A randomized study of formoterol fumarate in a porous particle metered-dose inhaler in patients with moderate-to-severe COPD

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KEYWORDS
Chronic obstructive pulmonary disease; Porous particle technology; Formoterol fumarate MDI

Summary
Background: Formoterol fumarate (FF) is a well-established long-acting β2-agonist. This represents the first clinical study of FF in a metered-dose inhaler (FF MDI) based on proprietary lipid-based porous-particle engineering technology.

Methods: In this randomized, double-blind, 5-period, crossover study (NCT00880490), subjects received 2.4, 4.8, and 9.6 mg of FF MDI, open-label Foradil® Aerolizer® (FA) 12 µg, and placebo. Spirometry was performed at baseline, 15 and 30 min, and 1, 2, 4, 6, 8, 10, 11.5, and 12 h post-dose.

Results: Thirty-four subjects were enrolled. Improvement in forced expiratory volume in 1 s (FEV1) was similar between FF MDI 9.6 µg and FA. Change in FEV1 area under the curve for 0–12 h (AUC0–12) for each FF MDI dose demonstrated superior efficacy versus placebo (P < .001 for all 3 doses). Over 12 h and at each time point, FF MDI 9.6 µg was non-inferior to FA for FEV1, AUC0–12 with the 95% CI’s supporting a maximum difference of approximately 45 mL. Peak and trough FEV1, forced vital capacity, peak expiratory flow rate, peak inspiratory capacity, and pharmacokinetics confirmed the primary endpoint, with dose ordering of the FF MDI 2.4, 4.8, and 9.6 µg, and comparability of FF MDI 9.6 µg to FA. All 3 doses of FF MDI were safe and well-tolerated, with a safety profile similar to that of placebo and FA.

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Introduction

Bronchodilator medications are central to alleviating the characteristic airflow limitation of chronic obstructive pulmonary disease (COPD) [1]. Metered-dose inhalers (MDIs) are the most commonly used devices to deliver bronchodilator treatment to patients with COPD and asthma [2]. Although they are easy to use and well-accepted, the reformulating of MDI products with hydrofluoroalkane (HFA) propellants that comply with stricter environmental regulations [3] has posed technical challenges.

HFA MDIs formulated upon a porous-particle platform using an inhaled drugs, leading to improved physical stability, the ability to formulate at very low doses, consistent dose-to-dose performance, high fine-particle fraction (FPF), and improved delivery of drug to the lower respiratory tract with minimized oropharyngeal exposure [4-6].

Formoterol fumarate (FF) is a well-established and extensively tested long-acting β2-adrenergic receptor agonist (LABA) indicated for the management of asthma and COPD, with Foradil® Aerolizer® 12 μg (FA; Merck & Co., Inc., Whitehouse Station, NJ, USA) twice daily (BID) being the approved dose in the United States. This study represents the first clinical study of FF in a metered-dose inhaler (FF MDI) based on proprietary lipid-based porous-particle engineering technology. It is postulated that this experimental FF MDI will result in improved lung function as assessed from FEV1 outcomes over a 12-h period compared with placebo.

It is anticipated that this formulation of FF MDI may provide advantages over currently available formulations at the same or lower doses in a patient cohort with moderate to severe COPD (GOLD definition [1]), particularly when co-formulated with a long-acting antimuscarinic agent (LAMA), and with an inhaled corticosteroid as a triple therapy. The study was designed to evaluate the single-dose administration of 3 doses of FF MDI in patients with moderate-to-severe COPD compared with open-label FA 12 μg as an active control in order to determine a dose that provides comparable bronchodilation and that does not exceed the systemic exposure.

