Original Research

Health Status of Patients with Moderate to Severe COPD after Treatment with Nebulized Arformoterol Tartrate or Placebo for 1 Year

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ABSTRACT

Purpose: Chronic obstructive pulmonary disease (COPD) is a progressive disease that impairs both objectively measured lung function and patient-reported health status. In a randomized clinical trial of patients with moderate to severe COPD, we compared changes in health status after adding arformoterol tartrate or placebo to patients' treatment regimens.

Methods: In this multicenter, double-blind trial, patients were randomized to receive nebulized arformoterol 15 μg BID (n = 420) or matched placebo (n = 421). Treatment with other COPD medications was permitted, except for long-acting β_2-agonists. Inclusion criteria were a forced expiratory volume in 1 second (FEV_1) ≤65% of predicted, FEV_1 >0.50 L, age ≥40 years, smoking history ≥15 pack-years, and a baseline breathlessness severity grade ≥2. The Clinical COPD Questionnaire (CCQ) was used to measure health status at randomization and at months 3, 6, and 12. CCQ scores range from 0 to 6, with higher scores indicating worse health status, and a decrease from baseline in total score by 0.4 point is considered clinically significant. Outcomes were analyzed by using mixed models for repeated measures.

Findings: At baseline, patients' mean age was 63.8 years; 42.9% of patients were female, and 51.4% were current smokers. The mean baseline CCQ total scores were 2.88 and 2.91 for the arformoterol and placebo groups, respectively. A total of 841 patients were randomized to receive either arformoterol (n = 420) or placebo (n = 421); among them, 211 (50.1%) who received placebo and 255 (60.7%) who received arformoterol completed the trial. Arformoterol-treated patients had greater mean improvement from baseline in CCQ total score (−0.18 vs 0.02; $P = 0.001$), symptoms (−0.21 vs 0.01; $P = 0.002$), functional state (−0.15 vs 0.02; $P = 0.018$), and mental state (−0.18 vs 0.02; $P = 0.023$) than patients receiving placebo. At study end, 38.3% of the arformoterol-treated patients and 30.8% of patients receiving placebo reported clinically significant improvements on the CCQ ($P = 0.026$). These improvements were only modestly correlated with improvements in FEV_1 ($r = -0.15$; $P < 0.01$).

Implications: In this 52-week trial, arformoterol-treated patients had greater improvements in health status than patients receiving placebo. Assessing health status along with lung function seems to provide additional information regarding the effectiveness of COPD maintenance treatments. ClinicalTrials.gov identifier: NCT00909779. (*Clin Ther.* 2017;39:66–74)

Key words: arformoterol tartrate, Clinical COPD Questionnaire, COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive condition that results in worsening lung

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function and symptoms such as dyspnea and coughing.[1] Although COPD cannot be fully halted or reversed, comprehensive treatment plans can alleviate many symptoms and maintain patients' quality of life.[1] COPD and other chronic lower respiratory diseases are now the third leading cause of death in the United States.[2]

Accurate assessment is vital to creating an optimal treatment plan for the patient with COPD. Without a clear picture of the patient's overall health status, necessary treatment adjustments might not be implemented. Objective measures of lung function such as forced expiratory volume in 1 second (FEV_1) have been the standard means of assessing disease progression and drug efficacy.[3] Lung function, however, often correlates poorly with daily activity. Although lung function remains important, increasing evidence suggests that, given the heterogeneous nature of COPD, measures of symptoms and functional impairment are more integral to an understanding of the impact of COPD on patients' daily activities and quality of life (ie, how they "feel and function").[4–6] Thus, a more thorough disease evaluation measuring symptoms and functional outcomes would be helpful in reaching appropriate treatment decisions.[4]

As measurement of symptoms and overall health status are becoming more important to the management of COPD, one recommended measure of health status is the Clinical COPD Questionnaire (CCQ).[5] This brief, patient-completed questionnaire has been shown to have strong reliability, validity, and responsiveness.[7] The CCQ assesses symptoms, functional state, and mental state, as well as overall health status, of patients with COPD.

