

Dose- and Exposure-Response Modeling to Support Development of Formoterol Fumarate (FF) Metered Dose Inhaler (MDI) for COPD

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Abstract

Background: Pearl is developing FF MDI, using its porous particle technology, for use in patients with COPD. A recently completed single-dose, dose-ranging study (PT0050801) compared 3 doses of FF MDI to Foradil® Aerolizer®, 12 µg (FA) in patients with COPD. Dose response, safety and pharmacokinetic (PK) data support comparability of FF MDI 9.6 µg to FA. Non-inferiority (NI) analyses on improvement in FEV₁ confirm NI of FF MDI 9.6 µg to FA (data support NI bound of 45 mL).

Aims and Objectives: Perform dose- and exposure-response analysis of FEV₁ data using a maximum effect (E_{max}) model to further evaluate and compare the efficacy of FF MDI and FA.

Methods: Change from baseline FEV₁, AUC₀₋₁₂/12h was modeled using an E_{max} model driven by AUC₀₋₁₂ of FA, FF MDI and placebo data. The model adequately described the observed FEV₁ values, verified by goodness of fit criteria, and confirmed by visual predictive checks as the model prediction interval captured the majority of observed FEV₁ values.

Results: Data support comparable exposure-response relationship for FA and FF MDI, with the ED₅₀ (50% of the E_{max}) being achieved with similar systemic exposure to FF for each product (18.63 pg.h/mL or approximately 4.8 µg of FF MDI and 6 µg of FA). FF MDI 9.6 µg and FA 12 µg resulted in similar systemic exposure to FF (37.5 pg.h/mL; corresponding to 68% of the E_{max}), thus similar PD response would be observed for both treatments.

Conclusions: The E_{max} model supports the dose-response/PK-response data, and confirms comparability between FF MDI 9.6 µg and FA 12 µg. The model supports further evaluation of FF MDI 9.6 µg in patients with COPD, administered alone or in a combination product.

Introduction/Background

- Formoterol fumarate (FF) is a potent and selective long acting β-agonist (LABA) with a well established safety and efficacy profile in patients with COPD.
- Pearl Therapeutics novel porous particle based suspension technology allows better targeting of drugs to the airways via a pressurized metered dose inhaler (MDI), and enables the development of products with improved physical stability and content uniformity.
- Pearl Therapeutics recently completed a single dose, dose-ranging study (Study PT0050801) assessing the safety, efficacy and pharmacokinetics (PK) of FF MDI compared to Foradil® Aerolizer® (FA) and placebo. The objective of the study was to identify a dose of FF MDI that was comparable to FA from a PK and pharmacodynamic (PD) perspective to be included in a combination product with glycopyrrolate and as a monotherapy.
- In Study PT0050801, all 3 doses of FF MDI (2.4, 4.8 and 9.6 µg) demonstrated superior efficacy compared to placebo for forced expiratory volume in one second (FEV₁) area under the curve (AUC₀₋₁₂), the primary endpoint of the study (p<0.001). Only the 9.6 µg dose of FF MDI demonstrated comparable efficacy to FA and met pre-specified non-inferiority criteria. Dose linearity between FF MDI doses and systemic exposure was observed. The PK profile of FF MDI 9.6 µg was comparable to that of FA 12 µg. All 3 doses of FF MDI evaluated were found to be safe and well-tolerated with a safety profile similar to that of placebo and FA.

Aims and Objective

- To model the PK and PD data from Study PT0050801 using dose- and exposure-response analysis of FEV₁ data (FEV₁, AUC₀₋₁₂) to further evaluate and compare the efficacy of FF MDI and FA.

