

Prospective, open-label evaluation of a new albuterol multidose dry powder inhaler with integrated dose counter

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ABSTRACT

Background: Albuterol multidose dry powder inhaler (MDPI) with an integrated dose counter allows patients to track the number of remaining doses and to simplify dosing by eliminating the need to coordinate inhalation with actuation associated with metered-dose inhalers.

Objective: To evaluate the functionality, reliability, and accuracy of the albuterol MDPI integrated dose counter in a real-world clinical setting.

Methods: This open-label, phase III study enrolled patients ages ≥ 4 years with asthma or chronic obstructive pulmonary disease. Patients who demonstrated adequate MDPI inhaler technique and $\geq 90\%$ compliance with dosing and diary completion during a run-in period qualified for treatment with albuterol MDPI with a dose counter (2 inhalations/dose; 90 μg /inhalation) twice daily for up to 50 days. Patient-reported counter readings and patient-reported actuations were recorded in daily diaries and were used to assess dose counter accuracy. An ease-of-use and satisfaction questionnaire was given at the final visit.

Results: A total of 317 patients were enrolled in the study. The dose-cycle undercount (i.e., actuation occurred, but the counter display did not count down) was 2.05 per 200 actuations. The estimated mean $\pm$ standard error absolute value of the total discrepancy size after 200 actuations was 2.07 ± 0.140 . Most patients (83%) were somewhat or very satisfied, and $>90\%$ were satisfied with ease of holding and/or handling, using and taking, and inhaling a dose from the device. The albuterol MDPI was generally well tolerated.

Conclusion: The albuterol MDPI dose counter functioned reliably and accurately. Albuterol MDPI was well tolerated, with a high degree of patient satisfaction in a real-world setting. Clinical Trial number: NCT01857323.

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Inhaled albuterol is a short-acting β_2 -agonist that is used for treating symptoms of chronic obstructive pulmonary disease (COPD), treating acute asthma symptoms and exacerbations, and preventing exercise-induced bronchospasms.^{1–3} Delivery of inhaled albuterol is often achieved with conventional metered-dose inhalers (MDI), which require coordination of device actuation with inspiration to ensure that the drug is deposited correctly into the lungs.⁴ Failure to coordinate actuation and inspiration is a common error observed during conventional MDI use, particularly among children and elderly patients, which can result in delivery of a subtherapeutic dosage.^{5–8} Improper MDI technique has been associated with poor disease control.^{9,10} Breath-actuated inhalers were developed to

enhance inhaler technique by reducing these coordination errors.^{11–13}

By design, MDIs contain more propellant than required for the labeled number of actuations.^{14,15} As a result, the amount of active medication that remains after delivery of the labeled number of actuations can vary and result in a subtherapeutic dosage on subsequent actuations.¹⁵ Many conventional MDIs do not have reliable means to allow patients to track the amount of medication that remains in their inhaler. Dose tracking in a diary is one approach, but this is cumbersome, and few patients keep an accurate count of the doses used.¹⁶ MDIs with an integrated dose counter have been shown to be reliable and accurate in tracking the remaining number of doses.^{15,17} Moreover, patients who use MDIs with an integrated dose counter reported higher levels of satisfaction and greater ease in knowing when the inhaler should be replaced compared with MDIs without a dose counter.^{15,17}

Albuterol multidose dry powder inhaler (MDPI) (Teva Branded Pharmaceutical Products R&D, Inc., Frazer, PA) is a novel, inhalation-driven inhaler with an integrated dose counter that eliminates the need to coordinate actuation with inspiration and the necessity for dose tracking. The overall efficacy, pharmacokinetics, pharmacodynamics, and safety of the albuterol

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MDPI in patients with asthma were similar to those for albuterol delivered *via* a hydrofluoroalkane MDI.^{18–20} Although dry powder inhalers are available for the delivery of corticosteroid-based controller medications, albuterol MDPI is currently the only rescue dry powder inhaler approved by the U.S. Food and Drug Administration for the treatment of acute asthma symptoms. A dry powder rescue inhaler addresses an unmet need for the many patients who are unable to coordinate actuation with inhalation necessary for proper use with MDI rescue bronchodilators. The present study was designed to evaluate the functionality, reliability, and accuracy of the albuterol MDPI integrated dose counter in a real-world clinical setting.