Long-acting bronchodilators, including long-acting β-agonists (LABAs) and long-acting muscarinic antagonists, are the mainstay of maintenance treatment of COPD. Multiple studies have shown the efficacy of these drugs in improving lung function.[1,3] The nebulized method of administration may have important differences from handheld methods of administration in terms of ease of use and precise delivery of the dose, potentially making it a preferable choice of administration for patients who experience frequent exacerbations, have physical or cognitive impairment, or are elderly.[8–10] However, nebulized administration requires additional setup and cleanup, and for impaired patients, the assistance of a caregiver may be necessary. Patients with COPD and caregivers express high levels of satisfaction (~90%) with nebulizer use.[8]

Arformoterol tartrate is a nebulized LABA that is approved for the maintenance treatment of COPD and has been shown to be both safe and effective (at a dosage of 15 μg BID) for improvement of lung function in double-blind, randomized, placebo-controlled studies.[11,12] Although arformoterol was shown to be effective for lung function, little is known about how it affects patient-reported health status and how health status may relate to lung function.

The objective of the present study was to determine the effects of arformoterol tartrate 15 μg BID (ARF15-BID) on CCQ scores and to examine the potential relationship between CCQ and lung function outcomes in a randomized, placebo-controlled trial.

PATIENTS AND METHODS

Study Design and Data Source

Data from a 52-week, randomized, double-blind, placebo-controlled outpatient study conducted at 71 clinical sites in the United States were used in this analysis. The primary end point was time to respiratory death or first COPD exacerbation–related hospitalization. Health status outcome as measured by using the CCQ was a planned analysis. The study visits included screening (visit 1), baseline (randomization; visit 2), and follow-up at months 3, 6, 9, and 12 (visits 3–6). Patients were randomized 1:1 to receive ARF15BID or placebo (citrate-buffered saline administered BID via nebulization). Concomitant maintenance COPD medications other than LABAs could be continued, as long as the regimen was stable for ≥14 days before study entry and remained stable throughout the study. Patients were permitted rescue albuterol and supplemental ipratropium as needed, but the use of these rescue medications had to occur at least 6 hours before each visit.

All study procedures were in accordance with the principles expressed in the Declaration of Helsinki, and institutional review board approval was received. All patients or their legal representatives provided written informed consent. Further details regarding this study's design are available in the primary publication.[12]

Inclusion and Exclusion Criteria

All patients were at least 40 years of age with a documented primary clinical diagnosis of nonasthmatic

COPD. Each patient also met the following criteria: smoking history of ≥15 pack-years, baseline breathlessness severity grade ≥2 on the Modified Medical Research Council Dyspnea Scale, pre-bronchodilator FEV_1 ≤65% of predicted and >0.50 L at visit 1 or 2, and FEV_1/forced vital capacity ratio ≤70% at visit 1 or 2.

Measures

Health status outcomes were measured by using the CCQ. The CCQ data were collected at randomization and at the 3-, 6-, and 12-month follow-up visits. The CCQ is a 10-item patient-reported measure that rates patients' experience during the past week on the domains of symptoms, functional state, and mental state.[5] Each item's score ranges from 0 ("never" or "not limited at all") to 6 ("almost all the time" or "totally limited"), and the total is the average of the scores of all 10 items. The minimum clinically important difference (MCID) for the CCQ total score is 0.4 point.[13,14]

To better understand the relationship between change in CCQ scores and FEV_1 response, patients' FEV_1 responses to treatment were grouped into categories. The 3 FEV_1 response groups examined were improved (≥20% change), stable (0%–20% change), and reduced (<0% change).

Concomitant medications were classified based on the World Health Organization Anatomical Therapeutic Chemical (ATC) Classification System.[15] The ATC level II classes that were considered relevant to COPD and used by at least 5% of the sample were reported.

Statistical Methods

The impact of treatment on CCQ outcomes was assessed using a mixed model for repeated measures (MMRM) that adjusted for the following covariates: treatment, baseline smoking status, the relevant baseline CCQ score, baseline score by visit interaction, visit, and treatment-by-visit interaction. MCID (≥0.4-point improvement on CCQ total score) was assessed based on change from baseline to the last available observation, and statistical significance was assessed with a χ^2 test.

