

Beclomethasone dipropionate nasal aerosol with an integrated dose counter: Functionality and performance

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ABSTRACT

Consistent medication delivery is critical for disease control including symptom management of allergic rhinitis (AR). Available aqueous intranasal corticosteroid devices lack an accurate dose (actuation) counter, which may lead patients to prematurely discard a unit or use a unit beyond its labeled number of actuations, therefore impacting patient adherence. Beclomethasone dipropionate (BDP) nasal aerosol, a nonaqueous hydrofluoroalkane formulation in a device with a novel integrated dose counter and an established efficacy/safety profile, was approved to treat AR-associated nasal symptoms in adolescent and adult patients. This study was designed to evaluate performance of the BDP nasal aerosol device with an integrated dose counter in perennial AR (PAR) patients. In a 6-week, double-blind, placebo-controlled study in PAR patients (≥ 12 years), patients were randomized to receive once-daily BDP nasal aerosol at 320 micrograms or placebo. In addition to assessing the primary efficacy end point, patients evaluated the performance of the device and reliability, accuracy, and functionality of the dose counter. Concordance between daily patient-reported actuations and dose counter readings was assessed by classifying discrepancies into four categories: "fire not count," "count not fire," "count unknown fire," and "count up unknown fire." Analysis was performed for the total device completer population ($n = 374$), which included all randomized patients completing $\geq 80\%$ of actuations during the last 4 weeks of treatment. Low discrepancy rates were shown for all discrepancy categories. Of 41,891 patient-reported actuations, only 159 discrepancies (diary versus counter) were noted, resulting in an overall discrepancy rate of 0.38 per 100 actuations. The medically important discrepancy rate of "fire not count" was low (0.09 per 100 actuations). Overall, 79.1% of patients reported zero discrepancies, 9.4% reported one discrepancy, and 6.4% reported two discrepancies. These results showed the functionality and reliability of the BDP nasal aerosol device with an integrated dose counter in a clinical setting. (ClinicalTrials.gov identifier: NCT01134705.)

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Allergic rhinitis (AR), a prevalent and chronic condition of nasal mucosal inflammation, is associated with nasal symptoms such as congestion, rhinorrhea, pruritus, and sneezing, and eye symptoms such as itching, burning, tearing, and redness.^{1–3} Intranasal corticosteroids (INSs) are recommended as first-line therapy for the control of moderate-to-severe AR symptoms and persistent disease.^{1,2} Although INSs are

effective when the patient adheres to the treatment regimen, compliance with prescribed AR medications is limited; approximately two-thirds of patients take their medication inconsistently.⁴ Currently, many available aqueous INS formulations have been associated with undesirable sensory attributes such as unpleasant wetness ("dripping down the throat") after medication administration,^{5–7} which might lead to lack of adherence or discontinuation of the therapy. As an alternative therapeutic option, nonaqueous aerosol hydrofluoroalkane-propelled formulations have been developed that might increase patient adherence to INS therapy.^{5,6,8–10} Better adherence to prescribed aerosol-delivered AR medications, compared with aqueous INS formulations, has been associated with lower medical costs as a consequence of decreased use of other prescription medications.¹⁰

Beclomethasone dipropionate (BDP) nasal aerosol (Qnasl; Teva Respiratory, LLC), a hydrofluoroalkane-propelled nonaqueous aerosol formulation with a well-established efficacy and safety profile,^{11–14} has been approved for the treatment of symptoms associated with seasonal and perennial AR (PAR) in patients aged ≥ 12 years.¹⁵ BDP nasal aerosol is delivered from a pressurized metered-dose inhaler (MDI) device with

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an integrated numeric dose-counting mechanism, permitting patients to track the number of dispensed and remaining actuations.¹⁵ Patients who are unaware of how many doses remain in an MDI device lacking a device counter might persist in using the device even though little or no medication remains in the canister, therefore allowing for delivery of suboptimal doses. A reliable dose counter can help patients track their medication use, determine when to replace their inhaler, and inhibit them from actuating their inhaler beyond the labeled number of doses.^{16,17}

