Efficacy and safety of formoterol fumarate delivered by nebulization to COPD patients

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Received 25 September 2007; accepted 11 October 2007
Available online 3 December 2007

Summary

Nebulized solutions of long-acting bronchodilators provide an alternative to DPI and MDI delivery, particularly for COPD patients unable to use hand-held devices easily or correctly. The long-acting b2-agonist, formoterol fumarate, is differentiated by its onset of significant bronchodilation within 5 min of administration. In a randomized, double-blind, double-dummy trial, COPD subjects (n = 351, mean forced expiratory volume FEV1 = 1.3 L, 44% predicted) received nebulized formoterol fumarate (PerforomistTM inhalation solution; FFIS 20 μg) or DPI (Foradil® Aerolizer®; FA 12 μg), or placebo twice daily for 12 weeks. Efficacy was assessed with 12-h pulmonary function tests, and quality of life was assessed before and after treatment with the St. George’s Respiratory Questionnaire (SGRQ). At the 12-week endpoint, FFIS significantly increased FEV1 AUC0–12h relative to placebo (p < 0.0001). No evidence of tachyphylaxis was observed as indicated by maintained FEV1 AUC and reduced rescue albuterol use throughout treatment. FFIS also significantly increased peak FEV1, trough FEV1, and standardized FVC AUC0–12h compared with placebo. SGRQ assessment at Week 12 demonstrated significant and clinically meaningful improvements in total score (FFIS vs placebo, −4.9, p = 0.0067), symptom, and impact scores. No significant differences in efficacy were observed between the two active treatments. Drug related AEs in the FFIS arm with a frequency ≥1% and exceeding placebo were dry mouth, nausea, and insomnia.

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Nebulized FFIS provided significant improvement in respiratory status and quality of life in subjects with COPD relative to placebo and was well tolerated. The efficacy and safety profile of FFIS was comparable to FA DPI. © 2007 Elsevier Ltd. All rights reserved.

Introduction

While metered dose inhalers (MDIs) and dry powder inhalers (DPIs) are efficient, convenient, and economical, nebulized treatments are an important alternative for patients who are unable to use MDIs and DPIs easily or correctly, such as patients with poor coordination, physical or visual impairment, or very ill inpatients. Patients with chronic obstructive pulmonary disease (COPD) in particular, being elderly, often have these limitations. In addition, many COPD patients or their caregivers feel they obtain more benefit from nebulized treatments.1,2 Guidelines have been developed to ensure optimal device selection and use of nebulized treatment3, and have concluded that equally efficacious treatment can be provided with proper device use and training.3

Long-acting β-agonists (LABAs) are a key step in the algorithm for regular disease management in moderate-to-severe COPD patients.5 The current study evaluated a new nebulized formulation of the LABA, for meterol fumarate, in COPD. Formoterol has a rapid onset of action, comparable to that of albuterol and superior to salmeterol,6,7 along with greater selectivity for β2-adrenoceptors than albuterol8 and prolonged duration of action allowing for twice-daily dosing.8 The effectiveness of formoterol as maintenance treatment for COPD patients was demonstrated in several controlled trials using DPI delivery.9-11 Its tolerability has been demonstrated with long-term global use in treating airways disease and 10 million patient-years of use12 in the United States.

Dose-response studies indicated a nebulized dose of 20 μg formoterol fumarate inhalation solution (FFIS) was comparable to the marketed 12 μg dose of formoterol fumarate DPI (Foradil®) (unpublished). We now present the results of a 12-week, randomized, placebo-controlled, double-blind, double-dummy study comparing the efficacy and safety of the nebulized formulation to formoterol DPI in patients with moderate-to-severe COPD.

Methods

Subjects

Study participants were outpatients aged ≥40 years who gave written informed consent. Inclusion criteria required a current or prior history of ≥10 pack-years cigarette smoking and a diagnosis of COPD, including persistent cough, sputum production, and/or shortness of breath on effort. Subjects were included if the post-bronchodilator forced expiratory volume in 1 s (FEV1) was ≥30% and <70% predicted normal13 and FEV1/forced vital capacity (FVC) ratio <0.70.

