

A Novel Formoterol Fumarate Metered Dose Inhaler Formulation Demonstrates Comparable Bronchodilator Efficacy Relative to Foradil® Aerolizer® and Favorable Safety Outcomes in Patients with COPD

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Abstract

Rationale: Formoterol is a well-established and extensively tested long-acting β_2 adrenergic receptor-agonist that is clinically indicated for the management of asthma and COPD. Pearl's novel porous particle based suspension technology allows better targeting of drugs to the airways via pressurized metered dose inhaler (MDI). This type of application provides a method for stabilizing suspensions of drugs in hydrofluoroalkane propellants, leading to improved physical stability and content uniformity of the drug. Pearl Therapeutics is developing Formoterol Fumarate MDI (FF MDI) using this porous particle technology for the long-term management of COPD.

Methods: Study PT0050801, the first in-human study of the FF MDI formulation, was a randomized, double-blind, 5-period, placebo and active-controlled, cross-over, multi-center study evaluating single administration of 3 doses of FF MDI (2.4, 4.8 and 9.6 μg ex-actuator) in patients with moderate-to-severe COPD, with demonstrated β -agonist reversibility compared to open-label, marketed Foradil® Aerolizer®, 12 μg (FA) as an active control. Spirometry measures were performed at baseline, 15 and 30 minutes, and 1, 2, 4, 6, 8, 10, 11.5 and 12 hours post-dose.

Results: A total of 34 patients were enrolled (18 males, 16 females, mean age: 65 years). The mean change from baseline in FEV₁ over the 12-hour test period for each treatment is presented in Figure 1. All 3 doses of FF MDI demonstrated superior efficacy compared to placebo in terms of FEV₁ AUC_(0-12h), the primary endpoint of the study (p<0.05). Furthermore, the FF MDI 9.6 μg ex-actuator dose demonstrated non-inferior bronchodilator efficacy relative to FA 12 μg over the 12-hour period (p<0.001) and at every individual time point assessed (p<0.05). No substantial differences were noted between doses of FF MDI treatment groups and placebo in terms of safety and there were no trends in QTc changes or serum potassium values across doses. Two SAEs were reported, one following placebo MDI (small intestinal obstruction) and one following FF MDI 4.8 μg (Infective exacerbation of COPD), neither were deemed related to study drug administration by the Investigator.

Conclusions: This study demonstrates superior bronchodilator efficacy of FF MDI compared to placebo MDI at all doses tested and comparable efficacy relative to FA at the 9.6 μg ex-actuator dose. These findings support the use of the porous particle platform technology in the development of FF MDI for the management of patients with COPD.

Introduction

- Formoterol fumarate (FF) is a well established and extensively tested long-acting β -agonist approved for use in patients with COPD.
- Novel particle engineering technology has allowed the development of suspensions of drugs in hydrofluoroalkane propellants with improved physical stability and dose content uniformity.
- Pearl Therapeutics is developing FF metered dose inhaler MDI (PT005) for the long-term management of COPD.

Objective

- To identify a dose of FF MDI comparable to Foradil® Aerolizer® from a pharmacokinetic and pharmacodynamic perspective

Methods

Study Design

- Multi-center, randomized, double-blind, placebo and active controlled single dose 5-period crossover study with three doses of FF MDI (2.4, 4.8, and 9.6 μg) in patients with moderate to severe COPD compared to open-label Foradil® Aerolizer® 12 μg
- There was an interval of ≥ 3 days and no more than 10 days between each of the 5 single dose treatments.
- All COPD medications were withheld for at least 8 hours prior to dosing on each treatment day.

