

Prospective, open-label assessment of albuterol sulfate hydrofluoroalkane metered-dose inhaler with new integrated dose counter

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ABSTRACT

Metered-dose inhalers (MDIs) allow patients who require therapy for various respiratory diseases to deliver these therapies directly to the airways via inhalation. MDIs are designed to contain more propellant than required for administration of the labeled number of actuations; therefore, the amount of active medication/actuation remaining after administration of the labeled number of actuations may result in a lower than therapeutic dose of active medication. An MDI with an integrated dose counter provides the only reliable means by which a patient can track the amount of medication remaining in the MDI. This study evaluated the functionality, reliability, accuracy, and patient satisfaction with albuterol sulfate hydrofluoroalkane (HFA) MDI with a new integrated dose counter in the clinical setting. Patients aged ≥ 4 years with asthma, chronic obstructive pulmonary disease, or both, participated in this phase 4, prospective, open-label study. Treatment was twice-daily dosing with albuterol HFA MDI at 90 micrograms with dose counter for either 5 or 7 weeks. Concordance/agreement between daily patient recordings of actuations and counter readings was assessed with five discrepancy types: fire not count (undercount; primary end point), count not fire (overcount), fire count up within a dose (counter reading increased, instead of decreased, after MDI was actuated), count unknown fire (counter number at the beginning of a dosing session was less than counter number at the end of the previous session), and count up unknown fire (counter number at the beginning of a dosing session was greater than counter number at the end of the previous session). Responses to twelve questions designed to evaluate confidence, ease of use, and patient satisfaction were also analyzed. Overall discrepancy rate was 1.87 per 200 actuations. Primary end point (fire not count rate) was 0.30 per 200 actuations. Overall, ~ 95 – 97% of patients were “very satisfied” or “somewhat satisfied” with the albuterol HFA MDI with dose counter, its ease of use, and the ability to tell when it should be replaced. The albuterol HFA MDI with new integrated dose counter functioned reliably and accurately in the clinical setting. Overall patient satisfaction was high with the albuterol HFA MDI with new integrated dose counter and the device was shown to function reliably and accurately. Clinicaltrials.gov identifier: NCT01302587.

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Bronchodilator medications are central to symptom management in patients with respiratory diseases such as asthma, exercise-induced bronchoconstriction, and chronic obstructive pulmonary disease (COPD). When acute exacerbations of these diseases occur, short-acting β_2 -agonists are recommended to help reverse the underlying bronchoconstriction.^{1,2} Metered-dose inhalers (MDIs) allow patients who require therapy for various respiratory diseases to de-

liver these therapies directly to the airways *via* inhalation. This route of administration is desirable because it optimizes local effects while minimizing undesired systemic effects.³

Albuterol administered *via* conventional “press-and-breathe” MDIs is effective in the management of reversible bronchospasm.⁴ MDIs are designed to contain more propellant and formulation than required for administration of the labeled number of actuations; therefore, the amount of active medication/actuation remaining after administration of the labeled number of actuations can be variable and thus may result in a lower than therapeutic dosage of active medication.⁵ A survey of patients who used an MDI showed that $>50\%$ of patients did not know the labeled number of therapeutic doses contained in their inhalers. In the same study, only 8% reported counting the number of actuations used and replaced their inhalers at or before the manufacturer’s specified maximum number of actuations had been reached.⁶

In a study assessing patient satisfaction with their current MDIs, 62% of patients reported feeling anxious

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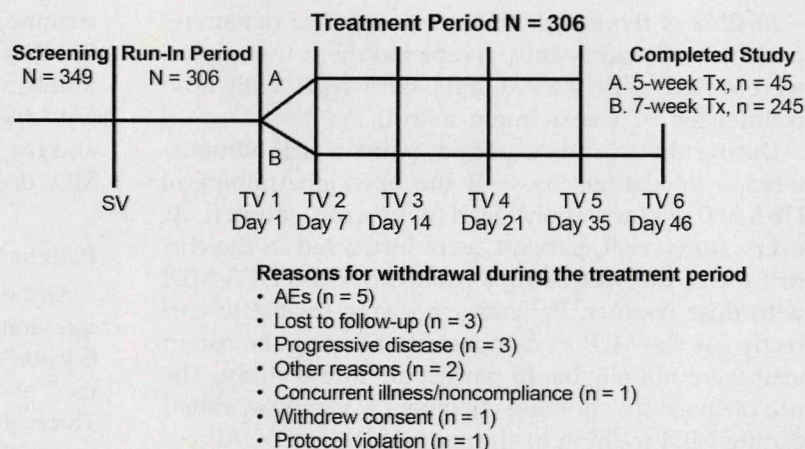


Figure 1. Study design. AE, adverse event; SV, screening visit; TV, treatment visit; Tx, treatment.

about not knowing the quantity of medication remaining in their inhalers. To assess remaining medication, 72% of patients reported shaking their inhalers. Almost one-half (42%) waited until they thought their MDI was not working anymore before replacing it. It is important to note that 24% of patients reported that they could never tell when their MDI was running out of medication.⁵ In an earlier study that evaluated how patients determined that pressurized MDIs were empty, 74% did not know how many actuations were left in their canisters.⁷

A dose counter provides the only reliable means by which a patient can track the amount of medication remaining in an MDI. Without a dose counter, patients may inadvertently continue to use their MDIs even when no active medication remains.⁵⁻⁷ As such, the inclusion of a dose counter should remain a priority in the development of MDIs.