METHODS

Patients

Male patients and nonpregnant or nonlactating female patients ages ≥ 4 years were eligible if they had a physician diagnosis of asthma or COPD with symptoms of bronchoconstriction that required short-acting β_2 -agonist use. Eligible patients must have been receiving stable asthma or COPD controller treatment regimens for at least 4 weeks, were able to demonstrate satisfactory inhaler use and technique, and had no concomitant condition or treatment that could interfere with the study conduct, influence interpretation of results, or place the patient at increased risk. Women of childbearing potential agreed to use a reliable contraception method for the entire study duration. The patient cohort was stratified by disease type to ensure that $\sim 50\%$ had asthma and 50% had COPD; the patients with asthma were further stratified by age, such that 25% were ages 4–11 years, 50% were ages 12–64 years, and 25% were ages ≥ 65 years. All patients provided written informed consent before participating in the study.

Patients were excluded if they had a history of life-threatening asthma or COPD (that required intubation and/or that was associated with hypercapnia, respiratory arrest, or hypoxic seizures); culture-documented or suspected infection of the upper or lower respiratory tract, sinus, or middle ear that had not resolved within 2 weeks of screening or that occurred between screening and enrollment; asthma exacerbation within 2 months or COPD exacerbation within 1 month of screening that required oral corticosteroids; or had been hospitalized for asthma or COPD within 4 months of screening or were being treated with a long-acting β_2 -agonist alone.

Study Design

This was a prospective, open-label, phase III study conducted at 30 centers in the United States from May to September 2013. After screening, patients entered a

7- to 14-day (± 2 days) run-in period, during which they self-administered 2 inhalations of a placebo MDPI twice daily. To qualify for enrollment, the patients were required to demonstrate adequate MDPI inhaler technique and $\geq 90\%$ compliance with dosing and diary completion during the last 7 consecutive days of the run-in period. Enrolled patients self-administered 2 inhalations/dose ($90 \mu\text{g}/\text{inhalation}$) of the albuterol MDPI with a dose counter twice daily for up to 50 days. Treatment visits were scheduled on days 1, 8, 15, 22, 36, and 50. The initial 15% (~ 45 patients) of enrolled patients completed the study in 5 weeks. The MDPI devices were retrieved from those patients and shown to contain $\sim 30\%$ of the initial 200 doses on *in vitro* pharmaceutical performance testing. The remaining patients who qualified for enrollment used the albuterol MDPI for 7 weeks. The 7-week treatment period with twice-daily dosing was considered optimal for using the 200 doses contained in the device while evaluating the accuracy of the integrated dose counter. The study was reviewed and approved by an institutional review board or independent ethics committee at each site and was conducted in accordance with the International Council on Harmonisation Good Clinical Practice Consolidated E6 guidelines and all applicable national and local laws and regulations.

Handling Characteristics of the Albuterol MDPI

Patients received a paper diary at each treatment visit (except the final visit) and were asked to record the following information: study drug administration (2 inhalations per dose session twice daily), time of day of each dose session (A.M. or P.M.), number of actuations per dosing session, dose-counter number before and after each 2-inhalation dosing session, number of inhalations of rescue medication (albuterol hydrofluoroalkane MDI), adverse events (AE), device ruggedness (*e.g.*, dropping device), and any inhaler performance problems. The completed diary was collected at each visit, and the data were entered by study center personnel directly into the clinical data management system. If any noncompliance was noted, the study center personnel reeducated and retrained the patient on the importance of complying with the study requirements for dosing and diary completion.

Dose-Counter Performance

To assess the performance of the integrated dose counter, patient-reported MDPI dose-counter readings before and after each dose were compared with the patient-reported actuations recorded in the diaries. Discrepancies were classified into one of four categories: dose-cycle undercount (*i.e.*, the patient completed the full actuation but the counter display did not count down; the primary end point); dose-cycle overcount

(*i.e.*, the patient completed the full actuation but the counter display decreased by >1 count); count unknown dose cycle (*i.e.*, the counter display at the beginning of a dosing session was lower than the counter number at the end of the previous dosing session); and count up unknown dose cycle (*i.e.*, the counter display at the beginning of a dosing session was higher than the counter number at the end of the previous dosing session). In addition, the total inhaler discrepancy size was determined to reduce apparent discrepancies that may have resulted from the patient misreading the dose counter. This was calculated as the difference between the beginning and end counter readings minus the patient-recorded number of actuations and was adjusted for any gaps in diary data. The total inhaler discrepancy size provides a relevant measure for ensuring that the MDPI does not exhaust its supply of albuterol before the counter records the labeled 200 actuations.

