

Novel Combination of Glycopyrrolate and Formoterol MDI (GFF-MDI) Provides Superior Bronchodilation Compared to Its Components Administered Alone, Tiotropium DPI, and Formoterol DPI in a Randomized, Double-Blind, Placebo-Controlled Phase 2b Study in Patients with COPD

C. Reisner¹, C. Fogarty², S. Spangenthal³, L. Dunn⁴, E.M. Kerwin⁵, D. Quinn⁶, J. P. Seale⁷, M. Thomas⁸, E. St. Rose¹, C. Orevillo¹

¹Redwood City CA/US, ²Spartanburg SC/US, ³Charlotte NC/US, ⁴Clearwater FL/US, ⁵Medford OR/US, ⁶Wellington NZ/US, ⁷Glebe NSW/AU, ⁸Toowong QLD/AU



Introduction

- Bronchodilator medications are central to the symptomatic management of chronic obstructive pulmonary disease (COPD).
- Glycopyrrolate (GP) is a well established anticholinergic drug that is approved in the United States (US) and worldwide in oral and parenteral formulations.
- Formoterol fumarate (FF) is a potent and selective long-acting β -agonist approved in the US and worldwide 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 content uniformity.
- Pearl Therapeutics is developing Glycopyrrolate and Formoterol Fumarate (GFF) MDI for the long term management of COPD.

Objective

- This study had two parts, Part A and Part B. Each part had separately defined key objectives.
- Part A: Compared the improvement in lung function following administration of the combination (GFF MDI) versus the individual components (GP MDI and FF MDI).
- Part B: Compared the improvement in lung function following administration of FF MDI versus placebo.

Methods

Study Design

- Multicenter, randomized, double-blind, chronic dosing (7-day), customized, unbalanced, incomplete block, crossover study in patients with moderate to very severe COPD that evaluated the efficacy and safety of GFF MDI (PT003), FF MDI (PT005), and GP MDI (PT001) compared to placebo, Foradil Aerolizer (open-label) and Spiriva Handihaler (open-label) as active controls.
- The study was recruited in two parts, Part A and Part B (patients recruited to Part A were not eligible for Part B), and all study patients underwent the same study procedures.
- Patients took each of their 4 assigned treatments for 1 week, followed by at least a 1 week washout between treatments.
- Each sequence in Part A included 4 of 8 treatments:

Placebo MDI twice daily	GFF MDI 72/9.6 μ g twice daily
Spiriva Handihaler 18 μ g once daily	FF MDI 7.2 μ g twice daily
Foradil Aerolizer 12 μ g twice daily	FF MDI 9.6 μ g twice daily
GFF MDI 36/9.6 μ g twice daily	GP MDI 36 μ g twice daily

- Each sequence in Part B included the following 4 treatments:

Placebo MDI twice daily	FF MDI 7.2 μ g twice daily
Foradil Aerolizer 12 μ g twice daily	FF MDI 9.6 μ g twice daily

Key Inclusion Criteria

- Current or ex-smokers 40 to 80 years of age
- Clinical history of COPD with post-albuterol FEV₁ \leq 80% of predicted normal and \geq 750 mL or 30% 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, anticholinergics, oral/long-acting β -agonists, leukotriene antagonists, theophylline, p-glycoprotein inhibitors, CYP3A4 inhibitors
- Participation in acute phase of pulmonary rehabilitation or will enter a pulmonary rehabilitation program during the study

Primary Endpoint (Evaluated on Treatment Day 7)

- FEV₁ AUC₀₋₁₂ relative to baseline following chronic dosing

Secondary Endpoints Included

- Peak FEV₁ (Day 1 and 7)
- Time to onset of action (\geq 10% improvement in FEV₁) (Day 1)
- Proportion of patients with \geq 12% improvement in FEV₁ (Day 1)
- Improvement in morning pre-dose FEV₁ (Day 7)
- Peak improvement in inspiratory capacity (Day 1 and Day 7)
- Trough FEV₁ (Day 7)
- Mean daily peak expiratory flow (PEFR) during each sequence

Results

Safety Endpoints

- ECGs, vital signs, clinical laboratory tests, monitoring for paradoxical bronchospasm, assessment of symptoms of tremor and dry mouth and adverse events

Subject Disposition

- 4 sentinel subjects were enrolled. There were no clinically relevant changes in vital signs, ECGs, lung function or any AEs of clinical concern. Dosing opened for remaining 118 patients
- 118 subjects in ITT, 104 met criteria for MITT (completed at least two of the four 1-week treatment periods)

Table 1: Demographics mITT Population

Total (Male/Female)	104 (59/45)
Age (years)	63.3 (\pm 8.6)
Smoking history (pack years)	52.3 (\pm 28.7)
Screening FEV ₁ : Pre-dose L (% predicted)	1.303 (44.4%)
Screening FEV ₁ : Post-dose L (% predicted)	1.494 (50.9%)
Disease severity (moderate/severe/very severe)	(53%/44%/3%)