Methodology

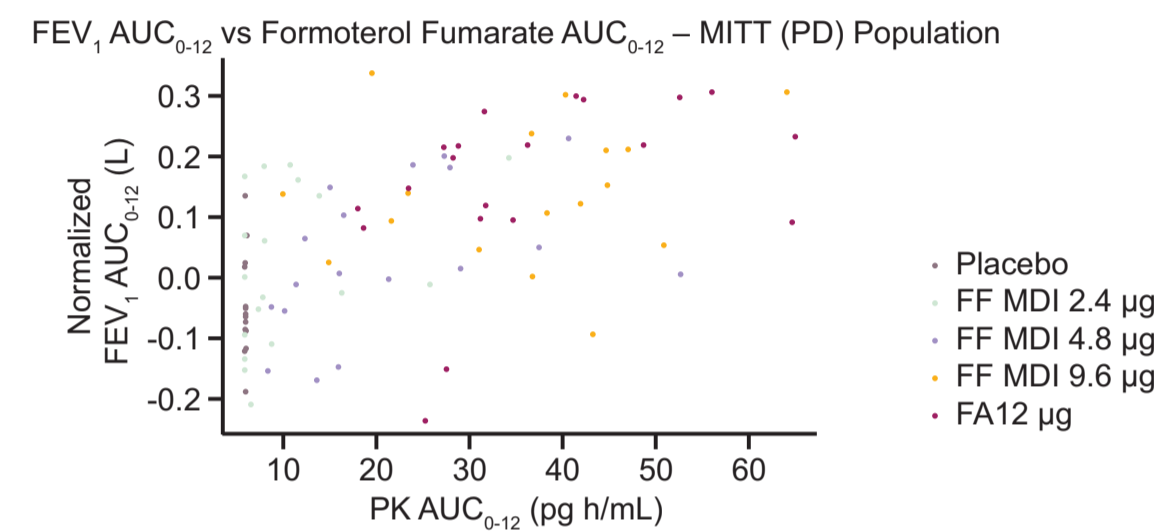
Dose-Response Modeling

- Use of an E_{max} model to describe the relationship between dose and FEV₁, AUC₀₋₁₂ was not successful. No further models as a function of dose were attempted.
- However, on visual observation, a relationship between systemic exposure (AUC₀₋₁₂) and improvement in FEV₁, AUC₀₋₁₂ was observed and thus exposure response modeling was further evaluated.

Exposure-Response Modeling

- The relationship between the PD parameter (normalized FEV₁, AUC₀₋₁₂) and formoterol fumarate exposure (AUC₀₋₁₂) from both FF MDI and FA was fitted using a PK/PD model. The relationship between normalized FEV₁, AUC₀₋₁₂ and formoterol fumarate exposure (AUC₀₋₁₂) appears to be saturable as illustrated in Figure 1.

Figure 1. Relationship between FEV₁, AUC₀₋₁₂ and Formoterol Fumarate Exposure



- Based on the above observations, the exposure-response of normalized FEV₁, AUC₀₋₁₂ was modeled as a function of formoterol fumarate exposure over the same timeframe. An E_{max} model was identified as the best model for the exposure-response analysis of normalized FEV₁, AUC₀₋₁₂. The following equation was used to assess the relationship between the systemic exposure of formoterol fumarate (AUC₀₋₁₂) and the resulting effect on normalized FEV₁, AUC₀₋₁₂:

$$\text{Normalized FEV}_1, \text{AUC}_{0-12} = E_0 + E_{\text{max}} \times \left[\frac{\text{AUC}_{0-12}}{\text{AUC}_{0-12} + \text{EC}_{50}} \right]$$

where E_{max}=maximal effects, EC₅₀=AUC associated to 50% of E_{max}, E₀ = baseline effects (placebo effect). Random effects were tested on E₀, E_{max}, and EC₅₀.