Subjects were excluded if they had a current or past diagnosis of asthma, a respiratory tract infection or acute exacerbation of COPD within the past month, required long-term oxygen therapy, had an electrocardiographic QTc interval >0.46 s, recent myocardial infarction, or other clinically significant comorbidities. Inhaled or oral corticosteroids (equivalent to prednisone ≤10 mg daily) were permitted if the dose was stable for the previous month.

Study design

The study was a multicenter, double-blind, randomized, parallel-group, active- and placebo-controlled study conducted at 38 centers in the United States (clinicaltrials.gov NCT00215436). Approval was obtained by the Institutional Review Board for each center prior to patient recruitment; the study was conducted in accordance with GCP and ICH guidelines and the Declaration of Helsinki. Following screening, subjects entered a single-blind run-in period of 4–14 days, during which they received placebos matched to both Aerolizer® and nebulizer for twice daily (b.i.d.) administration. Albuterol MDIs (90 μg/puff) were provided as rescue medication during screening and treatment periods of the study.

Eligible subjects were randomized to 12 weeks of double-blind, double-dummy treatment with FFIS (Perforomist™ inhalation solution 20 μg/2 mL, Dey, L.P., Napa, CA) delivered by the PARI LC Plus jet nebulizer with PARI PRONEB® compressor, formoterol fumarate DPI 12 μg (FA; Foradil®) and nebulizer for twice daily (b.i.d.) administration. Albuterol MDIs (90 μg/puff) were provided as rescue medication during screening and treatment periods of the study.

Variables

Prior to entry and at study completion, subjects underwent physical examination, medical history, laboratory evaluations, Holter monitoring, and 12-lead ECG. Visits were scheduled on the first day of study drug administration and every 4 weeks thereafter. Quality of life (QoL) was measured before the first dose of study medications and at study completion using St. George’s Respiratory Questionnaire (SGRQ).14,15 A study diary documented the daily use of rescue and study medication.

Pulmonary function tests were performed using spirometry.13,16 The pre-dose baseline FEV1 on Day 1 was within 15% of the screening pre-bronchodilator FEV1, and <70% predicted normal. Spirometry at Day 1 and Weeks 4, 8, and 12 was performed 30 min prior to the morning dose, and at 5 and 30 min, and 1, 2, 3, 6, 9, 12 h post-dose. Post-dose spirometry began at the end of nebulization.

The primary outcome was standardized absolute FEV1 area under the curve (AUC) over 12 h following the morning dose of study medication after 12 weeks of treatment.
Secondary outcomes included the standardized AUC for FEV₁ and FVC measurements on all visit days, peak FEV₁, 12 h, trough FEV₁, rescue medication use, and SGRQ scores on Day 1 and Week 12 for total and component (symptom, activity, impact) scores.

**Statistical analysis**

For the primary outcome, FEV₁ AUC₀₋₁₂, a standard deviation of 0.400 L² was assumed. A sample of 115 subjects per treatment group ensured 90% power to detect a difference of 0.172 L in standardized FEV₁ AUC₀₋₁₂ (two-sided α = 0.05) between FFIS and placebo.

Analysis of the primary efficacy variable was performed with the modified intent-to-treat (ITT) and completer populations using the last observation carried forward (LOCF) method for subjects with missing values in the ITT population. Primary efficacy analysis of the completer population included subjects who received ≥1 dose of study medication, had no major efficacy protocol violations, and had pre-dose and hour 12 FEV₁ measurements at the Week 12 visit. The difference in treatment group least-squares (LS) means was presented to make statistical inferences. An analysis of covariance (ANCOVA) model was used to estimate treatment differences for endpoints derived from spirometry and included fixed effects for treatment and center; baseline values were a covariate. An ANOVA model was used to test for treatment differences between mean average daily albuterol use at each visit.