The relationship between change in FEV_1 and CCQ total score was assessed with a Pearson correlation coefficient using change to the last observation for both FEV_1 and CCQ. The difference between treatments in CCQ change, while controlling for FEV_1 response groups, was examined by using a 2-way ANOVA. The α level was set to 0.05, and all analyses were conducted by using SAS version 9.3 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Patients

A total of 841 patients were randomized to receive either ARF15BID (n = 420) or placebo (n = 421). The total number of patients who completed the 3-, 6-, and 12-month visits was 335 (79.8%), 304 (72.4%), and 255 (60.7%) for ARF15BID and 295 (70.1%), 253 (60.1%), and 211 (50.1%) for placebo, respectively. Table I provides the patients' baseline characteristics; there were no significant differences between the ARF15BID and placebo groups. Most patients were white, approximately one half were current smokers, and a majority had smoking histories of ≥30 pack-years. Table II lists commonly used concomitant medications; there were no significant differences between the ARF15BID and placebo groups.

CCQ Outcomes

The descriptive scores across time for each of the CCQ scores are shown in Table III. The baseline mean [SD] total scores were similar between the 2 groups (ARF15BID, 2.88 [1.20]; placebo, 2.91 [1.17]).

Significant difference in treatment effects across the follow-up visits between ARF15BID and placebo were observed for the total score (−0.177 [0.042] vs 0.024 [0.046]; $P = 0.001$), symptom domain (−0.205 [0.046] vs 0.008 [0.050]; $P = 0.002$), functional domain (−0.150 [0.050] vs 0.024 [0.054]; $P = 0.018$), and mental domain (−0.184 [0.060] vs 0.019 [0.065]; $P = 0.023$). The MMRM estimated change over time and visit-wise comparisons between ARF15BID and placebo for the CCQ total score, as well as for the 3 domain scores, are shown in Figure 1. An MCID ≥0.4 on the CCQ was observed for 38.3% (151 of 394) of the ARF15BID group and 30.8% (119 of 387) of the placebo group ($P = 0.026$).

CCQ Correlation With FEV_1

The correlation between changes in CCQ and changes in FEV_1 from the beginning of the study to study end point was −0.15 ($P < 0.01$). Interestingly,

Table I. Baseline characteristics. All patients randomized to treatment received ≥1 dose of study medication and comprised the intention-to-treat population. Values are given as mean (SD) or no. (%).

Characteristic	Placebo (n = 421)	ARF15BID (n = 420)	All Patients (N = 841)
Age, y	63.3 (9.5)	64.2 (9.3)	63.8 (9.4)
Sex			
Male	243 (57.7)	236 (56.2)	479 (57.0)
Female	178 (42.3)	183 (43.6)	361 (42.9)
Race			
White	374 (88.8)	372 (88.6)	746 (88.7)
Black	43 (10.2)	45 (10.7)	88 (10.5)
Asian	2 (0.5)	2 (0.5)	4 (0.5)
American Indian/Alaskan native	1 (0.2)	1 (0.2)	2 (0.2)
Other	1 (0.2)	0	1 (0.1)
Ethnicity			
Hispanic/Latino	15 (3.6)	9 (2.1)	24 (2.9)
Non-Hispanic/Latino	402 (95.5)	411 (97.9)	813 (96.7)
Not reported/unknown	4 (1.0)	0	4 (0.5)
COPD exacerbations in last year	0.8 (1.1)	1.0 (1.4)[*]	0.9 (1.3)[†]
Baseline COPD symptoms			
Coughing	320 (76.0)	321 (76.4)	641 (76.2)
Wheezing	303 (72.0)	298 (71.0)	601 (71.5)
Bringing up mucus	289 (68.6)	283 (67.4)	572 (68.0)
Chest tightness	199 (47.3)	195 (46.4)	394 (46.8)
Shortness of breath	391 (92.9)	395 (94.0)	786 (93.5)
Other	17 (4.0)	23 (5.5)	40 (4.8)
None	6 (1.4)	6 (1.4)	12 (1.4)
Mean MMRC Dyspnea Scale score[‡]			
2	101 (24.0)	95 (22.6)	196 (23.3)
3	224 (53.2)	220 (52.4)	444 (52.8)
4	96 (22.8)	105 (25.0)	201 (23.9)
Percent predicted FEV_1	39.4 (13.9)[§]	39.7 (13.2)	39.5 (13.5)[‖]
Baseline smoking status			
Current	218 (51.8)	214 (51.0)	432 (51.4)
Former	203 (48.2)	206 (49.0)	409 (48.6)
No. of current packs per day[f]			
0	203 (48.2)	206 (49.0)	409 (48.6)
>0–1	159 (37.8)	145 (34.5)	304 (36.1)
>1–2	50 (11.9)	60 (14.3)	110 (13.1)
>2–4	7 (1.7)	6 (1.4)	13 (1.5)
No. of pack-years smoked			
≥15 to <25	41 (9.7)	40 (9.5)	81 (9.6)
≥25 to <30	36 (8.6)	29 (6.9)	65 (7.7)
≥30	344 (81.7)	351 (83.6)	695 (82.6)