Nasal spray or nasal aerosol devices with either integrated dose indicators without a numeric display¹⁸ or dose indicators indicating the remaining actuations in groups of 5 or 10 actuations¹⁹ have been developed. Nasal spray devices normally require a minimum of 2 actuations/day (1 actuation/nostril) to multiple actuations per day, depending on the prescribed optimal daily dose. Therefore, consistent daily medication delivery may be limited by the patient's inability to recall the number of actuations administered when >1 actuation is needed to reach their full prescribed daily dose.²⁰ To avoid any subtherapeutic daily dose of medication, it is beneficial to have a dose counter that counts each individual actuation. The BDP nasal aerosol device is the first nasal MDI device with an integrated dose counter that can count downward and numerically display every actuation starting from 120 (124 before priming) when the

medication canister is full to 0 when the canister is empty (Fig. 1), thus allowing patients to track every actuation administered.¹⁵ In accordance with the United States Food and Drug Administration recommendation that all dose counter mechanisms be evaluated for accuracy and performance,²¹ the current study evaluated the functionality, reliability, and accuracy of the BDP nasal aerosol device with an integrated dose counter in patients with PAR.

METHODS

Study Design

Device performance was evaluated as part of a randomized, double-blind, parallel-group, placebo-controlled, multicenter, efficacy and safety phase 3 study in adolescent and adult patients with PAR. Detailed study design, the primary end point of efficacy over the 6-week treatment period, and additional efficacy and safety outcomes have been previously reported (ClinicalTrials.gov identifier: NCT01134705).¹¹ The study was approved by Quorum Review (Seattle, WA) and conducted in compliance with Good Clinical Practice guidelines and in accordance with the principles of the revised version of the Declaration of Helsinki. All patients gave written informed consent or assent before any study activity, as age appropriate. The study consisted of two periods: a placebo run-in period (7–21 days from the screening visit to the randomization visit), followed by a 6-week treatment period (Fig. 2). Patients were randomly assigned in a 1:1 ratio to receive BDP nasal aerosol (320 µg/day: 80 µg/actuation, 2 actuations/nostril) or placebo nasal aerosol (vehicle: 2 actuations/nostril) for 6 weeks. BDP nasal aerosol and placebo devices were identical in appearance and blinded to patients, investigators, and personnel at the study center. During the treatment period, patients self-administered the study medication once daily in the morning (A.M.); assessed their nasal symptoms twice daily, in the A.M. and evening; and recorded the assessments in a paper AR assessment diary.

At both the randomization and the first treatment visits (TVs), patients were provided with a Nasal De-

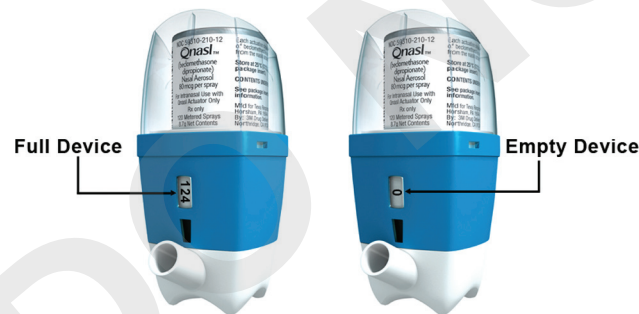


Figure 1. Beclomethasone dipropionate (BDP) nasal aerosol device with integrated mechanical dose counter.

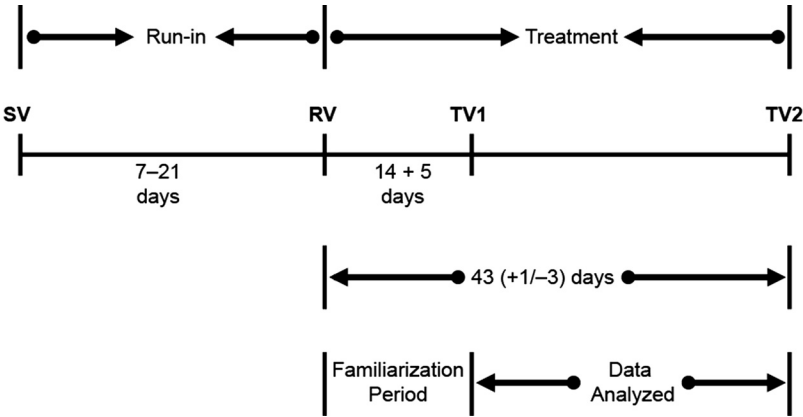


Figure 2. Study design. RV, randomization visit; SV, screening visit; TV1, treatment visit 1; TV2, final treatment visit.