Teva Branded Pharmaceutical Products R&D, Inc., has developed an integrated dose counter for use with MDI products, including ProAir hydrofluoroalkane (HFA; albuterol sulfate) inhalation aerosol MDI (Teva Respiratory, LLC, Frazer, PA).⁴ The current study was designed to evaluate the functionality, reliability, accuracy, and patient satisfaction with albuterol HFA MDI with a new integrated dose counter during real-world use.

METHODS

Patients

Eligible patients included male or nonpregnant/non-lactating female patients ≥ 4 years of age with a diagnosis of COPD and/or asthma requiring the use of short-acting β_2 -agonists three or more times per week during the 2 weeks before the start of the study. Patients were stratified by disease, such that $\sim 50\%$ of the study population had a diagnosis of COPD and the rest of the population had a diagnosis of asthma. Patients with a diagnosis of asthma were further stratified by age, such that 50% were 12–64 years old, 25% were 4–11 years old, and 25% were ≥ 65 years old. Patients

were in general good health and free of any concomitant conditions or treatments that could interfere with study conduct, on a stable treatment regimen for ≥ 4 weeks before the start of the study, and able to show proper MDI use and technique.

Exclusion criteria included a history of life-threatening COPD or asthma and culture-documented or suspected infection of the upper or lower respiratory tract, sinus, or middle ear that was not resolved within 2 weeks of the screening visit or that occurred between the screening visit and enrollment visit. Patients were not allowed to be receiving a long-acting β_2 -agonist alone or to be currently treated with Ventolin HFA (albuterol sulfate) inhalation aerosol MDI (Glaxo-SmithKline, Research Triangle Park, NC).⁸ Patients with a history of COPD exacerbation requiring oral corticosteroids within 1 month of the screening visit, asthma exacerbation requiring oral corticosteroids within 2 months of the start of the study, or hospitalization for COPD or asthma within 4 months of the screening visit were excluded.

Study Design and Procedures

This was a phase 4, prospective, open-label study conducted at 25 centers throughout the United States. The study consisted of two periods (Fig. 1). During the 7- to 14-day run-in period, diary and medication compliance and MDI technique were assessed. Patients qualified for enrollment in the open-label study if they showed adequate MDI technique and were $\geq 90\%$ compliant with dosing and with completion of the diary on the last 7 consecutive days of the run-in period. They were enrolled in one of two treatment cohorts, which consisted of six or seven study visits (depending on the cohort). The first 45 patients enrolled in the study ($\sim 15\%$ of the total population) were assigned to the 5-week treatment cohort. After 5 weeks of twice-daily (b.i.d.) treatment with the albuterol HFA MDI with dose counter, devices were retrieved for pharmaceutical performance testing (*i.e.*, inhalers that contained

~20–25% of the initial 200 actuations). The remaining patients who successfully completed the run-in period were dosed with the albuterol HFA MDI with dose counter for ~7 weeks (main cohort).

During the treatment period, patients self-administered 2 inhalations b.i.d. of the open-label albuterol HFA (90 µg/actuation) MDI with dose counter. At every study visit, patients were instructed in the correct use of the MDI using a primed placebo HFA MDI with dose counter. Patients who were unable to correctly use the MDI as demonstrated during the run-in visit were not eligible to participate in the study. The use of spacers or holding chambers was not permitted during MDI training or throughout the study. All patients provided age-appropriate written informed consent or assent before study participation. The study was reviewed and approved by Copernicus Group Institutional Review Board (Research Triangle Park, NC) and was conducted in accordance with the principles of the revised version of the Declaration of Helsinki.

Dose Counter Performance

To assess dose counter performance, patients recorded the number of doses dispensed and the dose counter reading before and after each of the b.i.d. dosing sessions. Patient-reported MDI dose counter readings and patient-reported actuations recorded in the diaries were compared, and discrepancies were classified into one of five categories:

- Fire (actuation) not count (*i.e.*, undercount)—MDI was actuated, but counter did not advance.
- Count not fire (*i.e.*, overcount)—counter advanced, but MDI was not actuated.
- Fire count up within a dose—counter reading increased, instead of decreased, after MDI was actuated (ending counter reading was greater than beginning counter reading within a dosing session).
- Count unknown fire—counter advanced, but MDI was not knowingly actuated (counter number at the beginning of a dosing session was less than counter number at the end of the previous dosing session).
- Count up unknown fire—counter reading increased (*e.g.*, from 50 to 52), instead of decreased, but MDI was not knowingly actuated (counter number at the beginning of a dosing session was greater than counter number at the end of the previous dosing session).