Methods

Study design

This randomized, double-blind, 5-period, placebo- and active-controlled, crossover, multicenter study was conducted at clinical study centers in Australia and New Zealand between November 2008 and May 2009. The primary objective of the study was to assess the effects following a single dose of FF MDI in doses of 2.4, 4.8, and 9.6 µg on forced expiratory volume in the first second (FEV1) area under the curve from 0 to 12 h (AUC0-12) compared with open-label FA 12 µg and placebo among study patients with moderate-to-severe COPD. Secondary objectives included a) the assessment of a change from test-day baseline in mean peak FEV1, mean peak expiratory flow rate (PEFR), mean forced vital capacity (FVC), trough FEV1 (tFEV1), and mean peak inspiratory capacity (IC); b) confirm non-inferiority by comparing FF MDI with FA 12 µg based on change in FEV1 AUC0-12; c) assess the safety profile; and d) to define a dose of FF MDI that provided comparable systemic concentrations to open-label FA 12 µg. Approvals were obtained from institutional ethics committees at each investigator site. Written informed consent was obtained from each study patient prior to entry into the trial. The study was listed on all appropriate clinical trial registries including the United States (US) National Institutes of Health’s ClinicalTrials.gov (NCT00880490) as well as the Australia/New Zealand Clinical Trial Registry (ACTRN12609000191291).

Study patient population

Males and females, aged ≥40 to <80 years with a cigarette-smoking history of at least 10 pack-years, and an established clinical history of COPD in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) definition [7] were eligible for study participation. Study patients also were required to demonstrate reversibility to a short-acting β-agonist (SABA); defined as >12% and >150 mL improvement in baseline FEV1 30 min following administration of 4 puffs of salbutamol MDI, or >200 mL improvement in baseline FEV1 30 min following administration of 4 puffs of salbutamol MDI. Exclusion criteria included a primary diagnosis of asthma, poorly controlled COPD, active tuberculosis, lung cancer, other active pulmonary disease or clinically significant medical conditions, and hypersensitivity to any β-agonist or any component of the MDI and/or constituents of the dry powder product (lactose). Study patients were randomly allocated using a permuted block randomization algorithm.

Assessment of bronchodilator response

Both forced expiratory spirometry for derivation of FEV1, FVC, and PEFR, and slow vital capacity maneuvers for IC determination were assessed using a spirometer that met or
exceeded minimum performance recommendations of the ATS. At Randomization, spirometry was conducted 1 h and 0.5 h prior to study drug administration. The average of these 2 assessments was used to establish test day baseline FEV₁, FVC, and PEFR. Following study drug administration, spirometry was obtained at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 11.5, and 12 h post-dosing. FEV₁, FVC, and PEFR data were analyzed for primary and secondary assessments.

IC assessments were obtained on 6 occasions immediately prior to standard spirometry assessments: baseline (the average of the assessments at –1 h and –0.5 h), 1, 2, 11.5, and 12 h post-dose. Change in peak IC compared with placebo was a key secondary endpoint. During post-randomization study visits, spirometry was obtained at the same time points as outlined for Visit 2. The baseline FEV₁ on each test day must have been within ±15% of the baseline FEV₁ obtained at randomization (Visit 2). If the test day FEV₁ was not within ±15% of randomization FEV₁, the visit could be rescheduled at the investigator’s discretion or the patient discontinued.

Study treatments

Treatments consisted of FF MDI in a porous-particle formulation suspended in an HFA propellant in strengths of 3, 6, and 12 μg ex-valve, corresponding to 2.4, 4.8, and 9.6 μg ex-actuator for open-label FA 12 μg, and placebo, respectively. One dose concentration of test product (FF MDI) was used during this study. That is, each actuation released 3 μg (ex-valve) of the test product, which corresponded to a therapeutic amount of approximately 2.4 μg (ex-actuator), with multiple inhalations to achieve the different doses. In order to maintain blinding, it was necessary for study patients to inhale study drug from two different MDIs on each test day.

Prior to randomization, all study patients treated with inhaled corticosteroids (ICS) in combination with LABA or a LAMA discontinued those medications and were provided salbutamol MDI, ipratropium MDI, or a combination of ipratropium/salbutamol MDI per physician discretion. Theophylline in any formulation was discontinued. Study patients underwent a washout period of at least 1 week, but no longer than 4 weeks prior to the initiation of study medication. Study patients were asked to withhold all COPD medications for at least 8 h prior to study visits. There was at least 3 days and no more than 10 days between doses. Between test days, study patients resumed their previous COPD medications as defined at the Screening Visit. Subjects and all study-related staff were blinded to study patient assignment. This applied to the FF MDI and placebo treatments; FA 12 was open-label. Emphron Informatics Pty Ltd prepared the randomization scheme that was used to allocate patients to a study treatment sequence.