vice Performance Diary to record the daily device performance. Daily diary entries made between the randomization visit and the first TV (first 2 weeks of the treatment period) were considered as training to familiarize patients with proper data recording (familiarization period); data from daily diary entries made during the remaining 4 weeks of the treatment period were included in the device performance analyses (Fig. 2). At the time of daily dosing (A.M.), patients recorded the dose counter display number before actuation, the number of actuations used, the dose counter display number after the actuations had been used, and comments about discrepancies (if any) between the counter display and actuations used. Patients also recorded any unusual circumstances surrounding device use, such as dropping the device. As a supplemental assessment of dosing accuracy, trained staff weighed devices (canister and actuator) for all treatment medications before dispensing and again after the last TV (pretreatment and posttreatment). Differences in pretreatment and posttreatment device weight were analyzed to correlate the estimated actuations used (as determined by device weight difference and per actuation weight), total actuations recorded in the diary, and final dose counter readings.

Patients

Patients aged ≥ 12 years, of either sex and of any race, with a history of PAR for ≥ 2 years, in general good health, and free of any concomitant conditions or treatment that could interfere with study conduct were eligible for the study. Patients were required to have PAR symptoms on the day of screening. Patients with a history of nasal polyps or other clinically significant respiratory tract malformations, recent nasal biopsy, nasal trauma (e.g., nasal piercing) or surgery, atrophic rhinitis, or rhinitis medicamentosa, all within 60 days of screening, were not eligible for the study. Individuals with known hypersensitivity to any corticosteroid or any excipient in the study medication, and individuals with history of respiratory infection or disorder within 14 days of screening or development of respiratory infection during the placebo run-in period, were also not eligible (additional eligibility and exclusion criteria have been previously described¹¹).

To qualify for randomization, patients must have achieved average minimum protocol-defined symptom scores (baseline), adequately completed their assessment diary, and taken their single-blind study medication at least 80% of the time during the placebo run-in period.

Dose Counter Performance Outcomes and Analysis

Concordance/agreement between patient-reported nasal aerosol device dose counter readings and patient-reported actuations recorded in the Nasal Device Per-

formance Diaries was analyzed, and discrepancies (i.e., disagreement between these numbers) were classified into four categories:

- “Fire not count” (i.e., undercount)—actuation without advancement of counter display.
- “Count not fire” (i.e., overcount)—counter display advancement without actuation.
- “Count unknown fire”—counter display advancement (counter counting downward) but the device has not knowingly been fired (counter number at the beginning of a dosing session less than counter number at the end of the previous dosing session).
- “Count up unknown fire”—counter counting upward rather than downward but the device has not knowingly been fired (counter number at the beginning of a dosing session greater than counter number at the end of the previous dosing session).

For each category of discrepancy, the rate of discrepancies per 100 actuations was estimated. The total number of diary card discrepancies of any type per patient was categorized and the magnitude of each type of discrepancy and mean total discrepancy size were determined. Differences in device weights measured before and after use, recorded between TV1 and TV2, were summarized descriptively. Correlations were generated by calculating Pearson correlation coefficients among the estimated number of actuations used per patient diary entries, the patient-reported number of actuations recorded in the diary, and the number of actuations indicated as used on the nasal aerosol device dose counter at device return. To evaluate the handling characteristics (e.g., ruggedness) of the nasal aerosol device with integrated dose counter, patients’ recordings of any problems or malfunctions of the device or the dose counter as well as recordings of mishandling (e.g., dropping of or physical impact sustained by the device) were analyzed.