MDPI Ease of Use and Patient Satisfaction

At the final study visit, the patients (or their caregivers if the patient was <12 years of age) completed a self-administered questionnaire on the ease of use and patient satisfaction with the device. Answers were scored on a 7-point scale (very satisfied, satisfied, somewhat satisfied, neither satisfied nor dissatisfied, somewhat dissatisfied, dissatisfied, or very dissatisfied).

Safety

AEs were monitored throughout the study until 7 days after the last dose of study medication. Physical examinations were performed, and vital signs were measured at the screening and final visits.

Statistics

The primary population used for the device accuracy and satisfaction analyses was the per-protocol (PP) population, which comprised patients who completed ≥ 180 doses with no major protocol violations. Based on this definition, the initially enrolled patients who completed the study within 5 weeks were not included. The analyses were also performed for the intent-to-treat (ITT) population, which comprised all enrolled patients. For the primary end point (dose-cycle undercount), the total number of discrepancies and the rate per 200 actuations were summarized by using descriptive statistics for the PP and ITT populations, and by disease group (asthma and COPD), and by age for the asthma group (4–11, 12–64, and ≥ 65 years).

The average rate of discrepancy per 200 actuations was estimated, and a 95% confidence interval (CI) was constructed by using a zero-inflated Poisson regression, with the number of patient-reported actuations as

an offset in the model and covariates for the COPD group and for the three age subgroups within the asthma group. The analyses of dose-cycle overcount, count unknown dose cycle, and count up unknown dose cycle (secondary end points) were performed as described for the primary end point. The total inhaler discrepancy size (secondary end point) was also summarized descriptively for each population and subgroup. A zero-inflated Poisson mixture regression model was used to estimate the mean of the absolute value of the total inhaler discrepancy size after 200 actuations and the probability that the absolute value exceeded 10 and 20 actuations. The satisfaction analyses were summarized descriptively. Safety end points were evaluated in all enrolled patients who received at least one dose of study medication; AEs were coded using the Medical Dictionary for Regulatory Activities, v16.0, and summarized descriptively.

RESULTS

Patient Disposition and Characteristics

A total of 345 patients were screened, and 317 patients were enrolled (ITT population) (Fig. 1); of these, 47 patients (15%) recorded <180 actuations, 16 patients (5%) discontinued early, and 1 patient ($<1\%$) was not treated. The remaining 253 patients (80%) completed the study and were included in the PP population. The ITT population had a median age of 59 years (range, 5–88 years); 53% of patients had asthma, and 47% had COPD (Table 1). The majority of patients were female (56%) and white (85%). During the treatment phase, four patients were not compliant with the study protocol (compliance rate of 75–90%), whereas the remaining 312 patients who received study treatment had compliance rates of $\geq 90\%$.

Performance of the MDPI with Integrated Dose Counter

The total number of patient-reported dose actuations in the PP population was 49,454. There were a total of 1263 discrepancies between the patient-reported MDPI dose-counter readings before and after each actuation compared with the patient-reported actuations recorded in the diaries (Table 2). Based on these data, the overall rate of discrepancies was 5.11 per 200 actuations. The primary end point of dose-cycle undercount occurred 506 times (rate of 2.05 per 200 actuations). Dose-cycle overcount was the most-frequent discrepancy (2.46 per 200 actuations), whereas count unknown dose cycle (0.43 per 200 actuations) and count up unknown dose cycle (0.17 per 200 actuations) occurred less frequently. The number of inhaler discrepancies reported per patient ranged from 0 to 47, with the majority of patients (57%) reporting 0–2 discrepancies

