparisons to be made. However, albuterol MDPI demonstrated PK and PD profiles similar to those of albuterol HFA and was well tolerated in this population of pediatric patients with persistent asthma, with a safety profile similar to that of albuterol HFA.

CONCLUSION

Analysis of these results indicated the potential of albuterol MDPI in the treatment of pediatric asthma, which has led to its further study compared with albuterol HFA in a randomized, placebo-controlled, phase II trial of patients ages 4 to 11 years (NCT01899144) and a random-

ized, placebo-controlled, phase III trial of patients ages 4 to 11 years (NCT02126839).

REFERENCES

1. 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.
2. Ramsdell JW, Klinger NM, Ekholm BP, and Colice GL. Safety of long-term treatment with HFA albuterol. *Chest* 115:945–951, 1999.
3. Tinkelman DG, Bleecker ER, Ramsdell J, et al. Proventil HFA and Ventolin have similar safety profiles during regular use. *Chest* 113:290–296, 1998.
4. Levy ML, Hardwell A, McKnight E, and 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* 22:406–411, 2013.
5. Hardwell A, Barber V, Hargadon T, et al. Technique training does not improve the ability of most patients to use pressurised metered-dose inhalers (pMDIs). *Prim Care Respir J* 20:92–96, 2011.
6. Scarfone RJ, Capraro GA, Zorc JJ, and Zhao H. Demonstrated use of metered-dose inhalers and peak flow meters by children and adolescents with acute asthma exacerbations. *Arch Pediatr Adolesc Med* 156:378–383, 2002.
7. ProAir RespiClick [package insert]. Horsham, PA: Teva Respiratory, 2016.
8. Raphael G, Taveras H, Iverson H, et al. Twelve- and 52-week safety of albuterol multidose dry powder inhaler in patients with persistent asthma. *J Asthma* 53:187–193, 2016.
9. Kerwin EM, Taveras H, Iverson H, et al. Pharmacokinetics, pharmacodynamics, efficacy, and safety of albuterol (salbuterol) multi-dose dry-powder inhaler and ProAir[®] hydrofluoroalkane for the treatment of persistent asthma: results of two randomized double-blind studies. *Clin Drug Investig* 36:55–65, 2016. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.