Key Inclusion Criteria

- Current or ex-smokers 40 to 80 years of age
- Clinical history of COPD with post-albuterol FEV₁/FVC ratio ≤ 0.70 , reversibility to albuterol ($>12\%$ and 150 mL or absolute improvement in FEV₁, >200 mL) and post-albuterol FEV₁ ≥ 40 and $\leq 80\%$ of predicted normal

Key Exclusion Criteria

- Poorly controlled COPD (hospitalized in last 24 weeks, use of corticosteroids or antibiotics in prior 6 weeks)
- Oxygen use >12 hours per day
- Use of systemic corticosteroids, >1000 μg of fluticasone propionate equivalent, anticholinergics, oral/long-acting β -agonists, leukotriene antagonists, theophylline, CYP3A4 inhibitors, non-potassium sparing diuretics
- Participation in acute phase of pulmonary rehabilitation or will enter a pulmonary rehabilitation program during the study

Primary Endpoint

- To evaluate the bronchodilatory efficacy [FEV₁ AUC_(0-12h)] of FF MDI (2.4, 4.8 and 9.6 μg) compared to placebo

Secondary Endpoints

- Time to onset of action ($>10\%$ improvement from test day baseline)
- Change in mean peak FEV₁, PEFR, FVC, trough FEV₁, and IC
- Non-inferiority assessment comparing FF MDI to Foradil® Aerolizer® based on change in FEV₁ AUC_(0-12h)

Safety

- Adverse events (AEs), vital signs, serial ECGs, laboratory testing, symptoms of tremor

Pharmacokinetics (PK)

- PK was evaluated in all patients through 12 hours post-dose

Statistical Methods

- Safety was analyzed in the ITT population, efficacy and PK were analyzed in a modified ITT population which included patients remaining in the study at least 6 hours post dosing.
- The primary efficacy endpoint was analyzed using a repeated measure ANOVA with treatment as a fixed effect and with subject errors correlated but between subject errors were independent. Covariates in the model included age, sex, weight, and test day baseline.
- 100 mL was used as an appropriate bound to establish non-inferiority with Foradil® Aerolizer®.¹

Results

Study Population

- A total of 34 patients were enrolled. Five withdrew prior to completion (3 due to AEs, 1 withdrew consent and 1 due to protocol defined stopping criteria [$>20\%$ decrease in FEV₁, although dyspnea, part of that stopping criterion, was not reported as an AE]).

Demographics and Screening Lung Function

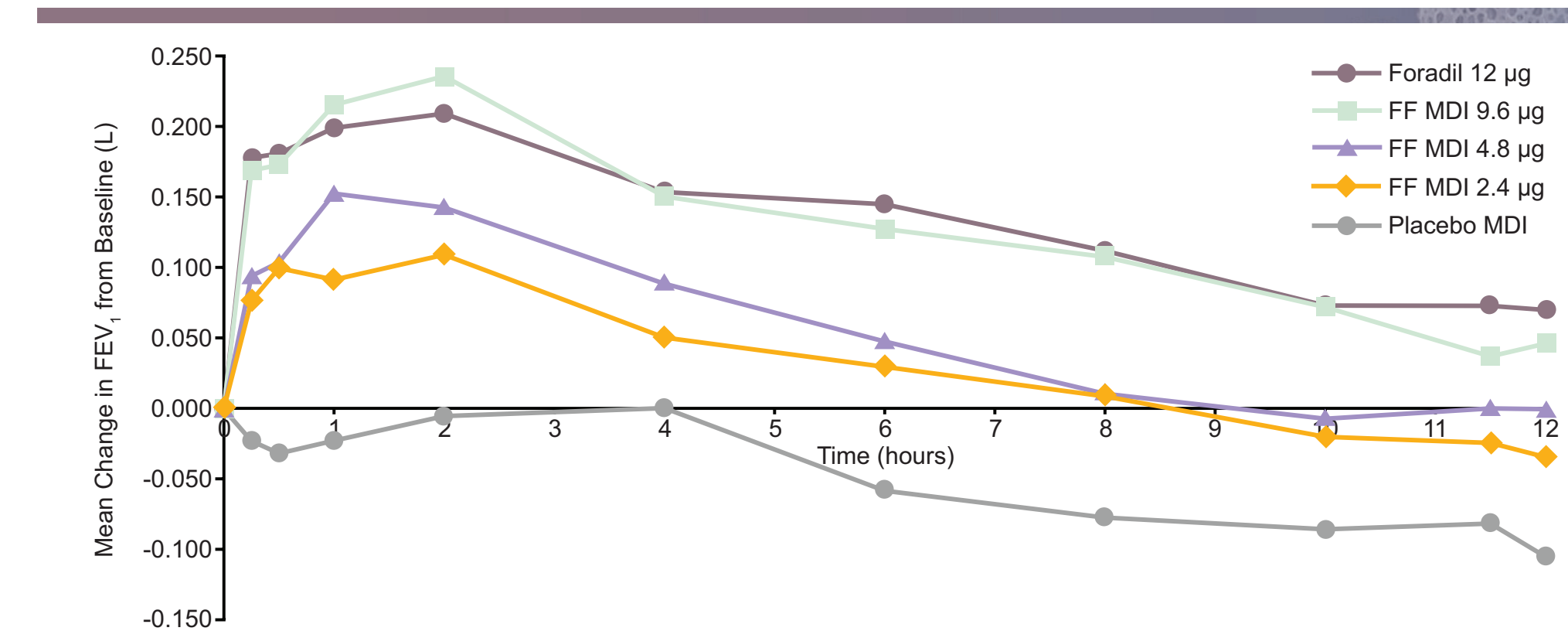
Table 1. Demographic and Screening Lung Function