**Results**

The study was conducted from March 2005 to September 2005. The disposition of study subjects is presented in Figure 1. All subjects randomized to treatment (n = 351) received ≥1 dose of study medication and were included in the ITT and safety populations. Fewer placebo- than active-treated subjects completed the study; the most common reason for discontinuation was adverse events.

Baseline demographics were similar across treatment groups with no statistically significant differences (Table 1). Pulmonary function was comparable among treatment groups and characteristic of a moderate-to-severe COPD population.

Inhaled corticosteroids (ICS) were used concomitantly by approximately 20%, 23%, and 19% of FFIS-, FA-, and placebo-treated subjects, respectively; whereas, oral corticosteroids were used at least once during the trial by 6%, 10%, and 12% of FFIS-, FA-, and placebo-treated subjects, respectively.

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**Figure 1** Subject disposition. FFIS: formoterol fumarate inhalation solution 20 μg BID and FA: formoterol fumarate DPI 12 μg BID.
Lung function

The standardized absolute AUC₀₋₁₂ for FEV₁ measured over 12 h following the AM dose of study medication at Week 12 (or early termination) in the ITT population was significantly improved in the FFIS group compared with placebo (Table 2). The LS mean difference between FFIS and placebo in the ITT and completer populations was 0.185 L (95% CI, 0.120–0.251, p < 0.0001) and 0.207 L (95% CI, 0.127–0.287, p < 0.0001), respectively. FFIS FEV₁ AUC₀₋₁₂ improvements seen on Day 1 were maintained at each subsequent visit, demonstrating no decrease in response, i.e. tachyphylaxis, over the 12-week treatment period (Table 2).

FFIS provided significant increases in FEV₁ compared to placebo at the first timepoint of 5 min after dosing and at every timepoint thereafter both at Day 1 and Week 12 (p < 0.0007; Figure 2). FEV₁ values at each timepoint at Weeks 4 and 8 were also significantly greater for FFIS than placebo (data not shown, p < 0.0003).

Peak FEV₁ remained higher in the FFIS group compared to placebo throughout the study, with a LS mean difference of 0.247 L at Week 12 (95% CI, 0.120–0.361, p < 0.0001; Figure 3). Trough FEV₁ values were also higher in the FFIS group relative to placebo group at each visit (Figure 3). The LS mean improvement in FVC AUC₀₋₁₂ compared with placebo at Week 12 was 0.341 L (95% CI, 0.191–0.491, p < 0.0001).

FFIS results for FEV₁ AUC₀₋₁₂, 12-h FEV₁ measurements, peak FEV₁, trough FEV₁, and FVC across all visits were

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**Table 1** Baseline demographics and values of all randomized patients.

<table>
<thead>
<tr>
<th></th>
<th>FFIS (n = 123)</th>
<th>FA (n = 114)</th>
<th>Placebo (n = 114)</th>
<th>Total (n = 351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (S.D.)</td>
<td>61.8 (8.6)</td>
<td>63.0 (9.4)</td>
<td>63.5 (9.2)</td>
<td>62.8 (9.1)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>71 (58)</td>
<td>61 (54)</td>
<td>65 (57)</td>
<td>197 (56)</td>
</tr>
<tr>
<td>Female</td>
<td>52 (42)</td>
<td>53 (46)</td>
<td>49 (43)</td>
<td>154 (44)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>60 (49)</td>
<td>61 (54)</td>
<td>61 (54)</td>
<td>182 (52)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>108 (88)</td>
<td>95 (83)</td>
<td>98 (86)</td>
<td>301 (86)</td>
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<td>Hispanic</td>
<td>4 (3)</td>
<td>6 (5)</td>
<td>3 (3)</td>
<td>13 (4)</td>
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<tr>
<td>Black</td>
<td>11 (9)</td>
<td>13 (11)</td>
<td>12 (10)</td>
<td>36 (10)</td>
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<tr>
<td>Asian</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bronchodilator reversible*, n (%)</td>
<td>71 (58)</td>
<td>73 (64)</td>
<td>58 (51)</td>
<td>202 (58)</td>
</tr>
<tr>
<td>Pre-bronchodilator % predicted FEV₁, mean (S.D.)</td>
<td>44.3 (11.5)</td>
<td>43.9 (11.6)</td>
<td>45.3 (13.2)</td>
<td>44.5 (12.1)</td>
</tr>
<tr>
<td>Baseline FEV₁ (L), mean (S.D.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-bronchodilator</td>
<td>1.35 (0.46)</td>
<td>1.30 (0.40)</td>
<td>1.36 (0.50)</td>
<td>1.34 (0.45)</td>
</tr>
<tr>
<td>Post-bronchodilator</td>
<td>1.51 (0.47)</td>
<td>1.49 (0.42)</td>
<td>1.51 (0.47)</td>
<td>1.50 (0.45)</td>
</tr>
<tr>
<td>Pre-bronchodilator FEV₁/FVC, mean (S.D.)</td>
<td>0.53 (0.10)</td>
<td>0.53 (0.10)</td>
<td>0.54 (0.10)</td>
<td>0.53 (0.10)</td>
</tr>
</tbody>
</table>