Analysis Population

The primary population for analysis of all variables reported here was the total device completer population ($n = 374$), a subset of the intent-to-treat (ITT; $n = 466$) population that included only those patients who had administered at least 80% of actuations during the last 4 weeks of the treatment period (TV1 to TV2) after randomization (Fig. 2). In this study, data for the device completer population of the placebo and BDP nasal aerosol treatment groups, unless otherwise noted, were combined (total device completer population) because medication was administered in a double-blind fashion and the devices used for both treatments were identical except for the ingredient (active drug or placebo) in the canisters. After diary data entry

Table 1 Patient demographics (total device completer population; *n* = 374)

	Total <i>n</i> = 374
Age, yr	
Mean (SD)	38.1 (14.1)
Median	39.0
Minimum–maximum	12–82
Sex, <i>n</i> (%)	
Female	260 (69.5)
Male	114 (30.5)
Race, <i>n</i> (%)*	
White	299 (79.9)
Black or African American	65 (17.4)
Asian	9 (2.4)
American Indian or Alaskan Native	2 (0.5)
Other	5 (1.3)
Ethnicity, <i>n</i> (%)	
Hispanic or Latino	49 (13.1)
Neither Hispanic nor Latino	325 (86.9)

*Patients were able to select more than one race type.

and locking of the database, minor data recording and entry errors by patients and entry personnel were detected in the nasal aerosol device performance diaries of 20 patients. Data from diary pages of those patients determined to have such data entry errors were excluded for the device completer population.

RESULTS

Study Populations and Patient Demographics

The combined ITT population included 466 patients (232 patients randomly assigned to BDP nasal aerosol and 234 patients to placebo) and has been described previously.¹¹ The total device completer population included 374 patients (BDP nasal aerosol, *n* = 189; placebo nasal aerosol, *n* = 185). The majority of patients in the total device completer population (Table 1) were white (79.9%) and female (69.5%). The mean age was 38.1 years (range, 12–82 years).

Dose Counter Performance

Discrepancy Number and Rates. The majority of patients (296/374; 79.1%) in the total device completer population reported no discrepancies in usage of the integrated dose counter. A small number of patients reported one discrepancy (35/374; 9.4%) or two discrepancies (24/374; 6.4%; Fig. 3).

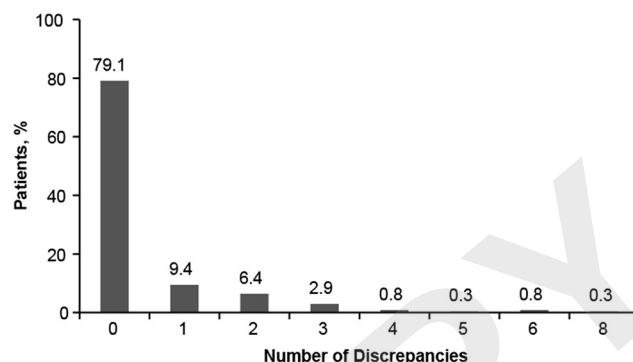


Figure 3. Number of diary card discrepancies per patient (total device completer population; *n* = 374). Note, excludes device count data from diary pages determined to have data entry errors. Data shown for combined placebo and beclomethasone dipropionate (BDP) nasal aerosol treatment groups in the total device completer population.

Table 2 Diary card discrepancy rates per 100 actuations (total device completer population; *n* = 374)

Discrepancy	BDP Nasal Aerosol <i>n</i> = 189	Placebo <i>n</i> = 185	Total <i>n</i> = 374
Fire not count	0.10	0.08	0.09
Count not fire	0.22	0.12	0.17
Count unknown fire	0.04	0.08	0.06*
Count up unknown fire	0.05	0.06	0.06#
Total number of actuation discrepancies	0.41	0.34	0.38

Note: Excludes device count data from diary pages determined to have data entry errors.

*Number of discrepancies = 26.

#Number of discrepancies = 24.