ARF15BID = arformoterol tartrate 15 μg BID; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; MMRC = Modified Medical Research Council.

[*]n = 418.

[†]n = 839.

[‡]Scores on the MMRC Dyspnea Scale range from 0 to 4, with a score of 4 indicating that a patient is too breathless to leave the house or becomes breathless when dressing or undressing. The highest numbered question to which the patient answered "Yes" was the dyspnea scale score. No patients had MMRC scores of 0 or 1; these values were therefore omitted.

[§]n = 420.

[‖]n = 840.

Table II. Concomitant medication use. The medications were grouped on the basis of Anatomical Therapeutic Chemical (ATC) Classification System Level II classes. The list was restricted to medication classes relevant to chronic obstructive pulmonary disease that were used by at least 5% of the sample. Values are given as no. (%).

ATC Level II Drug Class	Placebo (n = 421)	ARF15BID (n = 420)	All Patients (N = 841)
Glucocorticoids	238 (56.8)	241 (57.4)	479 (57.0)
Anticholinergics	206 (49.8)	225 (53.6)	431 (51.2)
Selective β_2-adrenoceptor agonists	113 (26.8)	112 (26.7)	225 (26.8)
Leukotriene receptor antagonists	30 (7.1)	36 (8.6)	66 (7.8)
Adrenergic agents and other drugs for obstructive airway disease	45 (10.7)	29 (6.9)	74 (8.8)
Other, such as supplemental oxygen	106 (25.2)	99 (23.6)	205 (24.4)
Influenza vaccines	55 (13.1)	49 (11.7)	104 (12.4)

ARF15BID = arformoterol tartrate 15 μg BID.

individuals who had greater improvements in FEV_1 tended to have greater improvements in CCQ. The change in CCQ total scores for patients with differing levels of change in FEV_1 are presented in Figure 2. A 2-way ANOVA found a marginally significant difference between the placebo and ARF15BID groups

Table III. Descriptive statistics for the Clinical COPD Questionnaire scores. The 25th and 75th columns give corresponding percentile scores.

		Placebo						ARF15BID					
Domain	Month	No.	Mean	SD	Median	25th	75th	No.	Mean	SD	Median	25th	75th
Total	0	419	2.91	1.17	2.80	2.00	3.80	416	2.88	1.20	2.80	2.00	3.60
	3	288	2.86	1.16	2.80	2.00	3.60	332	2.75	1.22	2.70	1.80	3.65
	6	250	2.93	1.23	2.90	1.90	3.80	302	2.67	1.24	2.60	1.70	3.60
	12	208	2.82	1.29	2.60	1.80	3.80	255	2.64	1.21	2.60	1.80	3.50
Symptoms	0	421	3.23	1.24	3.25	2.25	4.25	420	3.18	1.26	3.00	2.25	4.00
	3	288	3.18	1.27	3.25	2.25	4.25	332	3.07	1.26	3.00	2.00	4.00
	6	250	3.28	1.31	3.25	2.25	4.25	303	2.99	1.29	3.00	2.00	4.00
	12	208	3.07	1.34	3.00	2.00	4.13	255	2.94	1.27	3.00	2.00	3.75
Functional status	0	420	2.76	1.38	2.50	1.75	3.75	420	2.72	1.35	2.50	1.75	3.75
	3	288	2.67	1.31	2.50	1.75	3.50	332	2.60	1.41	2.50	1.50	3.50
	6	250	2.73	1.38	2.50	1.50	3.75	302	2.49	1.43	2.25	1.25	3.50
	12	208	2.67	1.46	2.50	1.50	3.75	255	2.47	1.35	2.25	1.50	3.25
Mental state	0	420	2.58	1.74	2.50	1.50	4.00	416	2.60	1.72	2.50	1.00	4.00
	3	288	2.58	1.67	2.50	1.00	4.00	332	2.42	1.66	2.00	1.00	3.50
	6	250	2.65	1.70	2.50	1.00	4.00	303	2.39	1.64	2.00	1.00	3.50
	12	208	2.62	1.72	2.50	1.00	4.00	255	2.39	1.66	2.00	1.00	3.50

ARF15BID = arformoterol tartrate 15 μg BID.