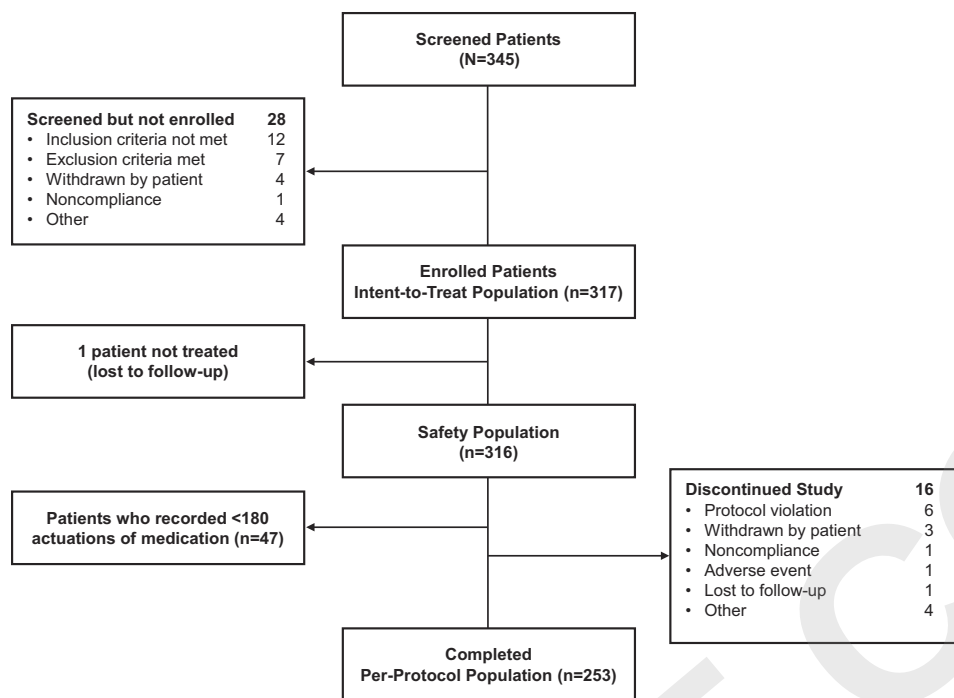


Figure 1. Patient disposition.

(Fig. 2). Similar results were observed in the ITT population (Table 2).

The total inhaler discrepancy size centered around a difference of zero, with a greater tendency for overcounting versus undercounting the inhalations (Fig. 3). Approximately 70% of patients had a total discrepancy size of ≤ 2 in absolute value, and 95% of patients had a total discrepancy of ≤ 6 in absolute value. Using a zero-inflated Poisson mixture regression model, the estimated mean $\pm$ standard error of the absolute value of the total inhaler discrepancy size was 2.07 ± 0.14 after 200 actuations (Table 3). The estimated probability of the absolute value of total discrepancy size that exceeded 10 dose cycles per 200 actuations (*i.e.*, the projected life of the MDPI) was low (0.0009), and the estimated probability of exceeding a total discrepancy size of 20 actuations was remote (≤ 0.000001).

When analyzed by age group, the highest discrepancy rate occurred in children (8.18 per 200 actuations), followed by patients ages ≥ 65 years (5.48 per 200 actuations) and then by patients ages 12–64 years (4.75 per 200 actuations). Patients with asthma had a higher discrepancy rate than those with COPD (5.70 versus 4.57 per 200 actuations), which likely reflected the inclusion of children in the asthma cohort. In these subgroups, the estimated absolute value of the total discrepancy size ranged from 3.23 for patients with asthma ages 4–11 years to 1.53 for patients with asthma ages ≥ 65 years (Table 3). The estimated probability of exceeding a total discrepancy size of 10 actuations was low in each subgroup.

Ease of Use and Satisfaction

Overall, 209 of the 253 PP patients (83%) reported being somewhat to very satisfied with the albuterol MDPI with the integrated dose counter, and another 21 patients (8%) expressed neither satisfaction nor dissatisfaction. The majority of patients were satisfied with the ease of holding and handling the inhaler (233/253 [92%]), of using or taking the inhaler (230/253 [91%]), and of inhaling a dose from the inhaler (229/253 [91%]). Most patients also were satisfied with the ease of learning to use the inhaler with the integrated dose counter (214/253 [85%]), and most judged that they had used the inhaler properly (242/253 [96%]). Comparable results were obtained for the ITT population.

Device Ruggedness

Only three patients reported non-counter-related device issues; of these, two issues were the result of impact damage to the inhaler. The third patient reported difficulty inhaling through the device and closing the mouthpiece cover. The latter device was returned for follow-up laboratory testing, and the issue was found to have resulted from patient misuse and/or handling problems.