Handling characteristics of albuterol HFA MDI with dose counter were assessed by the patient's recording in the diary of any mishandling (*e.g.*, dropping the device). As a supplemental assessment of dosing accuracy and as an additional measure of compliance, canisters were weighed before and after treatment to de-

termine the change in canister weight from baseline. Correlations were generated to compare the estimated number of actuations used based on canister weight with the number of actuations recorded in the diary and the number of actuations indicated as used on the MDI dose counter.

Patient Satisfaction

At the final treatment visit, patients completed a paper questionnaire consisting of 12 questions evaluating "confidence" with their previous inhaler, as well as "ease of use" and "satisfaction" with the current study inhaler. Three questions evaluated "confidence" with their previous inhaler, in which five possible responses/questions ranged from "very certain" to "not certain at all." Six questions evaluated "ease of use," in which five possible responses/questions ranged from "very easy" to "not easy at all" with the current study inhaler. Three questions evaluated "satisfaction," in which five possible responses/questions ranged from "very satisfied" to "not satisfied at all" with the current study inhaler.

Outcomes and Statistical Analysis

The main objective of the study was to evaluate rates of discrepancy per 200 actuations between patient-reported MDI counter readings and patient-reported actuations recorded in the diaries. Therefore, no efficacy outcomes for albuterol were collected. The primary end point was the rate of discrepancy for "fire not count." Secondary end points included rates of discrepancy for "count not fire," "fire count up within a dose," "count unknown fire," "count up unknown fire," confidence with previously used inhalers, and ease of use/satisfaction with the albuterol HFA MDI with dose counter. A secondary objective was to evaluate the handling characteristics (*e.g.*, ruggedness) of the albuterol HFA MDI with dose counter as assessed by patient's recording of any mishandling of the inhaler. Approximately 300 patients were recruited to participate to ensure that ~200 patients had used at least 90% of the required actuations contained in the albuterol HFA MDI with dose counter (excluding the actuations used for the weekly cleaning of the inhaler). A main focus of the study was to estimate discrepancy rates in the population of device users using a statistical model. The sample size was chosen to provide reasonably narrow confidence intervals around the point estimates.

The primary population for analysis of the primary end point was the per-protocol (PP) population, which included all patients who completed ≥166 actuations (*i.e.*, ≥90% of the 184 actuations as calculated based on 4 actuations/day for 46 dosing days; does not include doses used to clean or to prime the inhaler) of study medication and who did not experience any major protocol deviations before completing 166 actuations

of randomly assigned study medication. Patients assigned to the 5-week treatment group ($n = 45$) were not included in the PP population. The PP population excluded data identified as likely due to patient error, which were defined as follows: recorded number of doses within a given session that differed by >4 from the counter difference between the beginning and the end of the session, beginning counter number recorded as >204 , ending counter number recorded as >204 , first counter reading for an inhaler recorded as <196 , or counter difference (beginning counter number minus ending number from previous session) between succeeding dosing sessions of >4 if the sessions were on the same day or >8 if the sessions were 1 day apart.

Although the PP population was the primary population for dose counter performance and handling characteristic analyses, primary and secondary end point variables were also analyzed using the intent-to-treat (ITT) population. The ITT population included all patients who received ≥ 1 dose of albuterol from the HFA MDI with dose counter and had ≥ 1 postbaseline assessment. The safety population was the primary population for safety analyses and included all patients who received ≥ 1 dose of albuterol from the HFA MDI with dose counter. Additional analyses were performed for subgroups based on disease (asthma and COPD) and, within the asthma subgroup, by age (4–11, 12–64, and ≥ 65 years old).

RESULTS

Enrollment, Retention, and Adherence

A total of 349 patients were screened for enrollment and entered the run-in period of the study. Of the 306 patients who enrolled, 290 completed the study (45 patients in the 5-week treatment cohort and 245 patients in the 7-week treatment cohort; Fig. 1). Of the 16 patients who did not complete the study, the main reasons for discontinuation included adverse events (AEs) ($n = 5$), lost to follow-up ($n = 3$), and disease progression ($n = 3$). Of the 306 patients enrolled in the safety population, 293 (95.8%) were $\geq 90\%$ compliant with study medication during the treatment period; eight patients (2.6%) were $\geq 75\%$ to $<90\%$ compliant, three patients (1.0%) were $<75\%$ compliant, and two patients (0.7%) had missing compliance data.

Patient demographics and baseline characteristics of the safety and PP populations are presented in Table 1. It was decided subsequent to the data review and database lock to include one patient in the PP population who had only 165 actuations and had been included inadvertently in the PP population because of a programming error. The PP population included 235 patients who completed ≥ 166 actuations (*i.e.*, $>90\%$ of the 184 actuations, as calculated based on 4 actuations/day for 46 dosing days) and who did not experience

Table 1 Patient demographics and baseline characteristics of the safety and PP populations