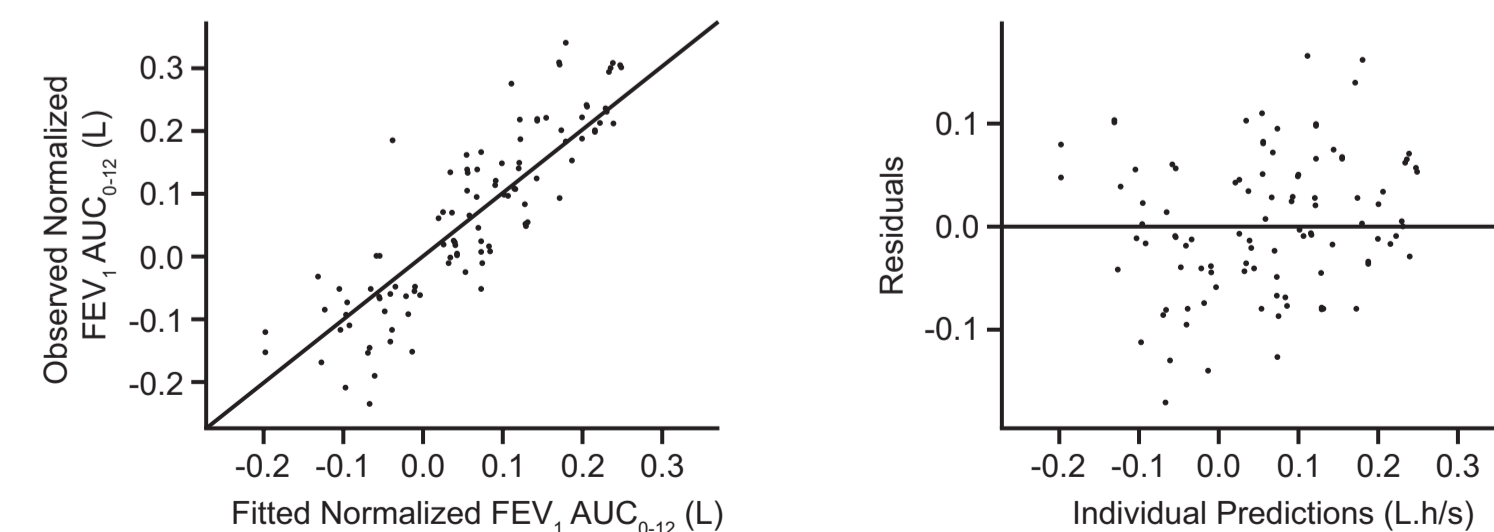
- In order to compare efficacy parameters (E_{max} and EC₅₀) between FF MDI (9.6 µg) and FA (12 µg), formoterol fumarate formulation was added as a covariate in the exposure-response model of FEV₁, AUC₀₋₁₂.

Results

Exposure-Response Modeling of FEV₁

- An E_{max} model provided the best quality of fit for the exposure-response analysis of FEV₁, AUC₀₋₁₂. Model performance is presented in Figure 2.

Figure 2. Model Performance: Analysis of Normalized FEV₁, AUC₀₋₁₂



- Individual observed FEV₁, AUC₀₋₁₂ values were well predicted with the proposed exposure-response model. This was demonstrated by the random distribution of data points around the identity line (Figure 2, left panel). The weighted residuals were homogeneous and distributed around 0, suggesting no bias in the predictions of high and low normalized FEV₁, AUC₀₋₁₂ values (Figure 2, right panel).