*10% increase in FEV₁ 30 min after inhaling two puffs of albuterol.
†30 min after inhaling two puffs of albuterol.

**Table 2** Baseline FEV₁ and standardized FEV₁ AUC₀₋₁₂ at each visit and at endpoint* (L).

<table>
<thead>
<tr>
<th></th>
<th>FFIS (n = 123)</th>
<th>FA (n = 114)</th>
<th>Placebo (n = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline FEV₁, mean (S.D.)</td>
<td>(0.43)</td>
<td>(0.39)</td>
<td>(0.48)</td>
</tr>
<tr>
<td>FEV₁ AUC₀₋₁₂, mean (S.D.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>1.52</td>
<td>1.48</td>
<td>1.37</td>
</tr>
<tr>
<td>(0.46)†</td>
<td>(0.46)†</td>
<td>(0.53)</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>1.54</td>
<td>1.48</td>
<td>1.34</td>
</tr>
<tr>
<td>(0.50)†</td>
<td>(0.45)†</td>
<td>(0.56)</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>1.51</td>
<td>1.48</td>
<td>1.35</td>
</tr>
<tr>
<td>(0.50)†</td>
<td>(0.44)†</td>
<td>(0.53)</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>1.49</td>
<td>1.47</td>
<td>1.33</td>
</tr>
<tr>
<td>(0.54)†</td>
<td>(0.45)†</td>
<td>(0.53)</td>
<td></td>
</tr>
<tr>
<td>Endpoint</td>
<td>1.51</td>
<td>1.49</td>
<td>1.33</td>
</tr>
<tr>
<td>(0.52)†</td>
<td>(0.46)†</td>
<td>(0.57)</td>
<td></td>
</tr>
</tbody>
</table>

*Baseline FEV₁ = Pre-bronchodilator FEV₁ at Day 1, Endpoint = Week 12 or early termination (LOCF).
†p < 0.0001 vs placebo, LS mean difference.
similar to those of FA. There were no statistically significant differences between FFIS and FA for any pulmonary function measurement at any time point at any visit.

Health-related quality of life

Subjects in the FFIS group experienced statistically significant and clinically relevant improvements from baseline in total SGRQ, symptom, and impact scores compared with placebo ($p \leq 0.03$; Figure 4). The LS mean differences between FFIS and placebo were $-4.91$ for total score ($95\%$ CI, $-8.45$ to $-1.37$, $p = 0.0067$), $-5.72$ for symptom score ($95\%$ CI, $-10.87$ to $-0.57$, $p = 0.0295$), and $-5.44$ for impacts score ($95\%$ CI, $-9.44$ to $-1.44$, $p = 0.0079$) with changes from baseline and differences from placebo above the threshold for clinical significance ($\geq 4$ units). FA-treated subjects demonstrated significant LS mean differences from placebo only for symptom scores. There were no statistically significant differences in total or component scores between the FFIS and FA groups.