Demographics	Safety ($n = 306$)	PP ($n = 235$)
Age, yr		
Mean (SD)	51.2 (21.8)	52.3 (21.4)
Median	58.4	59.0
Minimum–maximum	5–82	5–82
Age range, yr, n (%)		
4–11	39 (12.7)	28 (11.9)
12–64	155 (50.7)	117 (49.8)
≥ 65	112 (36.6)	90 (38.3)
Gender, n (%)		
Female	156 (51.0)	119 (50.6)
Male	150 (49.0)	116 (49.4)
Race, n (%)		
White	262 (85.6)	204 (86.8)
Black or African American	37 (12.1)	25 (10.6)
Asian	3 (1.0)	3 (1.3)
American Indian or Alaskan Native	3 (1.0)	2 (0.9)
Other	1 (0.3)	1 (0.4)
Ethnicity, n (%)		
Hispanic or Latino	23 (7.5)	16 (6.8)
Neither Hispanic nor Latino	283 (92.5)	219 (93.2)
Primary diagnosis, n (%)		
Asthma	152 (49.7)	112 (47.7)
COPD	154 (50.3)	123 (52.3)

COPD = chronic obstructive pulmonary disease; PP = per protocol; SD = standard deviation.

any major protocol violations before completing 166 actuations. The ITT population included 304 patients who received ≥ 1 dose of albuterol from the HFA MDI with dose counter and had ≥ 1 postbaseline assessment. Two patients received ≥ 1 dose of albuterol from the HFA MDI with dose counter but did not have ≥ 1 postbaseline assessment and were excluded from the ITT population but were included in the safety population ($n = 306$).

MDI with Integrated Dose Counter Performance

Discrepancy Number and Rates. For the PP population, the total number of patient-reported actuations was 41,720. The total number of discrepancies of all types was 391, with a calculated overall discrepancy rate of 1.87 discrepancies per 200 actuations. A total of 179 patients (76.2%) had two or fewer discrepancies (any type) between patient-reported actuations recorded in the diaries and patient-reported counter readings (Fig. 2). Discrepancy rates for the five categories are reported in

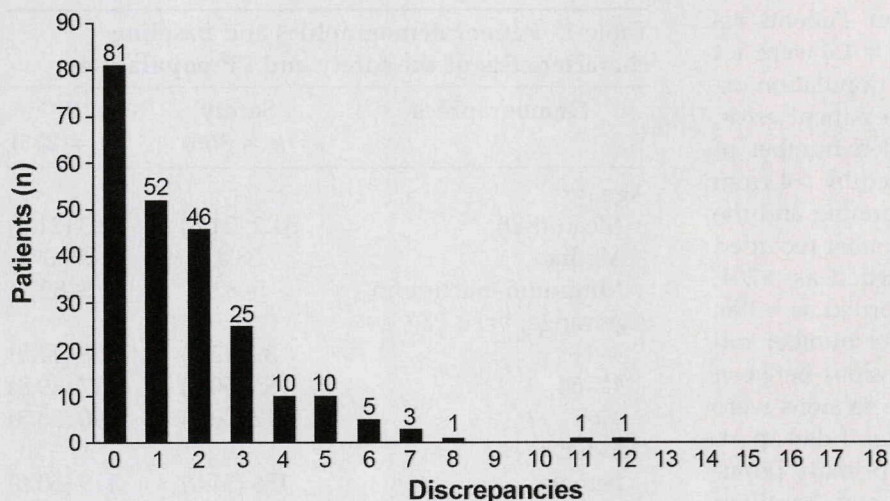


Figure 2. Number of patients with inhaler discrepancies (per-protocol [PP] population, $n = 235$).

Table 2 Discrepancy number and rate (per 200 actuations) by type of discrepancy (PP population, $n = 235$)

Discrepancy Type	Total No.	Rate*	Estimated Mean Rate#	SE	95% CI
Fire not count	62	0.30	0.29	0.055	0.18–0.40
Count not fire	54	0.26	0.22	0.044	0.13–0.31
Count unknown fire	180	0.86	0.93	0.081	0.77–1.09
Count up unknown fire	87	0.42	0.41	0.059	0.30–0.53
Fire count up within a dose	8	0.04	0.03	0.019	0.00–0.07
Total actuations	41,720	NA	NA	NA	NA

*Rate is calculated as the number of discrepancies divided by the total number of actuations (41,720) multiplied by 200.

#Zero-inflated Poisson regression model with age group and disease group covariates.

CI = confidence interval; NA = not available; PP = per protocol; SE = standard error.

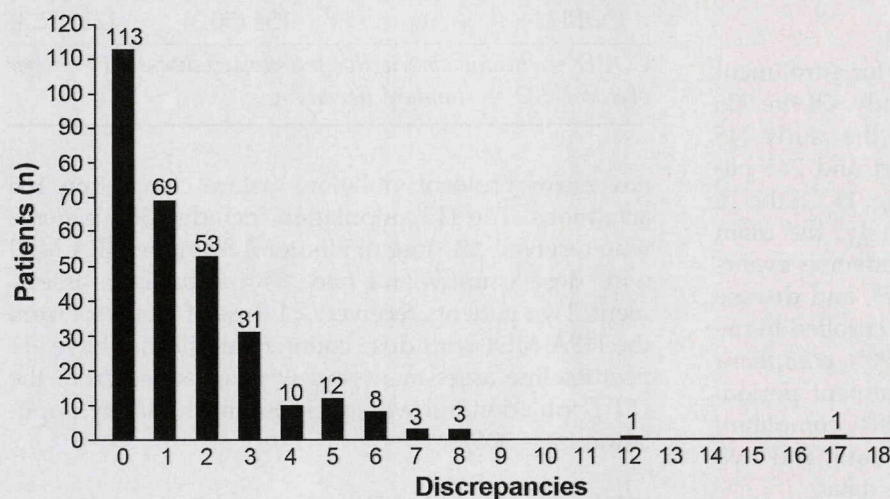


Figure 3. Number of patients with inhaler discrepancies (intent-to-treat [ITT] population, $n = 304$).