“Fire not count” (i.e., undercount) = actuation without advancement of counter display; “count not fire” (i.e., overcount) = counter display advancement without actuation; “count unknown fire” = counter display advancement (counter counting downward) but the device has not knowingly been fired (counter number at the beginning of a dosing session less than counter number at the end of the previous dosing session); “count up unknown fire” = counter counting upward rather than downward but the device has not knowingly been fired (counter number at the beginning of a dosing session greater than counter number at the end of the previous dosing session).

In the total device completer population, of the 41,891 total patient-reported actuations, 159 discrepancies were reported, resulting in a calculated overall discrepancy rate of 0.38 discrepancies per 100 actuations (Table 2). With 0.41 and 0.34 per 100 actuations,

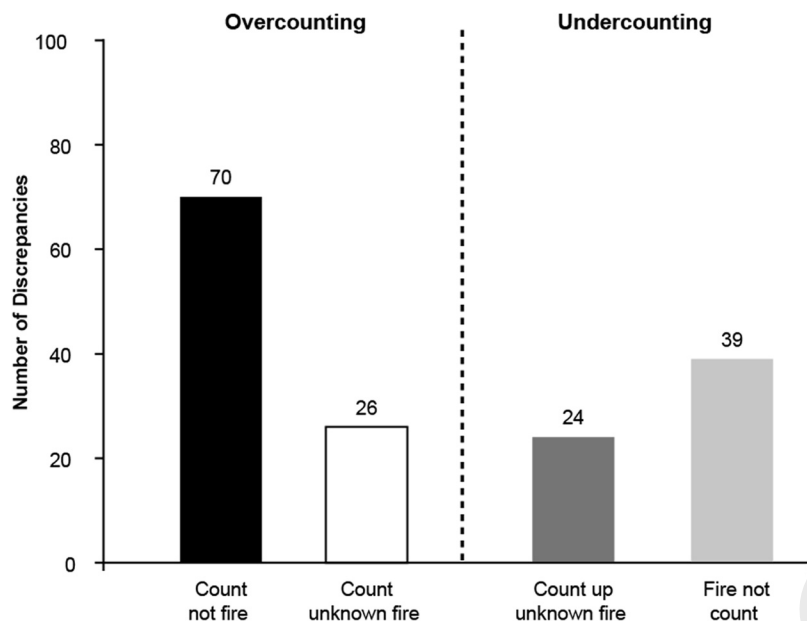


Figure 4. Number of overcounting and undercounting dose counter discrepancies observed in 41,891 actuations (total device completer population; $n = 374$). Note, excludes device count data from diary pages determined to have data entry errors. Data shown for combined placebo and beclomethasone dipropionate (BDP) nasal aerosol treatment groups in the total device completer population.

discrepancy rates were similar between the BDP nasal aerosol and placebo groups, respectively. Discrepancy rates were low for all discrepancy categories, ranging from 0.06 to 0.17 discrepancies per 100 actuations in the total device completer population (Table 2). Similar results were seen in the ITT population as well for all discrepancy categories (data not shown). The most commonly reported discrepancy, “count not fire,” an overcounting that occurred when the nasal aerosol device counter advanced but the device did not actuate, was observed in 70 of 159 discrepancies and occurred at a rate of 0.17 per 100 actuations (Fig. 4). A second overcounting discrepancy, “count unknown fire,” indicating that the nasal aerosol device counter advanced but the device had not knowingly been actuated, was observed more infrequently, with 26 discrepancies and a discrepancy rate of 0.06 per 100 actuations. Only 39 of the 159 discrepancies were related to undercounting due to “fire not count,” which is the most clinically relevant potential discrepancy, but occurred only rarely, at a rate of 0.09 per 100 actuations (Fig. 4). Discrepancies manifesting as a higher number on the counter than noted in the diary, in the absence of knowing actuations, “count up unknown fire” occurred the most infrequently, with 24 reports and a rate of 0.06 per 100 actuations.

Discrepancy Size. The mean total discrepancy size, derived from dividing the sum of all discrepancies reported (159) by the total number of patient-reported actuations (41,891) and multiplying this by the number of doses in each canister (120), was 2.8 actuations per device in the total device completer population. The mean discrepancy size for “fire not count” (undercounting) and “count not fire” (overcounting) events

was 2.3 actuations and 2.2 actuations per device, respectively.