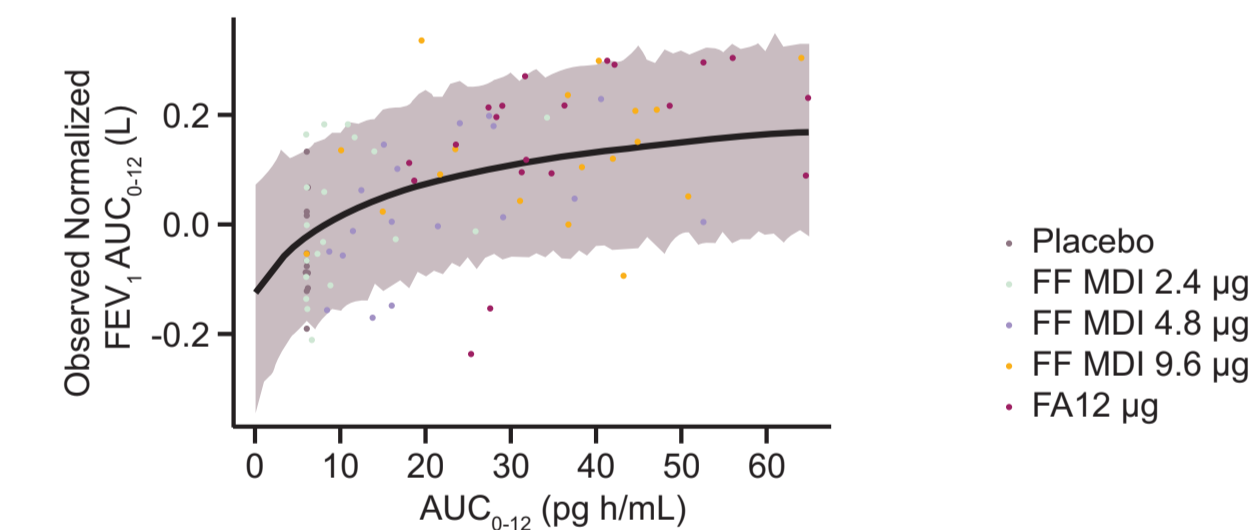
- Population parameters derived with the exposure-response model of normalized FEV₁, AUC₀₋₁₂ are presented in Table 1.

Table 1. Model Parameters: Exposure-Response of Normalized FEV₁, AUC₀₋₁₂

PD Parameters	Estimate	SE	p-value
Intercept (E ₀) (L)	-0.125	0.078	0.11
E _{max} (L)	0.396	0.054	<0.0001
EC ₅₀ (pg.h/mL)	18.6	0.978	<0.0001
Standard Error	0.08	–	–

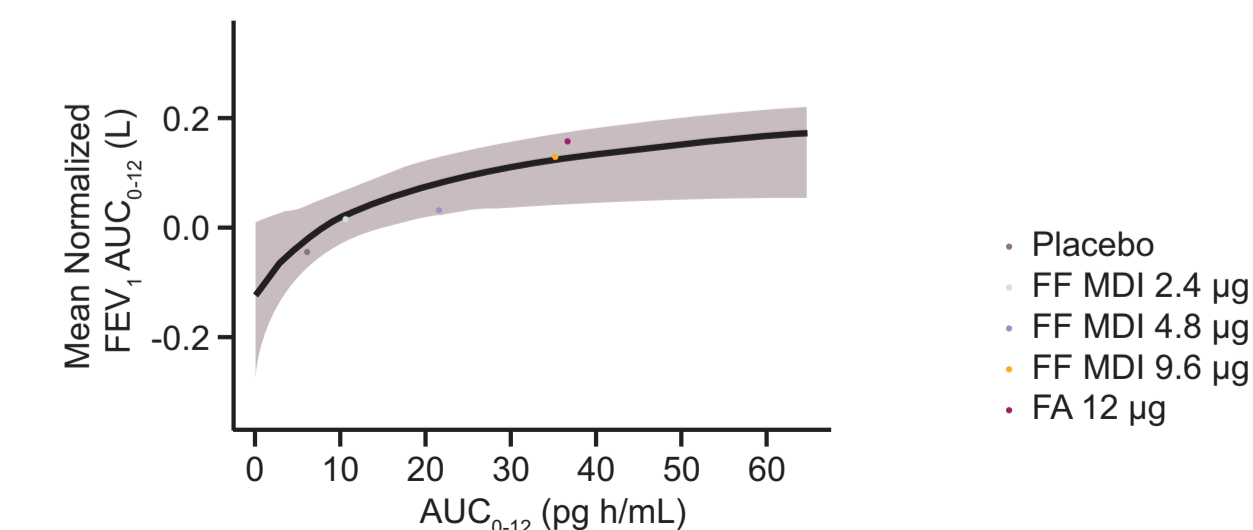
- The E_{max} of formoterol fumarate on normalized FEV₁, AUC₀₋₁₂ was 0.396 L and statistically greater than placebo (p-value <0.0001). The effective exposure of formoterol fumarate associated with 50% of the E_{max} (EC₅₀) on FEV₁, AUC₀₋₁₂ was 18.6 pg.h/mL, which approximates half of the exposure seen with FF MDI 9.6 µg and FA 12 µg.
- The performance of the model was determined by deriving prediction intervals of FEV₁, AUC₀₋₁₂ using the above population model, which included model estimates, uncertainty in the estimates, subject random effects and residual errors. Results of the 95% prediction intervals of FEV₁, AUC₀₋₁₂ are shown in Figure 3.