Table 2. For the primary end point, the discrepancy rate of “fire not count” (primary end point) was 0.30 discrepancies per 200 actuations. The discrepancy rates of “count not fire,” “fire count up within a dose,” “count unknown fire,” and “count up unknown fire” ranged from 0.04 to 0.86 discrepancies per 200 actuations in the PP population. Similar results were seen in the ITT population for all discrepancy types (Fig. 3).

“Fire not count” discrepancy rates for each disease (asthma or COPD) and for each asthma age subgroup (4–11, 12–64, and ≥ 65 years old) were variable. For the PP population, the discrepancy rate for the asthma subgroup was slightly higher than for the COPD subgroup (0.37 and 0.23, respectively). Discrepancy rates of 1.02, 0.23, and 0.04 were observed for the age groups 4–11, 12–64, and ≥ 65 years old, respectively. Results of

Table 3 Overall discrepancy rate for fire not count (primary end point) within a dosing session by subgroup and population

Populations	<i>n</i>	Total No. of Patient-Reported Actuations	Total No. of Fire Not Count Discrepancies	Discrepancy Rate* of Fire Not Count
Overall population				
PP population	235	41,720	62	0.30
ITT population	304	50,689	72	0.28
COPD subgroup				
PP population	123	21,944	25	0.23
ITT population	152	25,616	28	0.22
Asthma subgroup				
PP population	112	19,776	37	0.37
ITT population	152	25,073	44	0.35
Asthma (aged 4–11 yr)				
PP population	28	4913	25	1.02
ITT population	39	6290	29	0.92
Asthma (aged 12–64 yr)				
PP population	54	9511	11	0.23
ITT population	74	12,251	13	0.21
Asthma (aged ≥65 yr)				
PP population	30	5352	1	0.04
ITT population	39	6532	2	0.06

The PP population was primary population for analysis. Fire not count = undercount.

*The average rate of discrepancy per 200 actuations. The rate is calculated as number of discrepancies divided by the total number of actuations multiplied by 200.

COPD = chronic obstructive pulmonary disease; ITT = intent to treat; PP = per protocol.

the subgroup analyses were similar between the PP and ITT populations (Table 3).

Categorization of Total Discrepancy Size per Inhaler

Total discrepancy size was calculated as (beginning counter reading minus end counter reading) minus (patient-recorded number of actuations) and adjusted for gaps in the diary. For the PP population, 111 inhalers had total discrepancy sizes of 0; 28 inhalers had an undercount of 1 or 2, and 50 inhalers had an overcount of 1 or 2. No inhaler had an undercount of >12 or an overcount of >14 (Table 4). The estimated mean of the absolute value of the total discrepancy size per 200 actuations for all groups combined was 1.84 actuations (standard error [SE], 0.152; 95% confidence interval [CI], 1.54, 2.14) for the PP population. For the ITT population, the estimated mean of the absolute value of the total discrepancy size was somewhat higher (2.07 actuations [SE, 0.151; 95% CI, 1.77, 2.37]) than the comparable value for the PP population, in which likely patient errors were excluded. There are ~20 actuations available beyond the 200 label claim for albuterol HFA MDI with dose counter. The estimated probability of exceeding a discrepancy size of 20 actuations per 200 actuations was <1 in 1 million in the PP population.

Dosing Accuracy. Correlations were made between canister weights and diary-recorded actuations, as well as with dose counter readings, to further substantiate dosing accuracy and as a measure of compliance. For correlation with actuations, the coefficient of determination (r^2) was 0.82 (slope estimate of 0.03) in the ITT population (Fig. 4). The r^2 was lower in the PP population (0.12, with slope estimate of 0.03). However, this result was likely related to the fact that the range of doses available for evaluation in the PP population was small (165–196) and constrained.

Device Ruggedness. In the PP population, 23 patients (9.7%) reported mishandling errors. There were 19 patients (8.0%) who reported impact events (dropping the device), one patient (0.4%) reported that the device was exposed to moisture, and three patients (1.2%) reported other mishandling errors. Similar results were seen in the ITT population. Laboratory testing of the clinical complaint samples did not identify any mechanical or physical problem with the dose counter or the actuator.