Safety

There were no deaths during the study. One patient was discontinued from the study due to an AE (sinusitis). Most AEs were reported as mild (60 patients) or moderate (23 patients). A total of 85 patients (27%) in the safety population experienced AEs during the

Table 1 Patient demographics (ITT population)

Characteristic	ITT population (N = 317)
Age, y	
Mean $\pm$ SD	51.3 $\pm$ 22.7
Median (range)	59 (5–88)
Age group, no. (%)	
4–11 y	44 (14)
12–64 y	144 (45)
≥ 65 y	129 (41)
Sex, no. (%)	
Male	139 (44)
Female	178 (56)
Race, no. (%)	
White	268 (85)
Black	35 (11)
Asian	7 (2)
Other*	7 (2)
Ethnicity, no. (%)	
Hispanic or Latino	25 (8)
Non-Hispanic, non-Latino	292 (92)
Disease type, no. (%)#	
Asthma	167 (53)
4–11 y	44 (26)
12–64 y	80 (48)
≥ 65 y	43 (26)
COPD	150 (47)
40–64 y	64 (43)
≥ 65 y	86 (57)

ITT = intent-to-treat; SD = standard deviation; COPD = chronic obstructive pulmonary disease.

*Includes American Indian, Alaskan Native, and Pacific Islander.

#Only one disease type could be recorded on demographic information collection, even though some patients had a dual diagnosis of asthma and COPD.

study, most commonly headache (3%), sinusitis (2%), cough (2%), and upper respiratory tract infection (2%) (Table 4). Two patients experienced serious AEs. Of these, one patient had atrial fibrillation and supraventricular tachycardia, which was documented at the final treatment visit and considered possibly related to the study drug by the investigator. Both conditions resolved after treatment with a regimen that included adenosine, diltiazem, metoprolol, and aspirin. The other patient had a serious skin eruption ascribed by the investigator as due to treatment with metformin taken for diabetes.

DISCUSSION

These results demonstrated that the albuterol MDPI with the integrated dose counter was robust and func-

tioned reliably and accurately during twice-daily use for up to 7 weeks, consistent with the projected inhaler life of 200 inhalations. Treatment with the albuterol MDPI was generally well tolerated, consistent with the known safety profile of albuterol, and associated with a high degree of patient satisfaction. Concordance was high between patient-reported dose-counter readings and the number of actuations dispensed as recorded in the diary. The overall discrepancy rate was low: 5.11 per 200 actuations in the PP population and 5.67 per 200 actuations in the ITT population. These findings indicated that patients with asthma and patients with COPD were able to successfully use the MDPI with integrated dose counter. From a practical perspective, the dose counter lets patients know when the device should be replaced, thereby preventing patients from using the inhaler beyond its label recommendations and from discarding a functional inhaler before its medication has been exhausted.

Dose-cycle undercount was selected as the primary end point because it is crucial for reliable dose-counter performance. Dose-cycle undercount indicates that the counter did not count down after an actuation. From a clinical perspective, the dose-counter reading would be higher than the actual number of doses that remain in the inhaler. Toward the end of the inhaler life as the counter declines toward zero, the potential is increased for a patient to be without his or her rescue albuterol medication. In this study, the dose-cycle undercount rate was low: 2.05 per 200 actuations in the PP population and 2.34 per 200 actuations in the ITT population. These values reflected ~ 1 full dose of medication (2 inhalations). Dose-cycle overcount occurred slightly more often but also at a low rate: 2.46 per 200 actuations in the PP population and 2.62 per 200 actuations in the ITT population. In this case, the dose-counter reading would be lower than the actual number of remaining doses, which may lead a patient to replace the inhaler prematurely. This scenario is associated with a potential economic consequence rather than a clinical consequence. The other discrepancies measured changes in the counter display between the end of one dosing session and the beginning of the next, which occurred at much lower rates than dose-cycle undercount and overcount. Notably, the absolute value of the total inhaler discrepancy size was 2.07 after 200 inhalations, which indicates that upward and downward counter discrepancies partially balanced themselves.

Although the overall discrepancy rate was low with the albuterol MDPI with an integrated dose counter, it was somewhat higher than that reported previously with an albuterol MDI with an integrated dose counter when using an identical study design (1.87 discrepancies per 200 actuations).¹⁷ Both dose-cycle undercount (0.30 per 200 actuations) and dose-cycle overcount

Table 2 Number and rate of discrepancies

	PP population (<i>n</i> = 253)*		ITT population (<i>n</i> = 317)#	
	No. Discrepancies	Discrepancy Rate per 200 Actuations	No. Discrepancies	Discrepancy Rate per 200 Actuations
Total no. discrepancies	1263	5.11	1630	5.67
Dose-cycle undercount	506	2.05	673	2.34
Dose-cycle overcount	609	2.46	754	2.62
Count unknown dose cycle	106	0.43	140	0.49
Count up unknown dose cycle	42	0.17	63	0.22

PP = *per-protocol*; ITT = *intent-to-treat*.