Stopping criteria

A study patient was to be discontinued from participation if any of the following parameters or clinical signs were noted on 2 consecutive assessments conducted approximately 15 min apart at the discretion of the principal investigator:

- QTcF prolongation greater than 30 ms from test day baseline and >430 msec
- Heart rate (HR): 40 bpm greater than test day baseline and an HR > 120 bpm
- HR: 20 bpm lower than test day baseline and an HR < 45 bpm
- Systolic blood pressure (BP): 40 mmHg greater than test day baseline and a systolic BP > 160 mmHg
- Systolic BP: 20 mmHg lower than test day baseline and a systolic BP < 90 mmHg
- Diastolic BP: 20 mmHg greater than test day baseline and a diastolic BP > 110 mmHg
- Diastolic BP: 20 mmHg lower than test day baseline and diastolic BP < 60 mmHg
- FEV₁: greater than 20% decrease from test day baseline on two consecutive spirometry assessments obtained at least 15 min apart with associated symptoms of dyspnea

Determination of sample size

Power was calculated assuming a non-central t distribution for the relevant linear contrast and under the assumption that a Bonferroni correction would be applied. An effect size of 160 mL was assumed, which was considered conservative given the results of Dahl et al. [8] and Gross et al. [9]. Power calculations also assumed a within subjects standard deviation of 200 mL [10]. Based on these calculations, 25 study patients with moderate to severe reversible COPD were required to achieve a power of 90% for detecting a change in FEV₁ AUC₀–₁₂.

Statistical analysis

Demographic and safety analyses were based on the intent-to-treat (ITT) population, which included all study patients who were randomized and received at least one dose of study treatment. A modified ITT (mITT) population was used for the analysis of pharmacokinetic (PK), pharmacodynamic (PD), and efficacy variables and included study patients who remained in the study for at least 6 h post-dosing. Repeated measures analysis of variance (ANOVA) was performed in which treatment was a fixed-effect, and within-patient-errors were independent. Treatment group means and 95% confidence intervals (CI) were tabulated for efficacy variables. Linear contrasts and their associated 95% CIs were estimated for each dose versus placebo, and 95% CIs were calculated for the difference FA 12 μg mean minus FF MDI mean for each dose of FF MDI. The upper limit of this CI represents a reasonable estimate of the maximum likely difference between treatments. A negative value for this upper limit would imply that FF MDI is statistically superior to FA 12 μg. Non-inferiority comparisons using an a priori defined margin of 100 mL were conducted for FF MDI in comparison with FA 12 μg. The margin of 100 mL was selected because this represents a clinically meaningful difference [12]. Analogous statistical
analyses were conducted for secondary efficacy endpoints. Mean log PK parameters and 90% CIs of their ratios were calculated from the mixed-model analysis of variance. Repeated measures ANOVA were performed in which treatment was a fixed-effect. Relative bioavailability calculations and 90% CIs for bioequivalence were calculated from the parameters of the linear repeated measures analysis. Plasma AUC\textsubscript{0–12} and ratio of peak FEV\textsubscript{1} to maximum plasma concentration (\(C_{\text{max}}\)) were summarized by the number of events and study patients experiencing each event by treatment. Clinical laboratory variables, vital signs, and electrocardiograms (ECGs) were also tabulated.

Results

Baseline characteristics

In total, 34 study patients were enrolled, 29 of whom completed the study. The disposition of study patients is provided in Figure 1. The first enrolled patient served as a sentinel study patient who was administered treatment and observed for 24 h after Visits 2, 3, and 4. This sentinel patient experienced no clinically relevant changes in vital signs, ECG or spirometry tests, no AEs, and reported no new concomitant medications. After these observations, dosing was then opened for additional study patients at all sites.