Table 4 Categorization of total discrepancy size per inhaler (PP population, n = 235)

Category	Size of Inhaler Difference	No. of Inhalers
Undercount	Difference < -12	0
	-12 ≤ Difference < -10	1
	-10 ≤ Difference < -8	3
	-8 ≤ Difference < -6	1
	-6 ≤ Difference < -4	7
	-4 ≤ Difference < -2	9
	-2 ≤ Difference < 0	28
No discrepancies	Difference = 0	111
Overcount	0 < Difference ≤ 2	50
	2 < Difference ≤ 4	18
	4 < Difference ≤ 6	4
	6 < Difference ≤ 8	1
	8 < Difference ≤ 10	1
	10 < Difference ≤ 12	0
	12 < Difference ≤ 14	1
	Difference > 14	0

Counter record actuations = (beginning – end counter number) adjusting for days in which readings were not recorded. Total inhaler discrepancy size = (counter-recorded actuations – patient-recorded actuations).
PP = per protocol.

Patient Satisfaction

Results of the paper questionnaire evaluating “confidence” with patients’ previous inhaler experience, “ease of use,” and “satisfaction” with the current study device in the PP population are reported in Table 5. More than one-half of all patients (51.5%) responded that they were “not very certain” or “not certain at all” of how much medication remained in their previously used inhaler. Similarly, more than one-half of all patients (52.3%) reported that they were “not very certain” or “not certain at all” that it was time to refill medication or get a new inhaler. Almost one-half of all patients (48.5%) reported that they were “not very certain” or “not certain at all” that their inhaler was empty. In contrast, nearly all patients (97.9 and 98.3%, respectively) reported that the albuterol HFA MDI with dose counter was “very easy” or “somewhat easy” to use generally or to use properly as directed. Approximately the same percentages of patients reported that it was “very easy” or “somewhat easy” to tell how many doses remained and how many doses of the albuterol HFA MDI with dose counter they had used (95.7 and 97.0%, respectively). Nearly all patients reported that it was “very easy” or “somewhat easy” to avoid running out of medication with the albuterol HFA MDI with dose counter and to tell when it should be replaced (94.9 and 97.4%, respectively). Similarly,

patients’ “satisfaction” with the MDI with dose counter compared with other inhalers used in the past was quite high. Overall “satisfaction” with the albuterol HFA MDI with dose counter was high: 94.9% of patients responded that they were “very satisfied” or “somewhat satisfied”; 1.3% of patients were “not satisfied at all” or “not very satisfied.” A majority of patients (96.6%) were “very satisfied” or “somewhat satisfied” with ease of use of the albuterol HFA MDI with dose counter. Similarly, a high number of patients (97.0%) were “very satisfied” or “somewhat satisfied” with being able to tell when the albuterol HFA MDI with dose counter should be replaced.

Safety

Of 306 patients included in the safety analyses, 81 patients (26.5%) experienced one or more treatment-emergent AEs. The most frequently reported treatment-emergent AEs were headache in nine patients (2.9%) and upper respiratory tract infection in five patients (1.6%), followed by toothache, sinus headache, sinusitis, and viral infection (each occurring in four patients [1.3%]). A total of five patients experienced the following six AEs, which were considered possibly treatment related as assessed by the investigator: atrial fibrillation, worsening hypertension, ear pain, oral candidiasis, otitis media, and tinea versicolor. No treatment-related AEs resulted in study discontinuation. Two patients each experienced one serious AE (COPD exacerbation; anaphylactic reaction to pantoprazole) that resulted in withdrawal from the study; both events were considered unrelated to study treatment. No deaths occurred. Three patients each experienced one nonserious AE (pneumonia, insect bite, and back sprain—all requiring treatment with disallowed medications) that resulted in withdrawal from the study; all events were considered unrelated to study treatment. Incidence of AEs by subgroup (disease and age subgroups) was generally similar to that reported for the overall population.

DISCUSSION

The results of this study indicate that the albuterol HFA MDI with a new integrated dose counter is robust and functions reliably and accurately in the clinical setting. The addition of a dose counter to albuterol HFA MDI allows patients to track the number of actuations left in their inhaler. The dose counter studied here is designed to count downward from the labeled number of actuations to zero, letting patients know when a device is ready to be replaced. This feature should prevent patients from discarding a functional inhaler prematurely and potentially from using the inhaler beyond the label recommendations.

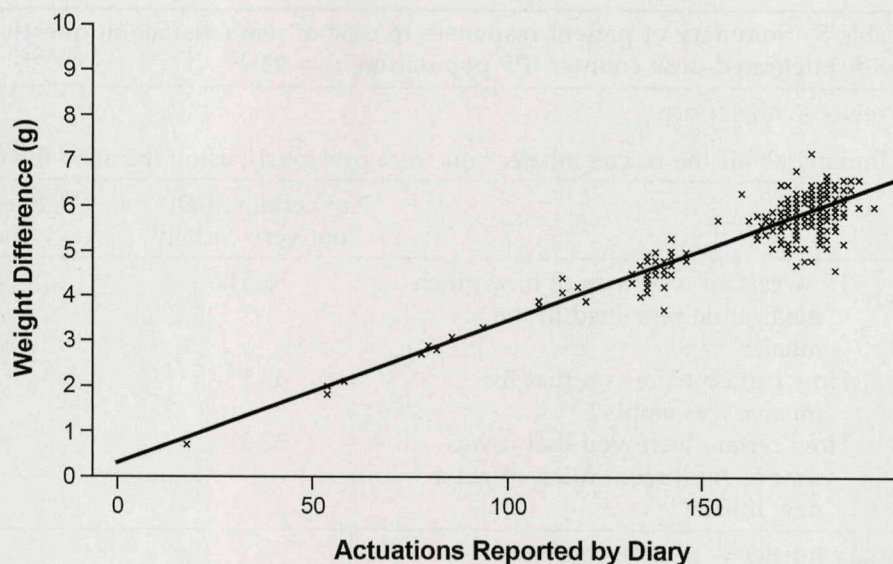


Figure 4. Canister weight differences versus diary-recorded actuations for individual patients (intent-to-treat [ITT] population, $n = 304$).