*The total no. of patient-reported actuations was 49,454.

#The total no. of patient-reported actuations was 57,471.

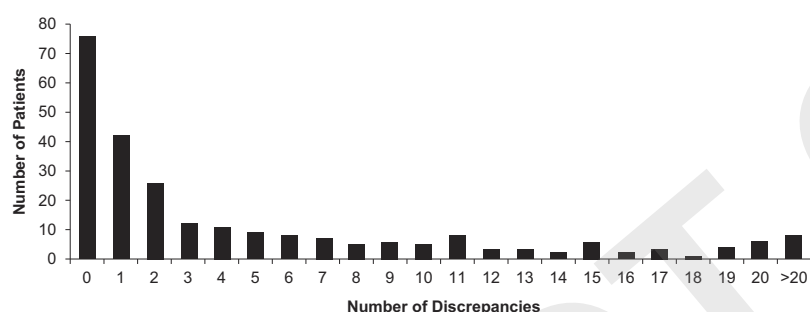


Figure 2. The number of inhaler discrepancies in the per-protocol population.

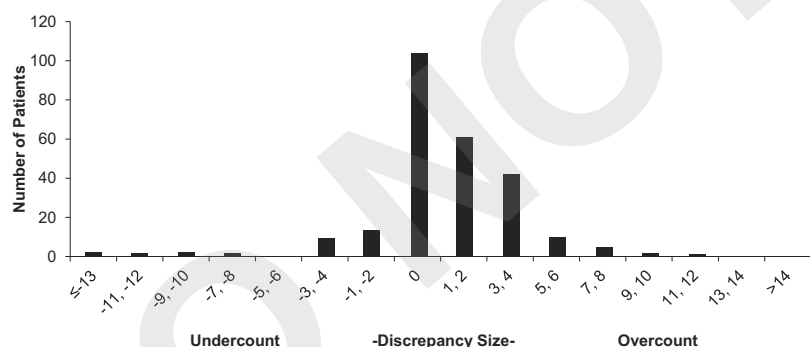


Figure 3. Categorization of the total discrepancy size per inhaler in the per-protocol population.

(0.26 per 200 actuations) occurred at lower rates in the previous study, whereas the count unknown dose cycle (0.86 per 200 actuations) and the count up unknown dose cycle (0.42 per 200 actuations) occurred at higher rates. Nevertheless, the estimated mean of the absolute value of the total discrepancy size of 1.84 after 200 actuations was similar to that measured in the present study. A number of other studies evaluated the performance characteristics of integrated numeric dose counters, including another albuterol MDI,¹⁵ a fluticasone propionate-salmeterol MDI,²¹ and a mometasone furoate-formoterol MDI.²² In these studies, the overall discrepancy rates ranged from 1.5 to 2.1 per 200 actuations, consistent with the present study. It remains to be determined whether dose counters integrated with dry powder inhalers have somewhat higher discrepancy rates than those integrated with MDIs. Regardless, the discrepancy rates for each dose counter were

low and unlikely to be of clinical significance to the patient.

The discrepancy rates were generally low in each of the subgroups evaluated. However, children (age range, 4–11 years) tended to have the highest discrepancy rates, followed by older adults (age ≥ 65 years) and then adolescent and adult patients (age range, 12–64 years). Discrepancy rates appeared higher among patients with asthma compared with patients with COPD, which likely reflected the inclusion of children in the asthma subgroup. Previous studies of integrated dose counters with albuterol MDIs also found the highest discrepancy rates among children and higher discrepancy rates among patients with asthma compared with patients with COPD.^{15,17} It should be noted that the differences in discrepancy rates across the subgroups were small in the present study as well as in the other studies and,

Table 3 Estimated absolute value of total discrepancy size after 200 actuations in PP population