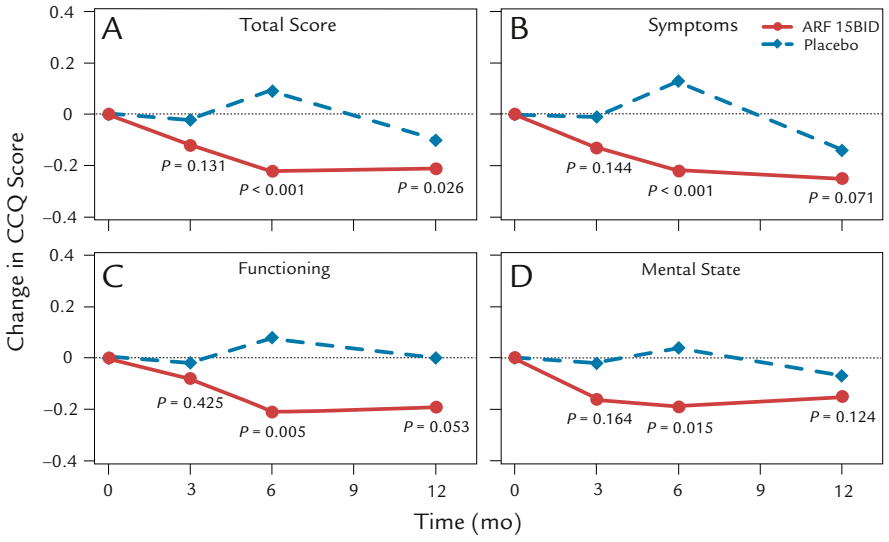

Figure 1. Change in Clinical COPD Questionnaire (CCQ) scores. A, total score; B, symptoms; C, functioning; and D, mental state. ARF15BID = arformoterol tartrate 15 μg BID.

in CCQ change, after controlling for FEV_1 change category (−0.16 for ARF15BID vs −0.02 for placebo; $P = 0.0545$). The improved CCQ score for patients treated with ARF15BID over the placebo group within different FEV_1 improvement categories suggests that the CCQ may capture an additional dimension of treatment response with ARF15BID.

DISCUSSION

In this randomized trial, treatment with ARF15BID improved the health status of patients with COPD, as measured by the CCQ, significantly more than placebo. These improvements were observed for the total score and each of the domain scores. When examining the differences at each visit, all of the CCQ scales were significant at the 6-month visit, but only the total score remained significant at the 12-month visit. The percentage of patients achieving clinically significant change was also higher for ARF15BID. FEV_1 change was correlated to CCQ change, but the correlation was not strong. In addition, after statistically controlling for FEV_1 category, CCQ scores improved more for patients treated with ARF15BID than for patients who received placebo. Thus, the CCQ seems to be capturing important information about health outcomes beyond lung function.

Although inclusion of measures such as the CCQ in clinical trials has been advocated in the literature,[5,16–18] this analysis is to the best of our knowledge the first to report CCQ-based health status outcomes for patients treated with nebulized arformoterol tartrate. A previous 4-week, randomized controlled trial reported that inhaled formoterol reduced the CCQ total score by −0.36 points, a significantly greater reduction than with placebo (−0.12; $P < 0.018$), as did multiple fixed doses of an ultra-LABA under development (AZD3199).[19] Similarly, in a real-world study that followed up patients treated with various bronchodilators (including LABAs) over 6 months, CCQ scores improved significantly by an average of −0.98 points.[20] Although there are no other studies specifically assessing CCQ outcomes for patients treated with arformoterol tartrate, outcome studies with other LABAs have reported consistent findings.