Demographic data and baseline characteristics are summarized in Table 1. The mean (SD) age of the study population was 64.8 (8.1) years (range 41–79 years), sex was approximately evenly distributed (16 females, 18 males), and 94% of study patients were Caucasian. Twenty-six percent of study patients were current smokers, and the mean (SD) smoking history was 46.7 (29.7) pack-years. At screening, the mean FEV\textsubscript{1} was 1.35 L pre-dose (46.9% of predicted) and 1.64 L post-dose (57.0% of predicted). Mean SABA reversibility was 0.29 L improvement in FEV\textsubscript{1} (10.1% predicted).

Efficacy

Primary endpoint

For the primary efficacy endpoint, change in FEV\textsubscript{1} AUC\textsubscript{0–12}, each FF MDI dose demonstrated significantly superior efficacy compared with placebo (\(P < .001\) for all 3 doses) with a clear dose–response relationship (Table 2). The normalized FEV\textsubscript{1} AUC\textsubscript{0–12} by FF dose for the mITT; (efficacy) population is represented in Figure 2. In general, compared with the test-day baseline the mean change in FEV\textsubscript{1} over time was similar between FF MDI 9.6 \(\mu\)g and open-label FA 12 \(\mu\)g, with nearly identical response curves over time (Figure 3). Tested with the a priori defined non-inferiority bound of 100 mL [12], FF MDI 9.6 \(\mu\)g was non-inferior to open-label FA 12 \(\mu\)g in terms of improvement from baseline in FEV\textsubscript{1} over 12 h and at each time point. Further analyses determined that the 95% CI’s support a maximum difference of approximately 45 mL, which provides further validation of the similar efficacy between the FF MDI 9.6 \(\mu\)g dose and FA 12 \(\mu\)g. The 2.4- and 4.8-\(\mu\)g doses of FF MDI were substantially lower than FA 12 \(\mu\)g at most time points assessed, and did not meet the pre-specified non-inferiority criteria for most of the assessments.
Secondary endpoints
In general, the analyses of the secondary endpoints (including peak and tFEV₁, FVC, PEFR, and peak IC) confirmed the findings of the primary endpoint, with dose-dependent responses of FF MDI 2.4, 4.8, and 9.6 μg, and the comparability of FF MDI 9.6 μg to FA 12 μg (Figures 4A, B, C). Both peak change in FEV₁ from test-day baseline and the mean change in FVC over time were significantly greater with each of the FF MDI doses compared with placebo. FF MDI 2.4, 4.8, and 9.6 μg demonstrated dose-ordering for the peak change from baseline in FEV₁ (0.172, 0.213, and 0.275 L, respectively, compared with 0.071 L for placebo). Improvements in the peak change from baseline in FEV₁ and FVC were generally similar for FF MDI 9.6 μg and FA 12 μg. However, at 30 min post-dosing there was a transient reduction in FVC occurring for the 4.8- and 9.6-μg doses. At the next sampling time (1 h post-dosing), the change from baseline had again increased and values were similar for FF MDI 9.6 μg and FA 12 μg. The differences between FF MDI 9.6 μg and FA 12 μg were not statistically significant, but there was a small numeric advantage with FA 12 μg. The mean change in FVC was significantly greater with FF MDI than placebo at 1 h for 2.4 μg; 15 min, 1 h, and 2 h for 4.8 μg; and from 15 min through 6 h and at 10 h for 9.6 μg (P < .001). Overall, the mean changes in PEFR, tFEV₁, and peak IC over time showed a dose-related trend among the FF MDI doses that was significantly different from placebo and that were similar between FF MDI 9.6 μg and FA 12 μg. The mean change in PEFR was significantly greater with FF MDI than placebo at all doses and time points except for the 2.4-μg dose at 10 h and 11.5 h (P < .042). For peak IC, the differences between FF MDI 9.6 μg and FA 12 μg were small and not statistically significant, although they showed a small numeric advantage for FF MDI 9.6 μg. There was a dose proportional increase in systemic exposure to formoterol observed with increasing doses of FF MDI as evidenced by the dose-related increases in AUC₀–₁₂ and Cₘₐₓ (Table 3), and FF MDI 9.6 μg demonstrated a similar concentration-time profile to that of FA 12 μg (Figure 5).