	Mean $\pm$ SE	95% CI	Estimated Probability of Exceeding 10 Discrepancies per 200 Actuations	Estimated Probability of Exceeding 20 Discrepancies per 200 Actuations
All PP patients	2.07 $\pm$ 0.14	1.80–2.35	0.0009	<0.000001
COPD	1.97 $\pm$ 0.17	1.63–2.31	0.0008	<0.000001
Asthma, all ages	2.14 $\pm$ 0.19	1.78–2.51	0.0011	<0.000001
Age				
4–11 y	3.23 $\pm$ 0.45	2.34–4.12	0.0214	$\leq$ 0.000001
12–64 y	1.84 $\pm$ 0.25	1.34–2.34	0.0005	<0.000001
$\geq$ 65 y	1.53 $\pm$ 0.25	1.03–2.03	0.0001	<0.000001

PP = per-protocol; SE = standard error; CI = confidence interval; COPD = chronic obstructive pulmonary disease.

Table 4 Incidence of adverse events that occurred in at least two patients in the safety population

Adverse Event	Safety population, no. (%) (N = 316)
Headache	8 (3)
Sinusitis	7 (2)
Cough	6 (2)
Upper respiratory tract infection	6 (2)
Nasopharyngitis	4 (1)
Nasal congestion	3 (<1)
Upper abdominal pain	3 (<1)
Chest discomfort	2 (<1)
Bronchitis	2 (<1)
Infected bites	2 (<1)
Urinary tract infection	2 (<1)
Animal bite	2 (<1)
Contusion	2 (<1)
Laceration	2 (<1)
Sunburn	2 (<1)
Arthralgia	2 (<1)
Sinus headache	2 (<1)
Oropharyngeal pain	2 (<1)
Wheezing	2 (<1)
Rash	2 (<1)

therefore, were likely to have little clinical significance.

Patients who have difficulty using an inhaler are likely to be dissatisfied with the product, and this, in turn, may lead to inadequate dosing and nonadherence.¹⁷ A large majority of patients in the present study were satisfied with the ease of use of the albuterol MDPI with the integrated dose counter. More than 90% of the patients responded that they were “very satisfied,” “satisfied,” or “somewhat satisfied” when queried about the ease of use in handling and holding the inhaler, in using the inhaler, and in inhaling a dose

from the inhaler. These responses were supported by the ruggedness of the albuterol MDPI with an integrated dose counter, which was reflected by only two reports of impact damage to the inhaler. Results of previous studies indicated that integration of a dose counter with an MDI was associated with greater satisfaction compared with an MDI without a dose counter.^{15,17,21} The inclusion of the dose counter may have been a contributing factor to the high satisfaction seen with the albuterol MDPI in the present study.

The use of paper diaries represents a potential limitation in this study, which required patients to record both the number of actuations and the counter number before and after each dose session. Paper diaries can be effective in studies that last several weeks to months when evaluated behaviors are discrete.²³ An electronic monitoring device that is simple to use and accurate has been developed for use with dry powder inhalers in clinical trials that evaluate treatment adherence and may prove useful in evaluating adherence in clinical studies.²⁴

Albuterol MDPI is currently the only breath-actuated, dry powder rescue inhaler to be approved by the U.S. Food and Drug Administration for the treatment of acute asthma symptoms. Although there are other dry powder inhalers on the market, they deliver inhaled corticosteroid-based daily maintenance medications.^{25,26} Asthma treatment guidelines recommend the combination of controller medication along with quick-relief rescue medication for the treatment of persistent asthma.¹ The availability of albuterol in the form of a MDPI allowed use of the same type of inhalation maneuver for both rescue and controller medications, which thereby required the patient to master only one inhalation technique. Reducing the different types of inhalation maneuvers a patient is required to use (rescue and maintenance) may improve overall asthma treatment outcomes by simplifying asthma treatment regimens.²⁷

CONCLUSION

The integrated dose counter with the albuterol MDPI was functional and provided the patients with a reliable and accurate indication of how many actuations remained in the device. This will help ensure that patients do not replace their inhaler prematurely and that they will have an inhaler with available doses when they need rescue medication.