	All Patients (N=34)
Sex (n) Male/Female	18/16
Age (years), Mean \pm SD	64.76 \pm 8.12
Smoking History (Pack Years), Mean \pm SD	46.68 \pm 29.70
Pre-dose FEV ₁ (L), Mean \pm SD	1.35 \pm 0.50
% Predicted Pre-dose FEV ₁ (%), Mean \pm SD	46.92 \pm 13.19
Post-Albuterol FEV ₁ (L), Mean \pm SD	1.64 \pm 0.54
% Predicted Post-Albuterol FEV ₁ , Mean \pm SD	56.97 \pm 13.26

Efficacy

- The mean change from baseline over the 12-hour test period for each treatment arm is presented in Figure 1

Figure 1. Mean Change from Baseline in FEV₁ Over Time



MITT population = 32 patients

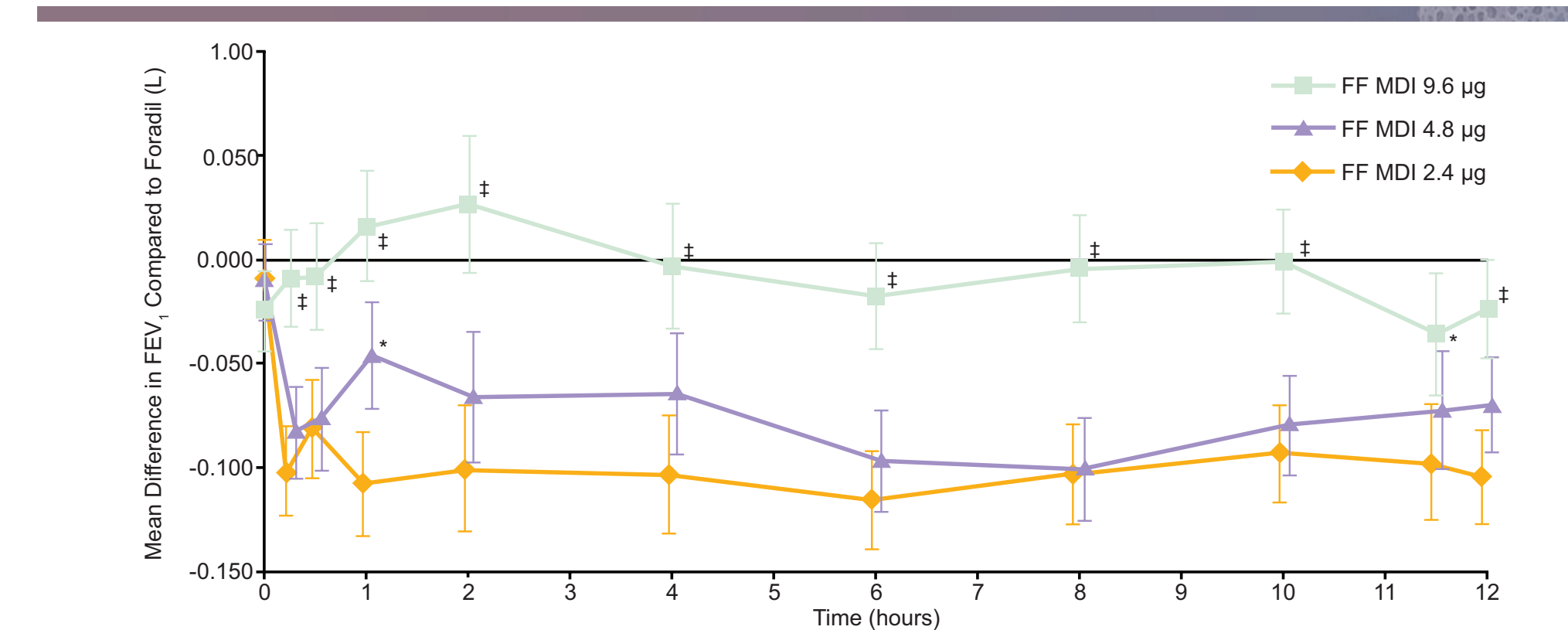
- All 3 doses of FF MDI demonstrated superior efficacy compared to placebo for the primary endpoint of the study (p<0.001, Table 2)