Pharmacokinetic endpoints
Exposure of formoterol (AUC₀–₁₂ and Cₘₐₓ) following administration of FF MDI appeared to increase in a dose-proportional manner across doses ranging from 2.4 to 9.6 μg. There was no obvious shift in Tₘₐₓ. A comparison of relative bioavailability of plasma formoterol concentrations (with 90% confidence intervals) for the three FF MDI treatment groups compared to FA 12 μg is presented in Table 4. The AUC₀–₁₂ of formoterol following administration of 9.6 μg of FF MDI was similar to that of observed with FA12 μg (34.0 and 36.1 pg h/mL, respectively). Furthermore, the Cₘₐₓ of formoterol following administration of 9.6 μg of FF MDI was similar to that of observed with FA 12 μg (6.36 and 6.35 pg/mL, respectively). For AUC₀–₁₂, the dose normalized estimated bioavailability in the FF MDI was

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Table 2  Primary efficacy endpoint: mean change in FEV₁ AUC₀–₁₂ compared with placebo (mITT efficacy population).

<table>
<thead>
<tr>
<th>Variable</th>
<th>FF MDI 2.4 μg</th>
<th>FF MDI 4.8 μg</th>
<th>FF MDI 9.6 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ AUC₀–₁₂ (L), Difference (Mean ± SE)</td>
<td>0.0815 ± 0.0185</td>
<td>0.1034 ± 0.0189</td>
<td>0.1759 ± 0.0195</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AUC₀–₁₂ = area under the curve for 0–12 h; FEV₁ = forced expiratory volume in 1 s; FF MDI = formoterol fumarate metered-dose inhaler; mITT = modified intent-to-treat; SE = standard error.

P values for comparisons with placebo from repeated measures analysis of variance (ANOVA), in which treatment was a fixed-effect, within-patient errors were correlated, and between-patient errors were independent. Covariates included in the model were age, sex, height, and test-day baseline.

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Figure 2  Normalized AUC₀–₁₂ FEV₁ vs Dose of Formoterol Fumarate (mITT Efficacy Population).

Figure 3  Mean change in FEV₁ over time by treatment compared with test-day baseline (mITT efficacy population).
1.06 (90% CI: 0.91–1.23) for 2.4 μg; 0.90 (90% CI 0.78, 1.05) for 4.8 μg, and 0.86 (90% CI 0.74, 0.99) for the 9.6 μg groups relative to FA 12 μg. For $C_{\text{max}}$ the dose normalized estimated bioavailability in the FF MDI 2.4 μg, 4.8 μg and 9.6 μg groups relative to FA 12 μg was 1.50 (90% CI: 1.21–1.86), 1.02 (90% CI 0.85 to 1.23) and 1.01 (90% CI: 0.84–1.22), respectively. Overall, the above results suggest that the administration of 9.6 μg of FF MDI resulted in comparable exposure to FA 12 μg. Mean $t_{1/2}$ values of formoterol were relatively consistent across treatments.

This study was not powered to assess bioequivalence; however, the assessment of the ratios of unadjusted $C_{\text{max}}$ and AUC of 9.6 μg of formoterol fumarate MDI vs. FA 12 μg was important to guide the appropriate dose selection and sample sizes for future studies. Unadjusted $C_{\text{max}}$ and AUC ratios of 9.6 μg of FF MDI vs. FA 12 μg were 98% and 96.8%, respectively. The ratio between the two formulations for these key assessments are within 100% ± 4% and CI’s support bioequivalence for AUC$_{0-12}$, but have limits that are just outside traditional bioequivalence bounds for $C_{\text{max}}$. Although bioequivalence was not unequivocally demonstrated, the bioavailability of FF MDI was generally comparable to, or lower than that for open-label FA 12 μg.