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. Weiler JM, Anderson SD, Randolph C, et al. Pathogenesis, prevalence, diagnosis, and management of exercise-induced bronchoconstriction: A practice parameter. *Ann Allergy Asthma Immunol* 105:S1–S47, 2010.
3. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2014). Global Initiative for Chronic Obstructive Lung Disease (GOLD). Available online at http://www.goldcopd.org/uploads/users/files/GOLD_Report2014_Feb07.pdf; accessed May 19, 2015.
4. Lavorini F. The challenge of delivering therapeutic aerosols to asthma patients. *ISRN Allergy* 2013:102418, 2013.
5. O'Connor R, Wolf MS, Smith SG, et al. Health literacy, cognitive function, proper use and adherence to inhaled asthma controller medications among older adults with asthma. *Chest* 147: 1307–1315, 2015.
6. Fink JB, and Rubin BK. Problems with inhaler use: A call for improved clinician and patient education. *Respir Care* 50:1360–1374; discussion 1374–1375, 2005.
7. Hagmolen of ten Have W, van de Berg NJ, Bindels PJ, et al. Assessment of inhalation technique in children in general practice: increased risk of incorrect performance with new device. *J Asthma* 45:67–71, 2008.
8. Burkhart PV, Rayens MK, and Bowman RK. An evaluation of children's metered-dose inhaler technique for asthma medications. *Nurs Clin North Am* 40:167–182, 2005.
9. Giraud V, and Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur Respir J* 19:246–251, 2002.
10. 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.
11. Price DB, Pearce L, Powell SR, et al. Handling and acceptability of the Easi-Breathe device compared with a conventional metered dose inhaler by patients and practice nurses. *Int J Clin Pract* 53:31–36, 1999.
12. Geoffroy P, Lalonde RL, Ahrens R, et al. Clinical comparability of albuterol delivered by the breath-actuated inhaler (Spiros and albuterol by MDI in patients with asthma. *Ann Allergy Asthma Immunol* 82:377–382, 1999.
13. Gross G, Cohen RM, and 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* 40:487–495, 2003.
14. Rubin BK, and Durotoye L. How do patients determine that their metered-dose inhaler is empty? *Chest* 126:1134–1137, 2004.
15. Wasserman RL, Sheth K, Lincourt WR, et al. Real-world assessment of a metered-dose inhaler with integrated dose counter. *Allergy Asthma Proc* 27:486–492, 2006.
16. Ogren RA, Baldwin JL, and Simon RA. How patients determine when to replace their metered-dose inhalers. *Ann Allergy Asthma Immunol* 75:485–489, 1995.
17. Given J, Taveras H, Iverson H, and Lepore M. Prospective, open-label assessment of albuterol sulfate hydrofluoroalkane metered-dose inhaler with new integrated dose counter. *Allergy Asthma Proc* 34:42–51, 2013.
18. Miller SD, Wayne D, Taveras H, et al. Cumulative dose comparison of the efficacy and safety of albuterol-multidose dry powder inhaler and albuterol-hydrofluoroalkane metered dose inhaler in adults with asthma. *Ann Allergy Asthma Immunol* 113(suppl):A46, 2014.
19. Raphael G, Taveras H, Iverson H, et al. Efficacy of albuterol multidose dry powder inhaler versus placebo in subjects 12 years of age and older with persistent asthma. *Ann Allergy Asthma Immunol* 113:A45–A46, 2014 (Abs. P74).
20. 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* 2015 (Epub ahead of print September 15, 2015.)
21. Sheth K, Wasserman RL, Lincourt WR, et al. Fluticasone propionate/salmeterol hydrofluoroalkane via metered-dose inhaler with integrated dose counter: Performance and patient satisfaction. *Int J Clin Pract* 60:1218–1224, 2006.
22. Weinstein C, Staudinger H, Scott I, et al. Dose counter performance of mometasone furoate/formoterol inhalers in subjects with asthma or COPD. *Respir Med* 105:979–988, 2011.
23. Tennen H, Affleck G, Coyne JC, et al. Paper and plastic in daily diary research: Comment on Green, Rafaeli, Bolger, Shrout, and Reis (2006). *Psychol Methods* 11:112–118; discussion 123–125, 2006.
24. Bogen D, and Apter AJ. Adherence logger for a dry powder inhaler: A new device for medical adherence research. *J Allergy Clin Immunol* 114:863–868, 2004.
25. Flovent Diskus [package insert]. Research Triangle Park, NC: GlaxoSmithKline, 2014.
26. Pulmicort Turbuhaler [package insert]. Wilmington, DE: Astra-Zeneca, 2003.
27. Price D, Chrystyn H, Kaplan A, et al. Effectiveness of same versus mixed asthma inhaler devices: A retrospective observational study in primary care. *Allergy Asthma Immunol Res* 4:184–191, 2012. □

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