Rescue medication use

At baseline (screening to Day 1), subjects in all treatment groups were treated with placebo and used similar amounts of albuterol, approximately 2.7 puffs per day (Figure 5). Albuterol use in the placebo group remained consistent throughout the study; however, use of rescue medication was reduced by 42% in the FFIS group during the first assessment period and maintained throughout treatment. From Weeks 8 to 12, the LS mean difference in daily albuterol use between FFIS and placebo-treated subjects
was −1.25 puffs (95% CI, −1.91 to −0.59, \( p = 0.0002 \)). Results for the FA group were similar to those of the FFIS group.

Adverse events

Over half of subjects reported at least one treatment-emergent adverse event (TEAE); the overall incidence was similar across treatment groups (Table 3). The incidence of COPD exacerbation was higher in the placebo group (7.9%) compared with the FFIS group (4.1%), a trend also seen for other respiratory events such as dyspnea, cough, and respiratory tract congestion. Also, differences were observed between FFIS and FA groups, respectively, in the rates of diarrhea (4.9% vs 1.8%), dizziness (2.4% vs 7.0%), and cough (1.6% vs 4.4%). Most TEAEs were mild-to-moderate in intensity. Overall, 16% of subjects experienced ≥1 drug-related TEAE; the incidence was comparable across treatment groups. Drug-related TEAEs experienced by ≥1% of FFIS subjects and with a frequency greater than placebo were dry mouth (2.4%), nausea (2.4%), and insomnia (1.6%).

No deaths occurred during the double-blind period of the study. Overall, 9/351 (2.6%) of the enrolled subjects experienced a treatment-emergent serious adverse event (SAE), 0.8%, 2.6%, and 4.4% in the FFIS, FA, and placebo groups, respectively. COPD exacerbation was the only SAE reported in more than one subject (two placebo-treated subjects). No SAE was categorized by the study site investigator as drug related. Discontinuations from the study due to TEAEs occurred in 3.3%, 3.5%, and 8.8% in the FFIS, FA, and placebo groups, respectively (Figure 1). The only TEAE that led to discontinuation in >1 subject was COPD exacerbation.

Other safety evaluations

Laboratory evaluations for most chemistry, hematology, and urinalysis parameters were within the normal range at baseline and endpoint across subjects in all treatment groups. Mean changes from screening were generally small and comparable among treatment groups. Very few subjects had clinically significant laboratory tests at the end of treatment or clinically significant changes from baseline. Mean serum glucose and potassium, analytes occasionally affected by \( \beta_2 \)-agonist treatment, were similar across treatment groups; no formoterol-treated subject had a post-treatment value or change from baseline of clinical significance. Additional cardiovascular safety outcomes are separately presented.

Discussion

In the current study, twice-daily nebulized formoterol provided improvements in pulmonary function that were comparable to DPI (Foradil \( 12 \mu g \) BID) and superior to placebo in subjects with moderate-to-severe COPD. The results are consistent with previously published studies with formoterol DPI treatment, and are the first to directly demonstrate comparable safety and efficacy of formoterol delivered by two different methods and doses.

Significant onset of bronchodilation was observed at the first spirometric timepoint (5 min) and continued throughout the 12 h of serial testing, relative to placebo. For the primary endpoint, \( \text{FEV}_1 \Delta \text{UC}_{0-12} \), a statistically significant
mean difference of 0.185 L between FFIS and placebo was observed. No decline in FEV1, AUC0–12 was observed between Day 1 and Week 12 in the FFIS-treated subjects. Similarly, the peak FEV1, trough FEV1, and FVC were significantly increased and maintained. The need for rescue medication was reduced by regular maintenance therapy with formoterol to almost half the level observed in the placebo group. Improvements in pulmonary function and rescue medication use were sustained over the 12-week treatment period with no evidence of tolerance/tachyphylaxis. In contrast, results of a similar clinical study with a single enantiomer formulation, arformoterol tartrate, suggested evidence of tolerance within 6 weeks at all doses tested.