Table 2. Primary Efficacy Endpoint: Mean Change in FEV₁ AUC_(0-12h) Compared to Placebo

	FF MDI 2.4 μg	FF MDI 4.8 μg	FF MDI 9.6 μg
FEV ₁ AUC _(0-12h) (L), Difference (Mean \pm SE)	0.0815 \pm 0.0185	0.1034 \pm 0.0189	0.1759 \pm 0.0195
p-value	<0.001	<0.001	<0.001

- Only the 9.6 μg dose of FF MDI demonstrated comparable efficacy to Foradil® Aerolizer®, with data supporting a non-inferiority bound of approximately 45 mL (Figure 2)

Figure 2. Non-inferiority to Foradil® Aerolizer® in Mean Change from Baseline in FEV₁ over Time



*p ≤ 0.05 and †p ≤ 0.001 for noninferiority compared to Foradil® Aerolizer® 12 μg based on repeated measures ANOVA.

Safety

- Table 3 summarizes AEs reported by > 2 patients.
- Two SAEs were reported during the study. Both SAEs were considered severe and not related to treatment.
 - One patient had a small bowel obstruction (placebo) which resolved 3 days later and the patient completed the study.
 - One had a COPD exacerbation (FF MDI 4.8 μg) and withdrew from the study.
- Three AEs resulted in withdrawal from the study: severe COPD exacerbation (FF MDI 4.8 μg), moderate dyspnea (Foradil® Aerolizer®), and mild atrial fibrillation (placebo).