Albuterol HFA MDI with dose counter showed a high degree of concordance between dose counter readings and the number of actuations actually dispensed, as recorded in the patient diary. The overall calculated discrepancy rate was <2 (1.87) per 200 actuations. Although there were documented reports of device mishandling, the low discrepancy rates observed support the ruggedness of the device. Undercounting is a less acceptable form of dose counter error because of the potential for administration of a subtherapeutic dose.⁹ The discrepancy rate of undercounting ("fire not count") was <1 occurrence per 200 actuations (0.30) over all groups combined.

The overall discrepancy rate reported in the current study (1.87 per 200 actuations or 0.94 per 100 actuations) is comparable to what has been previously reported in three other studies that have evaluated the performance of MDI numeric dose counters. Sheth *et al.* reported that the discrepancy rate with the fluticasone propionate/salmeterol MDI was 0.94 per 100 actuations,¹⁰ and the rate reported by Wasserman *et al.* with another albuterol MDI was 0.76 per 100 actuations.⁵ In the Weinstein *et al.* study evaluating the mometasone furoate/formoterol MDI, a discrepancy rate of 1.06 per 100 actuations was reported.¹¹ A study by Shah *et al.* investigated the functionality of the budesonide/formoterol MDI with an indicator-type dose counter rather than a direct numeric counter.¹² However, this study did not report discrepancy rates as calculated in the first three studies or in the current study, so a direct comparison cannot be made.¹²

Discrepancy rates between dose counter readings and number of actuations actually dispensed using albuterol HFA MDI with integrated dose counter were variable in the disease subgroups (asthma and COPD) and the asthma age subgroups (4–11, 12–64, and ≥ 65 years). Variable discrepancy rates also have been re-

ported in another albuterol HFA MDI study when assessed for age and disease subgroups. In the Wasserman study, the reported rate of discrepancy in the asthma subgroup was higher than in the COPD subgroup (0.86 and 0.60 per 100 actuations, respectively).⁵ As seen in the current study, subgroup analyses in the Wasserman study also revealed variability among age groups,⁵ with both studies reporting the highest discrepancy rates among 4- to 11-year-old patients. Compared with the overall discrepancy rate of 0.76 per 100 actuations, patients ≥ 65 years old reported a discrepancy rate of 0.42 per 100 actuations, and patients 4–11 years old reported a discrepancy rate of 1.19 per 100 actuations.⁵ In general, subgroup analyses by disease or by age group, in both albuterol HFA MDI studies, reveal low discrepancy rates.

In the current study, approximately one-half of all patients (48.5–52.3%) reported that they were "not very certain" or "not certain at all" of how much medication remained in their current inhaler, when their current inhaler was empty, or when their current inhaler needed to be refilled or replaced. Similar results have been reported in a previous study evaluating dose counters in MDIs where 62% of patients reported feeling anxious about not knowing the quantity of medication remaining in their inhalers.⁵ These findings further highlight the need for dose counters in inhalers.

Difficulty in using an inhaler may reduce patient satisfaction, resulting in inadequate dosing and nonvolitional nonadherence. Nearly all patients (97.9%) reported that albuterol HFA MDI with new integrated dose counter was "very easy" or "somewhat easy" to use. Overall satisfaction with albuterol HFA MDI with dose counter was high; 94.9% of patients reported that they were "very satisfied" or "somewhat satisfied." It is important to note that it may be difficult to differentiate satisfaction with the dose counter in particular

Table 5 Summary of patient responses to ease of use/satisfaction questionnaire with the albuterol HFA MDI with integrated dose counter (PP population, $n = 235$)

Previous inhaler use:

Thinking about the rescue inhaler you were previously using (prior to the start of this study), . . .

	"Not certain at all" or "not very certain"	"Neither certain nor uncertain"	"Somewhat certain" or "very certain"
How certain were you of how much medication remained in the inhaler?	51.5%	10.2%	38.3%
How certain were you that the inhaler was empty?	48.5%	8.5%	43.0%
How certain were you that it was time to refill medication or get a new inhaler?	52.3%	9.8%	37.9%

Study inhaler with dose counter:

Thinking about the albuterol HFA inhaler with integrated dose counter (study treatment inhaler), . . .