Concordance of Expected, Diary-Reported, and Counter-Recorded Actuations. Based on patients’ diary card records of daily study drug administration and counting each entry, stating that every dose of study medication had been taken as four actuations, 41,404 actuations were expected overall in the total device completer population. The patient-reported actual number of actuations was 41,991 and the number of actual actuations based on dose counter data recorded at device return was 41,884. The correlation coefficient (r) between expected (based on recording of study medication use in the diary card) and patient-recorded actuations was 0.82 and the r between patient-reported and actual actuations based on the dose counter-recorded actuations was 0.80. Overall correlations between the expected versus actual actuations was 0.62, showing concordance between all measures.

Dosing Accuracy Based on Device Weight. Across the total device completer population (combined placebo–BDP nasal aerosol treatment group) the predose mean device weight was 46.8 g, the postdose mean device weight was 40.3 g, and the mean difference in device weight between predose and postdose was 6.4 g. The estimated number of actuations (based on the formula “number of estimated actuations for each patient = [change in device weight in milligrams/59] – 4” and then summed for all patients in the total device completer population) was 39,001, which was lower than the patient-reported or actual dose counter-derived actuation totals. Within the BDP nasal aerosol treatment group device completer population, the esti-

mated number of actuations used based on device weight difference was 19,277, compared with 21,203 actuations based on dose counter data and 21,300 patient-reported actuations. The r between estimated actuations based on device weight and patient-reported actuations and the r between estimated actuations based on device weight and actual counter-recorded actuations were discrepant, at 0.28 and 0.34 for the device completer population, respectively (data not shown). A similar analysis for the ITT population suggested a trend toward linear correlation between weight difference and actual count (data not shown), with r values of 0.60 and 0.69 for estimated actuations based on device weight and patient-reported actuations and estimated actuations based on device weight and dose counter-recorded actuations, respectively.

Device Ruggedness

Overall, the devices were considered reliable and rugged by most of the patients during daily use. Fourteen patients reported complaints for 19 devices; reasons for returning devices for laboratory investigation included medicine not delivered ($n = 6$), counter error ($n = 11$), device getting stuck after spraying ($n = 1$), and spray intensity variation ($n = 1$). Each device was investigated to assess device functionality in the laboratory. No visual defects were noted. Counter readings were within expected ranges, counters decremented correctly, and actuators functioned as intended for all concerned units. Laboratory testing of these clinical complaint samples did not identify any mechanical or physical problem with the device or dose counter. Therefore, the causes of the complaints were considered not related to any device malfunction but rather to operational error by the users.

DISCUSSION

This is the first study to report the performance of an intranasal device, as well as the reliability, accuracy, and functionality of its dose counter. Overall, the results of this study confirmed that the BDP nasal aerosol device with an integrated dose counter functions reliably and accurately over its intended lifespan (1 month of continuous daily use) in a clinical setting. Patients using the nasal aerosol device reported a high degree of consistency between actual dose counter readings and number of actuations that they intended to administer and that they recorded, indicating that the integrated counter helps in effective and reliable tracking of daily medication use. The majority of patients (79.1%) reported no discrepancies over the 4 weeks of use of the integrated dose counter, whereas only 9.4% of patients reported one discrepancy and 6.4% patients reported two. The overall discrepancy rate was 0.38 discrepancies per 100 actuations in the total device

completer population; discrepancy rates were similar between the BDP nasal aerosol and placebo groups (0.41 and 0.34 per 100 actuations, respectively), which was as expected given the double-blind design of the study. Few apparent problems or malfunctions of the device or counter after daily use were reported; careful investigation attributed the causes to operational error. Therefore, the performance of the BDP nasal aerosol device with an integrated dose counter compares favorably with findings from other similar studies evaluating dose counters of MDI devices, reporting overall discrepancy rates of 0.13 (mometasone furoate/formoterol MDI [Dulera; Merck, Whitehouse Station, NJ]), 0.76 (albuterol hydrofluoroalkane MDI [Ventolin HFA with counter; GlaxoSmithKline, Research Triangle Park, NC]), 0.94 (fluticasone propionate/salmeterol hydrofluoroalkane HFA [ADVAIR HFA; GlaxoSmithKline]), and 0.94 (albuterol sulfate HFA [ProAir HFA; Teva, Horsham, PA]).^{16,20,22,23} Shah *et al.* investigated functionality of the budesonide/formoterol MDI with an indicator-type dose counter rather than a direct numeric counter but did not report discrepancy rates²⁴; therefore, a direct comparison can not be made with the BDP nasal aerosol discrepancy rate. In the current study, the medically most important discrepancy of “fire not count” (a dose being dispensed with no advancement in counter display), which could lead to device overuse, occurred very rarely (0.09 per 100 actuations).