Figure 3. Model Performance: 95% Prediction Interval



- The 95% prediction interval excluding inter-subject random effects is shown in Figure 4, with the mean of observed FEV₁, AUC₀₋₁₂ superimposed. The figure suggests close agreement between mean data and model predictions. More importantly, for a similar exposure, FEV₁, AUC₀₋₁₂ is very similar for both FF MDI 9.6 µg (yellow dot) and FA 12 µg (magenta dot).

Figure 4. Mean Normalized FEV₁, AUC₀₋₁₂ vs. Mean Exposure with 95% Prediction Interval



Testing for differences between FF MDI and FA in E_{max} and EC₅₀

- In order to compare efficacy parameters (E_{max} and EC₅₀) between FF MDI (9.6 µg) and FA (12 µg), formoterol fumarate formulation was added as a covariate in the exposure-response model of FEV₁, AUC₀₋₁₂.
- The effect of formoterol fumarate formulation on population parameters derived with the exposure-response model of normalized FEV₁, AUC₀₋₁₂ are presented in Table 2.

Table 2. Model Parameters: The Effect of FF MDI 9.6 µg and FA 12 µg on E_{max} and EC₅₀ of Normalized FEV₁, AUC₀₋₁₂

PD Parameters	FF MDI	FA	p-value
E _{max} (L)	0.362	0.402	0.28
EC ₅₀ (pg.h/mL)	24.6	19.4	0.44

- The p-value associated to E_{max} is 0.28, suggesting no evidence of a difference in E_{max} between the two formulations. The p-value for the EC₅₀ is 0.44, also suggesting no evidence of a difference in EC₅₀ between the two formulations.
- Overall, the models described in the previous sections suggest that FF MDI 9.6 µg and FA 12 µg achieve a similar FEV₁, AUC₀₋₁₂.

Conclusions

- In Study PT0050801, all three doses of FF MDI demonstrated superior efficacy compared to placebo in terms of FEV₁, AUC₀₋₁₂, the primary endpoint.
 - Only FF MDI 9.6 µg demonstrated comparable efficacy to FA 12 µg and met the protocol pre-specified non-inferiority criteria.
 - Across all FF MDI doses a clear linear relationship between dose and systemic exposure was seen, with FF MDI 9.6 µg demonstrating a comparable time concentration profile to FA 12 µg.
- The goal of the present analysis was to model the PK and PD data from Study PT0050801 using a dose- and exposure-response analysis of FEV₁, AUC₀₋₁₂ to further evaluate and compare the efficacy of FF MDI and FA.
- Exposure-response modeling of FEV₁, AUC₀₋₁₂ was performed using a simple E_{max} model. The E_{max} of formoterol fumarate on normalized FEV₁, AUC₀₋₁₂ was 0.396 L. The effective exposure of formoterol fumarate associated with 50% of the E_{max} (EC₅₀) on FEV₁, AUC₀₋₁₂ was 18.6 pg.h/mL, which approximates half of the exposure seen with FF MDI 9.6 µg and FA 12 µg.
- The modeling of the data show that E_{max} and EC₅₀ are comparable between FA and FF MDI.
- The exposure-response modeling confirms that for similar PK exposure, FF MDI and FA have similar FEV₁, AUC₀₋₁₂ profiles.
- These findings confirm comparability of FF MDI 9.6 µg and FA 12 µg, and support further evaluation of this dose of FF MDI administered alone or in combination with glycopyrrolate in patients with COPD.