The modest correlation between changes in CCQ and FEV_1 reported here is consistent with a systematic review reporting a statistically significant, but modest, correlation between improvements in FEV_1 and the patient-reported St. George's Respiratory Questionnaire.[6] Recent systematic literature reviews have also demonstrated that both change in FEV_1 and patient-reported outcome measures such as the St. George's

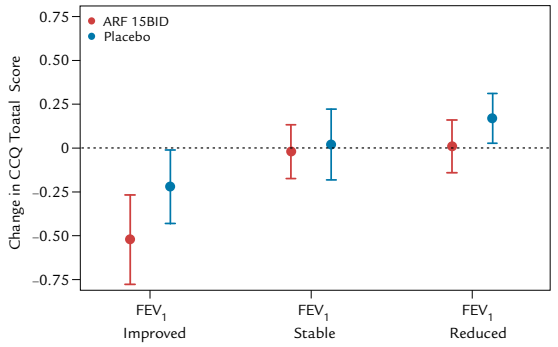

Figure 2. Relationship between Clinical COPD Questionnaire (CCQ) change and forced expiratory volume in 1 second (FEV_1) improvement. Error bars represent 95% CIs. FEV_1 change categories were defined as improved ($\geq$20% change), stable (0%-20% change), or reduced (<0% change). The respective sample sizes for arformoterol tartrate 15 μg BID (ARF15BID) and placebo, respectively, in each of the FEV_1 categories were as follows: FEV_1 improved, n = 72, n = 70; FEV_1 stable, n = 133, n = 116; and FEV_1 reduced, n = 139, n = 153. Although controlling for FEV_1 change categories, an ANOVA analysis found there was a marginally significant difference between change in CCQ total score between the ARF15BID and placebo treatments ($P = 0.0545$).

Respiratory Questionnaire are predictive of future exacerbations.[21,22] Multiple studies of CCQ scores have been found to be predictive of future exacerbations as well as future mortality.[23–27] Interestingly, predictions of primary care physicians' overall rating of COPD severity have been improved by adding patient-reported measures of health status to measure of lung function.[17] Multidimensional assessment of COPD should include measures of health-related quality of life and health status[16,28] because these factors seem to capture important aspects of treatment response.

Despite our analysis being based on a large, randomized study with long-term treatment data, there were some limitations to the findings. There were a significant number of treatment discontinuations, with only 50% to 60% of patients completing the 12-month visit. The analysis used MMRM models, which are valid if data are missing at random[29]; however, if the dropout was informatively missing, the results could be biased. Furthermore, concomitant medications were allowed in a manner consistent with usual clinical care, but this method could have contaminated the treatment effects.

CONCLUSIONS

Although earlier analyses of this clinical trial showed that treatment with ARF15BID offers significantly improved airflow to patients with COPD, this further analysis of CCQ scores revealed that ARF15BID treatment may also provide health benefits in areas affecting patient quality of life. The health status benefits of ARF15BID treatment were found for all domains measured by using the CCQ, including symptoms, functioning, and mental state. More patients treated with ARF15BID than receiving placebo experienced clinically significant improvements in CCQ total and domain scores. Assessing changes in health status along with changes in airflow seems to provide important information about the effectiveness of COPD maintenance treatments.

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All authors contributed substantially to the design of the study; the acquisition, analysis, and interpretation of data; and drafting the manuscript or revising it critically. All authors approved the final version as submitted.

CONFLICTS OF INTEREST

Dr. Donohue receives consultancy and advisory fees from Sunovion Pharmaceuticals Inc. Dr. Stensland is a full-time employee and sole stockholder in Agile Outcomes Research, Inc, a research consulting firm contracted by Sunovion to assist with this research. Dr. Nelson is an employee of RTI Health Solutions, a research consulting firm contracted by Sunovion to assist with this research. RTI Health Solutions is a research unit of RTI

International, a not-for-profit research institute. Dr. Ganapathy is an employee of Sunovion Pharmaceuticals Inc. At the time of this research, Dr. Bollu was an employee of Sunovion Pharmaceuticals Inc. The authors have indicated that they have no other conflicts of interest regarding the content of this article. The safety study was conducted by Sunovion Pharmaceuticals Inc as part of post-approval commitment to the FDA. As a study sponsor, Sunovion Pharmaceuticals Inc participated in the study design, analysis, interpretation of results, and preparation of the manuscript.

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