**Safety**

Sixty-two TEAEs were reported, 17 events occurred following treatment with placebo; 12, 10, and 6 events after treatment with FF MDI 2.4 μg, 4.8 μg, and 9.6 μg, respectively; and 17 events following treatment with FA 12 μg. Headache was the most frequently occurring TEAE. As a system class, the most frequent events were respiratory in nature and included cough and dyspnea, but these occurred more frequently in the placebo group. There were no notable differences among TEAEs following each treatment. Most of the TEAEs were mild or moderate and were considered not related or unlikely to be related to study treatment. A summary of the most frequent TEAEs is provided in Table 5. Two study patients experienced serious adverse events (SAEs) (small intestinal obstruction and exacerbation of COPD), both of which were considered to be unrelated to study treatment. Three study patients were withdrawn due to AEs (exacerbation of COPD, dyspnea, and atrial fibrillation), all of which were considered to be unrelated to study treatment. One study patient experienced tremor after the 9.6 μg dose. This event lasted approximately 6 h and was considered to be mild and probably related to study drug. The patient recovered with no residual effects.

In general, changes in hematology, clinical chemistry, and vital signs were small and no important trends were noted between FF MDI treatment and either placebo or FA 12 μg treatment. There was no evidence of hypokalemia and no study patient had a clinically significant abnormal serum potassium value. Mean changes from baseline in QTcF, and the number of study patients who experienced clinically significant changes in QTcF were small, and no differences or trends were noted between FF MDI treatment and either placebo or FA 12 μg treatment.

**Discussion**

Formoterol fumarate (FA 12 μg) is well established in clinical practice for the treatment of asthma and COPD. FF MDI has been formulated using a proprietary porous-particle engineering platform. The current study was undertaken to describe the bronchodilatory efficacy and systemic
exposure of a single dose at 3 dose levels of FF MDI in patients with moderate to severe COPD to identify a dose (s) that provide(s) comparable bronchodilation and that does not exceed the systemic exposure of FA 12 mg.

HFA MDIs formulated upon a porous-particle platform using a spray-drying method provide a scaffold for suspensions of inhaled drugs. The FF MDI evaluated in this study is based on these porous particles of a respirable aerodynamic size, comprised of dis-tearoylphosphatidylcholine (DSPC) and calcium chloride (CaCl₂) at a 2:1 M ratio. When co-suspended with micronized active pharmaceutical ingredient (API) crystals in HFA-134a, they form a stable suspension in the MDI. Both the DSPC and CaCl₂ components are endogenous components of human lung surfactant. In the humid environment of the lung, the structure of the porous particles collapse and dissolve in the lung fluid. As a result, the porous particles do not appear to affect drug absorption, and as the findings of this study suggest, FF MDI demonstrates comparable bronchodilation and PK profile compared with an approved LABA, FA 12 µg. Benefits of the porous particle technology include improved physical stability, the ability to formulate at very low doses, consistent dose-to-dose performance, high fine-particle fraction (FPF), and improved delivery of drug to the lower respiratory tract with minimized oropharyngeal exposure [46].

For the primary efficacy endpoint, mean change in FEV₁ AUC₀−₁₂ from test day baseline, each dose of FF MDI showed statistically significantly superior efficacy compared with placebo (p < .001 for all 3 dose levels) with an apparent dose-response relationship. The efficacy of FF MDI 9.6 µg in terms of improvement in FEV₁ was similar to that of FA 12 µg with nearly identical response curves over time. Although both FF MDI 2.4 µg and 4.8 µg demonstrated significantly greater improvements in FEV₁ than placebo, the magnitude of the improvements was substantially lower than that observed with FA 12 µg.