In the current study, treatment with racemic formoterol was well tolerated. Exacerbations of COPD, predefined and classified as adverse events, were less frequent in the FFIS group than the placebo group. With the exception of dry mouth, nausea, and insomnia, FFIS-treated subjects did not report increased drug-related TEAEs compared to those on placebo. Rates of TEAEs in the FFIS group were also similar to those in the FA group, with apparent differences in rates of diarrhea, dizziness, and cough observed in this 12-week study. The higher rates of diarrhea in the FFIS group and dizziness in the FA group are similar to results from another large 12-month open-label safety trial. In addition, results of extensive cardiovascular safety monitoring in the study, described in more detail in a separate publication, revealed no clinically significant cardiovascular effects of treatment.

Nebulized COPD treatments are a medical necessity for some patients. Evidence-based guidelines concluded that there are no significant efficacy or safety differences among aerosol delivery devices and selection should be based on variables including preference, cost, setting, age and ability to use the device, convenience, and, ultimately, compliance. Patients consider nebulizers helpful in managing COPD and maintaining well-being, and have reported greater bronchodilatory improvement with nebulizer therapy. Nebulized bronchodilators provide a needed alternative for those many patients who are unable to use a DPI or MDI for reasons including frailty, arthritis, visual impairment, compromised mental capacity, exacerbation, inability to understand how to use it, or inadequate hand/ breath coordination. In a trial of 316 asthma and COPD patients, 88.9% failed to use their MDI or DPI correctly, and another study reported that education failed to improve the > 75% rate of inhaler misuse. Although breath-actuated DPIs like FA have alleviated coordination difficulties, they require a high peak inspiratory flow to disaggregate and disperse the drug powder, which elderly COPD patients may be unable to generate. In the current study, health status was measured by SGRQ. FFIS treatment was associated with statistically significant and clinically meaningful improvements in total SGRQ score and its symptom and impact components compared to placebo, while FA improved only symptom scores. Others recently demonstrated superior quality-of-life improvements for patients using a combination of daily nebulizer and MDI treatment over MDI alone.

These results together suggest a possible quality-of-life advantage of nebulized treatments over hand-held aerosol delivery of the same medication. Studies using additional patient-centered endpoints such as 6-min walk test and BDI/BDI are warranted to establish subjective and objective benefits of nebulized formoterol.

Approximately 20% of study subjects used concomitant ICS, which were permitted during the trial. The rate of ICS use was similar across treatment groups in our study and lower than in similar multicenter studies of formoterol in COPD performed outside the United States. Cazzola et al. reported that in a single-dose, double-blind crossover study, the addition of ICS to formoterol influenced the onset of bronchodilation, with significantly faster onset in responsive subjects and greater improvement in FEV1. Further investigation to understand the potential influence of concomitant ICS use on the efficacy and safety of nebulized formoterol is warranted.

In conclusion, the current study demonstrated that twice-daily nebulized formoterol is an effective and well-tolerated alternative for maintenance treatment of moderate-to-severe COPD. FFIS provided rapid and sustained improvements in pulmonary function, quality of life and rescue medication use.

Conflict of interest statement

The authors received compensation as investigators in the study. In addition, Drs. Gross, Nelson, and Lapidus have served as advisors to Dey, L.P. M. Rinehart and Dr. Denis-Mize are employees of Dey, L.P.