Table 3. Adverse Events Reported in More Than 2 Patients Across Treatment Groups

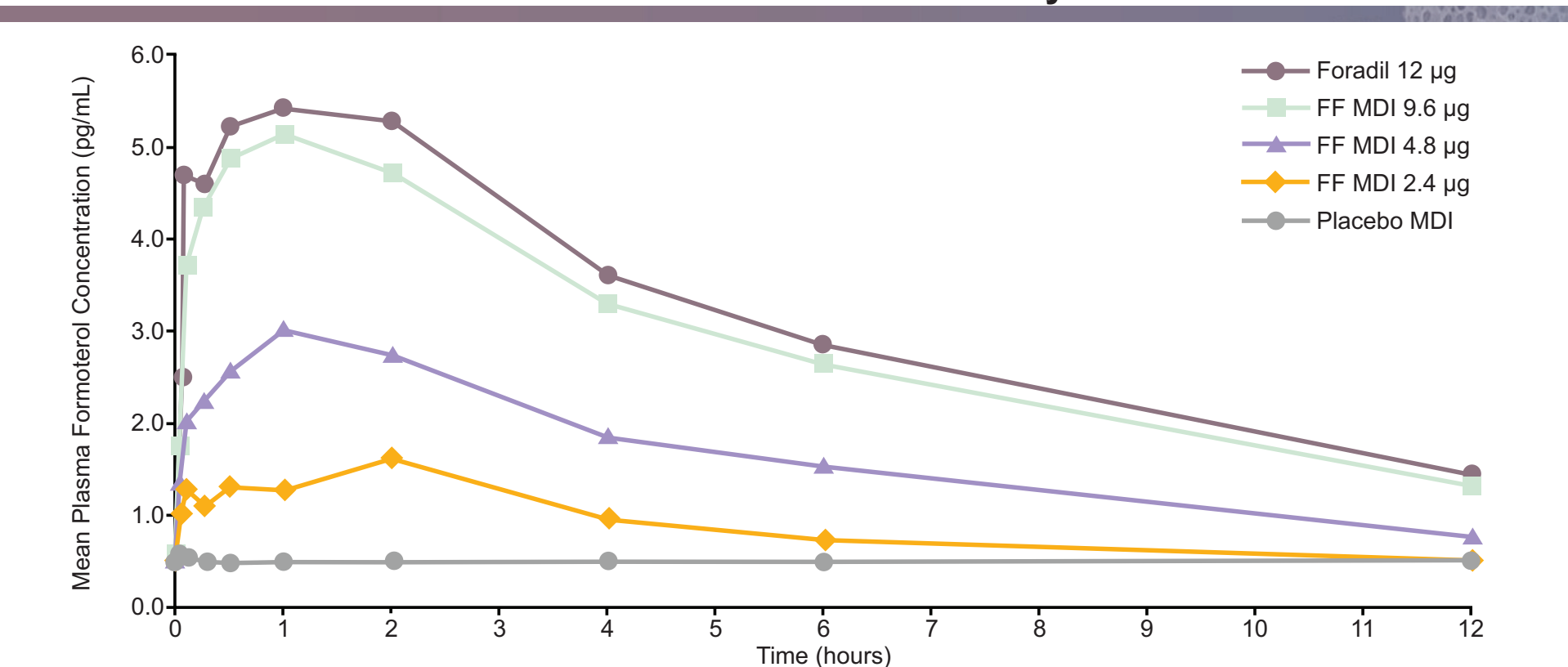
Preferred Term	Screening	Placebo	2.4 μg	4.8 μg	9.6 μg	FA 12 μg	Follow-up
Number of Patients Exposed	34	33	34	32	29	32	35
Total Number of Events	11	17	12	10	6	17	6
Cough	0	3	0	0	0	0	0
Headache	1	2	5	0	1	2	0
Actinic Keratosis	0	0	0	0	0	3	0

- The mean change from baseline QTcF were negligible across all treatments and did not exceed ± 7 msec at any time-point post-dose.
- A single patient experienced mild tremor following FF MDI 9.6 μg . The event lasted 6 hours and was considered probably related to study drug. The patient recovered with no residual effects.
- There were no clinically significant changes in vital signs, serum potassium or any other laboratory values.

Pharmacokinetics

- A clear linear relationship between dose and systemic exposure was seen across the assessed dose range of FF MDI (Figure 3).

Figure 3. Formoterol Fumarate Concentration-Time Plots by Treatment



Conclusions

- All three doses of FF MDI demonstrated superior efficacy compared to placebo in terms of FEV₁ AUC_(0-12h), the primary endpoint of the study.
- Only FF MDI 9.6 μg demonstrated comparable efficacy to Foradil® Aerolizer®.
- All three doses of FF MDI were safe and well tolerated and demonstrated a similar safety profile to Placebo and Foradil® Aerolizer®.
- A clear linear relationship between dose and systemic exposure was seen across the FF MDI dose range.
- FF MDI 9.6 μg demonstrated a comparable concentration time profile to Foradil® Aerolizer® 12 μg .
- The data from this study support the further evaluation of FF MDI for the long-term management of COPD.

References

- Donahue JF. Minimally clinically important differences in COPD lung function. *COPD*. 2005;2(1):111-124.
- ClinicalTrials.gov Identifier: NCT00880490.