The FF MDI 9.6 µg dose was shown to be statistically non-inferior to FA 12 µg in terms of improvement from baseline in FEV₁ at all timepoints tested using the a priori defined non-inferiority bound of 100 mL. On further analysis, the

### Table 3 Formoterol fumarate AUC₀−₁₂ and C_max (mITT pharmacokinetic population).

<table>
<thead>
<tr>
<th>Variable</th>
<th>FF MDI 2.4 µg</th>
<th>FF MDI 4.8 µg</th>
<th>FF MDI 9.6 µg</th>
<th>FA 12 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀−₁₂</td>
<td>n Mean (90% CI)</td>
<td>n Mean (90% CI)</td>
<td>n Mean (90% CI)</td>
<td>n Mean (90% CI)</td>
</tr>
<tr>
<td>(pg.hr/mL)</td>
<td>21 11.07 (6.32, 15.82)</td>
<td>21 18.53 (13.77, 23.29)</td>
<td>20 35.13 (30.28, 39.98)</td>
<td>23 38.67 (34.09, 43.25)</td>
</tr>
<tr>
<td>C_max</td>
<td>n Mean (90% CI)</td>
<td>n Mean (90% CI)</td>
<td>n Mean (90% CI)</td>
<td>n Mean (90% CI)</td>
</tr>
<tr>
<td>(pg/mL)</td>
<td>21 1.63 (0.64, 2.61)</td>
<td>21 3.38 (2.40, 4.37)</td>
<td>20 6.14 (5.13, 7.14)</td>
<td>23 6.21 (5.26, 7.16)</td>
</tr>
</tbody>
</table>

AUC₀−₁₂ = area under the curve for 0–12 h; C_max = maximum plasma concentration; FA = Foradil Aerolizer; FF MDI = formoterol fumarate metered-dose inhaler.

Non-compartmental parameter estimates were analyzed using a repeated-measures ANOVA, in which treatment was a fixed effect, within-patient errors were correlated, and between-patient errors were independent.

### Table 4 Relative bioavailability comparison of plasma formoterol fumarate (mITT pharmacokinetic population).

<table>
<thead>
<tr>
<th>Variable</th>
<th>FF MDI 2.4 µg</th>
<th>FF MDI 4.8 µg</th>
<th>FF MDI 9.6 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀−₁₂</td>
<td>Estimate (90% CI)</td>
<td>Estimate (90% CI)</td>
<td>Estimate (90% CI)</td>
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<tr>
<td></td>
<td>1.06 0.91, 1.23</td>
<td>0.90 0.78, 1.05</td>
<td>0.86 0.74, 0.99</td>
</tr>
<tr>
<td>C_max</td>
<td>1.50 1.21, 1.86</td>
<td>1.02 0.85, 1.23</td>
<td>1.01 0.84, 1.22</td>
</tr>
</tbody>
</table>

AUC₀−₁₂ = area under the curve for 0–12 h; C_max = maximum plasma concentration; FA = Foradil Aerolizer; FF MDI = formoterol fumarate metered-dose inhaler; mITT = modified intent-to-treat; AUC₀−₁₂ = area under the curve for 0–12 h.

Mean log PK parameters and 90% confidence intervals (CIs) of their ratios were calculated from the mixed model analysis of variance. These estimates and CIs were exponentiated to give CIs on the relative availability (rather than log relative availability) scale. Relative bioavailability calculations were performed for each FF MDI group versus FA 12 µg. Ninety percent confidence intervals for bioequivalence were calculated from the parameters of the linear repeated measures analysis.
Table 5 Summary of treatment-emergent adverse eventsa (safety population).

<table>
<thead>
<tr>
<th>System organ class</th>
<th>FF MDI 9.6 µg (n = 29)</th>
<th>FF MDI 4.8 µg (n = 32)</th>
<th>FF MDI 2.4 µg (n = 34)</th>
<th>FA 12 µg (n = 32)</th>
<th>Placebo (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td>2</td>
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<td>Skin and subcutaneous tissue disorders</td>
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<td>Actinic keratosis</td>
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<td>3</td>
<td>0</td>
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</tbody>
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FA = Foradil Aerolizer; FF MDI = formoterol fumarate metered-dose inhaler.

a Occurring with a greater frequency than 3 study patients.

data support a non-inferiority bound of approximately 45 mL, which provides further assurance of the comparability of the 9.6 µg dose to FA 12 µg. The 2.4 and 4.8 µg doses were found to be inferior to FA 12 µg at almost every time point assessed. In general, the secondary endpoints (time to onset of effect, peak and trough FEV1, FVC, PEFR, and peak IC) confirmed the findings of the primary endpoint, with dose ordering of the 2.4 µg, 4.8 µg and 9.6 µg doses of FF MDI, and comparability of the 9.6 µg dose of FF MDI to FA 12 µg.