Device weights taken before and after patient treatment were used as an additional measure of tracking the actuations used in this study. Trained technicians determined the expected range by measuring the weight per actuation (shot weight) *in vitro* in a laboratory. In this study, the r between estimated actuations based on device weight and patient-reported actuations and the r between estimated actuations based on device weight and actual counter-recorded actuations were discrepant, at 0.28 and 0.34 for the device completer population, respectively. This discrepancy is likely caused by possible errors in weighing the devices and subsequent device weight-based indirect estimation of the number of actuations used by the patients. The BDP nasal aerosol device is manufactured as an integrated single unit, from which the canister can not be easily removed and reassembled, as is done with other inhaled MDI products. This is intended as an added safety feature to provide a consistent and reliable product for the patient to use without having to learn and understand the process of device assembly. Therefore, in this study, the entire device was weighed before dispensing and after treatment. This process was different from that in other similar published studies in which the individual canisters were weighed without the associated actuator.²⁴ This weighing of the device rather than weighing of the canister

only could have introduced additional variability into this study. The trend toward linear concordance observed in the overall ITT population between device weight and counter reading further suggests this inherent and potential variability of device weight measurements.

This study relied on patient diaries to assess and track counter performance, and, although this is an acceptable data collection method, it may lead to over- or underestimation of doses administered, such as inadvertent or deliberate reporting of higher than actual adherence, which has been shown to be discrepant in AR patients in daily practice.^{25,26} However, the current study results support a high degree of concordance between prescribed, patient-recorded and actual counter readings, suggesting very good adherence to study medication and potentially allowing patients to accurately track dispensed doses of their prescribed medication. Moreover, in a separate analysis of data from this study by Gross *et al.*²⁷ patients expressed a high degree of overall satisfaction with the device and nearly 90% found the device “very easy” or “somewhat easy” to use, both of which may lead to greater willingness to adhere to self-administration of daily medication. Better adherence to prescribed aerosol-delivered AR medications, compared with aqueous formulations of INs, has been associated with lower medical costs as a consequence of decreased use of other prescription medications.¹⁰

To our knowledge, this is the first published study to evaluate the device performance and dose counter accuracy of a nasal aerosol or nasal spray device. In this study, a BDP nasal aerosol device with an integrated dose counter was shown to be accurate and functional during use by adult and adolescent patients with PAR. The novel integrated dose counter, which accounts for each actuation, provides patients with a reliable method to track their daily medication usage, to determine when to replace their device, and to prevent them from actuating their device beyond the labeled number of doses. Additionally, the BDP nasal aerosol device presents clinicians with an objective means of assessing patient adherence to their medication.

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REFERENCES

1. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and Its Impact on Asthma (ARIA) 2008 update. *Allergy* 63(suppl 86): 8–160, 2008.

2. Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: An updated practice parameter. *J Allergy Clin Immunol* 122:S1–S84, 2008.
3. Greiner AN, Hellings PW, Rotiroti G, and Scadding GK. Allergic rhinitis. *Lancet* 378:2112–2122, 2011.
4. Marple BF, Fornadley JA, Patel AA, et al. Keys to successful management of patients with allergic rhinitis: Focus on patient confidence, compliance, and satisfaction. *Otolaryngol Head Neck Surg* 136:S107–S124, 2007.
5. Luskin AT, Blaiss MS, Farrar JR, et al. Is there a role for aerosol nasal sprays in the treatment of allergic rhinitis: A white paper. *Allergy Asthma Proc* 32:168–177, 2011.
6. Meltzer EO. Formulation considerations of intranasal corticosteroids for the treatment of allergic rhinitis. *Ann Allergy Asthma Immunol* 98:12–21, 2007.
7. Naclerio RM, Hadley JA, Stoloff S, and Nelson HS. Patient and physician perspectives on the attributes of nasal allergy medications. *Allergy Asthma Proc* 28:S11–S17, 2007.
8. Fromer LM, Ortiz G, Ryan SF, and Stoloff SW. Insights on allergic rhinitis from the patient perspective. *J Fam Pract* 61(suppl 2):S16–S22, 2012.
9. Mahadevia PJ, Shah S, Leibman C, et al. Patient preferences for sensory attributes of intranasal corticosteroids and willingness to adhere to prescribed therapy for allergic rhinitis: a conjoint analysis. *Ann Allergy Asthma Immunol* 93:345–350, 2004.
10. Hankin CS, Cox L, Lang D, et al. Medical costs and adherence in patients receiving aqueous versus pressurized aerosol formulations of intranasal corticosteroids. *Allergy Asthma Proc* 33:258–264, 2012.
11. Meltzer EO, Jacobs RL, LaForce CF, et al. Safety and efficacy of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with perennial allergic rhinitis. *Allergy Asthma Proc* 33:249–257, 2012.
12. Nayak AS, Andrews CP, Bernstein DI, et al. Long-term (52-Week) treatment with beclomethasone dipropionate hydrofluoroalkane nasal aerosol (320 mcg Once Daily) is safe and effective in adult and adolescent subjects with perennial allergic rhinitis. Presented at the Annual Scientific Meeting of the American Academy of Allergy, Asthma, and Immunology, Orlando, FL, March 3–8, 2012.
13. Segall N, Mansfield L, Amar N, et al. Once daily treatment with beclomethasone dipropionate hydrofluoroalkane nasal aerosol is safe and effective in children (6–11 years of age) with seasonal allergic rhinitis. Presented at the Annual Scientific Meeting of the American Academy of Allergy, Asthma, and Immunology, Orlando, FL, March 3–8, 2012.
14. van Bavel JH, Ratner PH, Amar NJ, et al. Efficacy and safety of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with seasonal allergic rhinitis. *Allergy Asthma Proc* 33:386–396, 2012.
15. Teva Respiratory, LLC. Qnasl (beclomethasone dipropionate) nasal aerosol for intranasal use only prescribing information. Horsham, PA; March 2012.
16. 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.
17. Sander N, Fusco-Walkert SJ, Harder JM, and Chipps BE. Dose counting and the use of pressurized metered-dose inhalers: Running on empty. *Ann Allergy Asthma Immunol* 97:34–38, 2006.
18. GlaxoSmithKline. Veramyst (fluticasone furoate) nasal spray prescribing information. Research Triangle Park, NC; August 2012.
19. Sunovion Pharmaceuticals Inc. Zetonna (ciclesonide) nasal aerosol for intranasal use only prescribing information. Marlborough, MA; January 2012.

20. 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.
21. U.S. Department of Health and Human Services, U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research. Guidance for industry: Integrations of dose counting mechanisms into MDI drug products. FDA, 1–7, 2003. Available online at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071731.pdf; accessed January 14, 2013.
22. 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.
23. 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.
24. 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.
25. Loh CY, Chao SS, Chan YH, and Wang DY. A clinical survey on compliance in the treatment of rhinitis using nasal steroids. *Allergy* 59:1168–1172, 2004.
26. Spector SL, Kinsman R, Mawhinney H, et al. Compliance of patients with asthma with an experimental aerosolized medication: Implications for controlled clinical trials. *J Allergy Clin Immunol* 77:65–70, 1986.
27. Gross GN, Settipane RA, Ford LB, et al. Patient satisfaction with beclomethasone dipropionate nasal aerosol device with integrated dose counter during daily use. *Allergy Asthma Proc* 34:527–533, 2013. □

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