Acknowledgements

The authors would like to thank all of the principal investigators and personnel at these study sites in the Formoterol Study Group: Dr. Charles Andrews, Diagnostics Research Group, San Antonio, TX; Dr. Donald Auerbach, Delaware Valley Clinical Research, Cherry Hill, NJ; Dr. George Bensch, Bensch Research Associates, Stockton, CA; Dr. Shari Bazykni, Institute of Health Care Assessment, Inc., San Diego, CA; Dr. William Busse, University of Wisconsin Medical School, Madison, WI; Dr. B. Lauren Charous, Advanced Healthcare, SC, Milwaukee, WI; Dr. Edward Cordasco, Remington-Davis, Inc., Columbus, OH; Dr. Leonard Dunn, Clinical Research of West Florida, Clearwater, FL; Dr. Charles Fogarty, Spartanburg Pharmaceutical Research, Spartanburg, SC; Dr. Glenn Giessel, Pulmonary Associates of Richmond, Inc., Richmond, VA; Dr. Gregory Gottschlich, New Horizons Clinical Research, Cincinnati, OH; Dr. Nicholas Gross, Edward Hines, Jr. VA Hospital, Hines, IL; Dr. Thomas M. Hyers, CARE Clinical Research, St. Louis, MO; Dr. Harold Kaiser, Clinical Research Institute, Minneapolis, MN; Dr. Edward M. Kerwin, Clinical Research Institute of Southern Oregon, PC, Medford, OR; Dr. Kenneth T. Kim, West Coast Clinical Trials, Long Beach, CA; Dr. Robert Lapidus, Rocky Mountain Center for Clinical Research, Wheat Ridge, CO; Dr. Lauro Lapuz, Lovelace Scientific Resources, Inc., Henderson, NV; Dr. James F. Lawless, FFM Clinical Research, Camillus, NY; Dr. Lydia Lawson, Loveless Scientific Resources, Inc., Albuquerque, NM; Dr. Irene P. Leech, Irene P. Leech M.D., Inc., Long Beach, CA; Dr. Bernard Levine, Pulmonary Associates, PA, Phoenix, AZ; Dr. Mark Lindley, ClinSite, Inc., Ann Arbor, MI; Dr. William Lumry, AARA Research Center, Dallas, TX; Dr. Lon Lynn,
Clinical Research of West Florida, Inc., Tampa, FL; Dr. Frank P. Maggiacomo, New England Center for Clinical Research, Cranston, RI; Dr. Manuel R. Modiano, Arizona Clinical Research Center, Tucson, AZ; Dr. Anjuli Nayak, Sneezee, Wheeze, & Itch Associates, LLC, Normal, IL; Dr. Harold Nelson, National Jewish Medical & Research Center, Denver, CO; Dr. Michael Noonan, Transitional Clinical Research, Inc., Portland, OR; Dr. Parimal Parikh, Best Clinical Trials, New Orleans, LA; Dr. Keith Popovich, The Office of Keith J. Popovich, Butte, MT; Dr. Albert Razzetti, University Clinical Research, DeLand, FL; Dr. Mercedes B. Samson, Associated Pharmaceutical Research Center, Inc., Buena Park, CA; Dr. Paul Scanlon, Mayo Clinic Pulmonary Clinical Research Center, Rochester, MN; Dr. Thomas M. Siler, Midwest Chest Consultants, PC, St. Charles, MO; Dr. Selwyn Spangenthal, American Health Research, Inc., Charlotte, NC; Dr. Robert Sussman, Pulmonary & Allergy Associates, Summit, NJ; Dr. Manuel S. Villareal, Fragge Allergy and Asthma Clinic, Florence, KY; Dr. Steven F. Weinstein, Allergy & Asthma Specialists Medical Group, Huntington Beach, CA; Dr. Jan H. Westerman, Jasper Summit Research, LLC, Jasper, AL; Dr. Bram D. Wieskopf, North Georgia Clinical Research, Woodstock, GA; Dr. Robert Wolfe, Southern California Institute for Respiratory Diseases, Los Angeles, CA; Dr. Richard ZuWallack, St. Francis Hospital and Medical Center, Hartford, CT. The authors acknowledge the contribution of LaTanya Tomlinson to clinical operations.

The study sponsor was Dey, L.P., Napa, CA. Employees of Dey were involved in the study design; in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Authors were assisted by a professional medical writer, Elizabeth Field, Ph.D., in the preparation of the manuscript.

References

25. American Association for Respiratory Care. AARC supports patient education on MDIs/DPIs, appropriate dispensing fee for nebulizer drugs in new comments. Available at: [http://www.aarc.org/healthlines/phsyfee/index.asp] [accessed 26.03.07].