	"Not easy at all" or "not very easy"	"Neither easy nor uneasy"	"Somewhat easy" or "very easy"
How easy is the inhaler to use?	0.4%	1.7%	97.9%
How easy was it to tell how many doses remained?	1.3%	3.0%	95.7%
How easy was it to monitor how many doses you used?	0.9%	2.1%	97.0%
How easy was it to avoid running out of medication?	4.3%	0.9%	94.9%
How easy was it to tell when the inhaler should be replaced?	0.4%	2.1%	97.4%
How easy was it for you to properly use the inhaler?	0.4%	1.3%	98.3%

Satisfaction with the study device:

Compared with other rescue inhalers that you have used, . . .

	"Not satisfied at all" or "not very satisfied"	"Neither satisfied nor unsatisfied"	"Somewhat satisfied" or "very satisfied"
How satisfied are you with the albuterol HFA inhaler?	1.3%	3.8%	94.9%
How satisfied are you with the albuterol HFA inhaler, based on ease of use?	0.4%	3.0%	96.6%
How satisfied are you that you will be able to tell when the albuterol HFA inhaler should be replaced?	1.3%	1.7%	97.0%

HFA = hydrofluoroalkane; MDI = metered-dose inhaler; PP = per protocol.

versus satisfaction with the MDI as a whole. This difficulty might potentially have been offset by the study's exclusion of patients who were current users of a short-acting β -agonist with a dose counter (*i.e.*, Ventolin HFA inhalation aerosol MDI), thereby achieving a population that could provide more accurate feedback

on comparison of devices with and without a counter rather than a comparison of two different types of counters. Three other studies specifically assessed patient preference or satisfaction with an inhaler with dose counter or indicator compared with the patient's previous inhaler without a dose counter. In a similar

study with another albuterol HFA MDI, it was reported that 80% of patients were more satisfied with an MDI containing a dose counter compared with an MDI without a dose counter.⁵ Similarly, compared with MDIs without dose counters, high levels of satisfaction also were reported with mometasone furoate/formoterol HFA MDI and fluticasone propionate/salmeterol HFA MDI.^{10,13} The high levels of patient satisfaction reported in the current study are similar to those reported in previous studies with MDIs with dose counters.^{5,12,13}

A potential limitation of the study is the use of paper questionnaires. After reviewing the available literature, Tennen *et al.* proposed that paper diaries can be effective in situations where behaviors being studied are discrete.¹⁴ Several electronic monitoring devices have been developed^{15,16} and used extensively to document medication adherence in clinical trials but are impractical for real-world use because of issues related to accuracy and additional cost.

Overall, albuterol HFA MDI with integrated dose counter was well tolerated. Furthermore, inclusion of the integrated dose counter did not alter the safety profile associated with the marketed product albuterol HFA MDI.⁴ In summary, the addition of a new integrated dose counter with albuterol HFA MDI has been shown to be functional and to provide patients with a reliable indication of how many actuations remain, allowing health care providers to be more confident that patients are receiving therapeutic doses from their MDI.

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REFERENCES

1. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the diagnosis and management of asthma: summary report 2007. *J Allergy Clin Immunol* 120(suppl 5):s94–s138, 2007.
2. Pauwels RA, Buist AS, Calverley PMA, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Global Initiative for

Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 163:1256–1276, 2001.

3. Hübner M, Hochhaus G, and Derendorf H. Comparative pharmacology, bioavailability, pharmacokinetics, and pharmacodynamics of inhaled glucocorticosteroids. *Immunol Allergy Clin North Am* 25:469–488, 2005.
4. Teva Respiratory, LLC. PROAIR HFA (albuterol sulfate) inhalation aerosol prescribing information. Horsham, PA; July 2010.
5. 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.
6. 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.
7. Rubin BK, and Durotoye L. How do patients determine that their metered-dose inhaler is empty? *Chest* 126:1134–1137, 2004.
8. GlaxoSmithKline. VENTOLIN HFA (albuterol sulfate) inhalation aerosol prescribing information. Research Triangle Park, NC; July 2009.
9. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for industry: Integration of dose-counting mechanisms into MDI drug products. March 2003. Available online at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071731.pdf; accessed July 24, 2012.
10. 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.
11. 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.
12. Shah S, White M, Uryniak T, and O'Brien CD. The functionality of a budesonide/formoterol pressurized metered-dose inhaler with an integrated actuation counter. *Allergy Asthma Proc* 31:40–48, 2010.
13. LaForce C, Weinstein C, Nathan RA, et al. Patient satisfaction with a pressurized metered-dose inhaler with an integrated dose counter containing a fixed-dose mometasone furoate/formoterol combination. *J Asthma* 48:625–631, 2011.
14. Tennen H, Affleck G, Coyne JC, et al. Paper and plastic in daily diary research: Comment on Green, Rafaeli, Bolger, Shrout, and Reis. *Psychol Methods* 11:112–118, 2006.
15. Gong H Jr, Simmons MS, Clark VA, and Tashkin. Metered-dose inhaler usage in subjects with asthma: Comparison of Nebulizer Chronolog and daily diary recordings. *J Allergy Clin Immunol* 82:5–10, 1988.
16. Julius SM, Sherman JM, and Hendeles L. Accuracy of three electronic monitors for metered-dose inhalers. *Chest* 121:871–876, 2002. □

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