Systemic exposure to formoterol from FF MDI demonstrated a clear linear relationship across the assessed dosage range. Formoterol fumarate MDI at a dose of 9.6 µg demonstrated a comparable pharmacokinetic profile to FA 12 µg, with similar concentration-time plots and similar AUC0–12 and Cmax. There was no evidence of a difference between FF MDI and FA 12 µg in terms of the relationship between formoterol exposure and spirometry response.

These data represent the first attempts to quantify the dose-related efficacy of FF MDI delivered via a porous-particle platform compared with open-label FA 12 µg in patients with moderate to severe COPD. Since current best clinical practices rely on the use of a LABA in combination with a LAMA as first-line therapy for the long-term management of COPD, further research that focuses on these questions regarding the porous particle platform for the delivery of LAMA/LABA in combination should be undertaken.

All 3 doses of FF MDI were found to be safe and well-tolerated in this study. The safety profile for FF MDI was similar to that of placebo and FA 12 µg. No important safety trends or signals were noted for FF MDI in terms of AEs, QTc changes, or changes in serum potassium or other laboratory values.

Study limitations

Although the study incorporated only a single-dose, under these conditions, a single-dose is appropriate. However, since there was no intermediate dose between 4.8 and 9.6 µg, and there was no separation between 2.4 and 4.8 µg, it is unclear if the minimal effective dose was achieved. Because of the differences in delivery device, FA 12 µg was administered open-label. Whether this aspect of the study may have influenced the outcomes is undetermined. The study enrolled patients with a clinical history of COPD and functional reversibility to bronchodilator administration. This is a specific sub-set of COPD patients, therefore care should be taken in extrapolating the results to clinical conditions other than those examined within this study.

Conclusions

FF MDI 9.6 µg demonstrated significantly superior bronchodilator efficacy compared with placebo and comparable bronchodilator efficacy compared with FA 12 µg. The 2.4- and 4.8-µg doses of FF MDI showed bronchodilator efficacy that was statistically significantly superior to placebo over the 12-h post-dose period but those doses were generally numerically inferior to FA 12 µg. However, further evaluation of doses between 4.8 and 9.6 µg in subsequent studies is warranted. FF MDI 9.6 µg demonstrated a comparable PK profile to FA 12 µg. All 3 doses of FF MDI were safe and well-tolerated with a safety profile similar to that of placebo and FA 12 µg.

Roles of contributors

DQ was a study investigator, and contributed to the development of the manuscript. JPS was a study investigator, and contributed to the development of the manuscript. CR oversaw the design of the study, and contributed to the development of the manuscript. TF contributed to the design of the study, and contributed to the development of the manuscript. MG contributed to the design, conduct and oversight of the study, and to the development of the manuscript. CF contributed to the development of the manuscript. PD contributed to the statistical interpretation and the development of the manuscript. ESR contributed to the development and submission of the manuscript. MG contributed to the development of the statistical analysis plan, and the analysis of the study results. GT contributed to the development of the manuscript. CF contributed to the design of the study, oversaw the conduct of the study, and contributed to the development of the
manuscript. All authors read and approved the final manuscript.

Disclosures

((Authors: please update disclosures for the past 12 months; Authors are specifically asked to reflect on financial conflicts of interest (such as employment, consultancy, stock ownership, honoraria and paid expert testimony))

Dr Quinn is a consultant and investigator for Pearl Therapeutics, Inc. Dr. Quinn has no conflicts of interest to disclose.

Professor Seale is a consultant and investigator for Pearl Therapeutics, Inc. Professor Seale has no conflicts of interest to disclose.

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Study protocol

Details regarding the protocol are available at: www.clinicaltrials.gov: http://clinicaltrials.gov/ct2/show/NCT00880490?term=pt0050801&rank=1

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References