Efficacy

- All actives superior to placebo for the primary endpoint, FEV₁ AUC₀₋₁₂ on Day 7, p<0.0001
- GFF MDI 72/9.6 μ g and GFF MDI 36/9.6 μ g were significantly greater than individual components, GP MDI 36 μ g and FF MDI 9.6 μ g, for primary endpoint [GFF MDI 72/9.6 μ g: LSM treatment difference versus components: 109 and 116 mL, respectively (p<0.0001); GFF MDI 36/9.6 μ g: LSM treatment difference versus components: 101 and 109 mL, respectively (p<0.0001)]

Figure 1: Change from Baseline in FEV₁ (Day 7) Anticholinergic Containing Treatment Arms and Placebo (mITT Population)

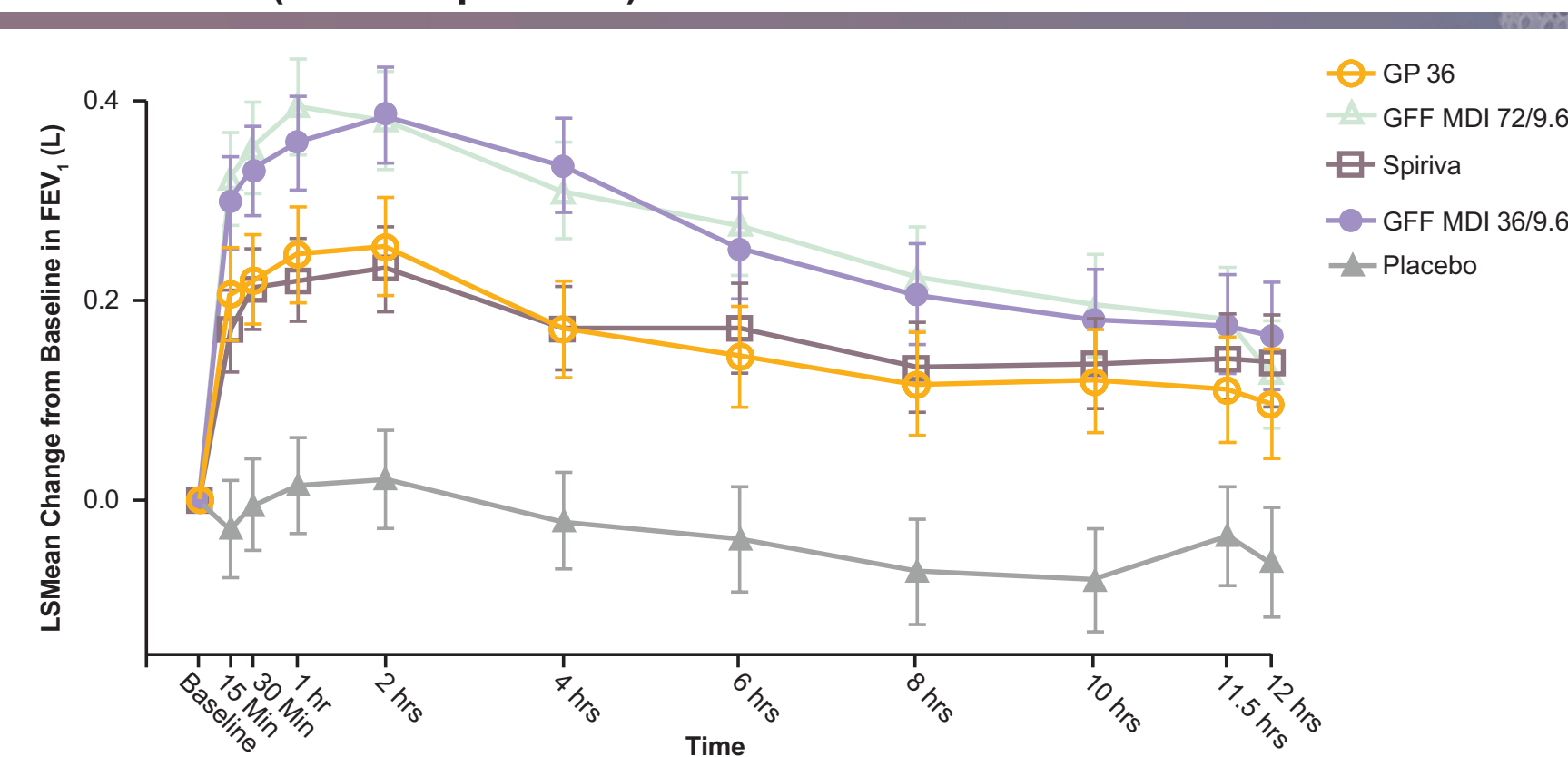


Figure 2: Change from Baseline in FEV₁ (Day 7) Formoterol Fumarate Containing Treatment Arms and Placebo (mITT Population)

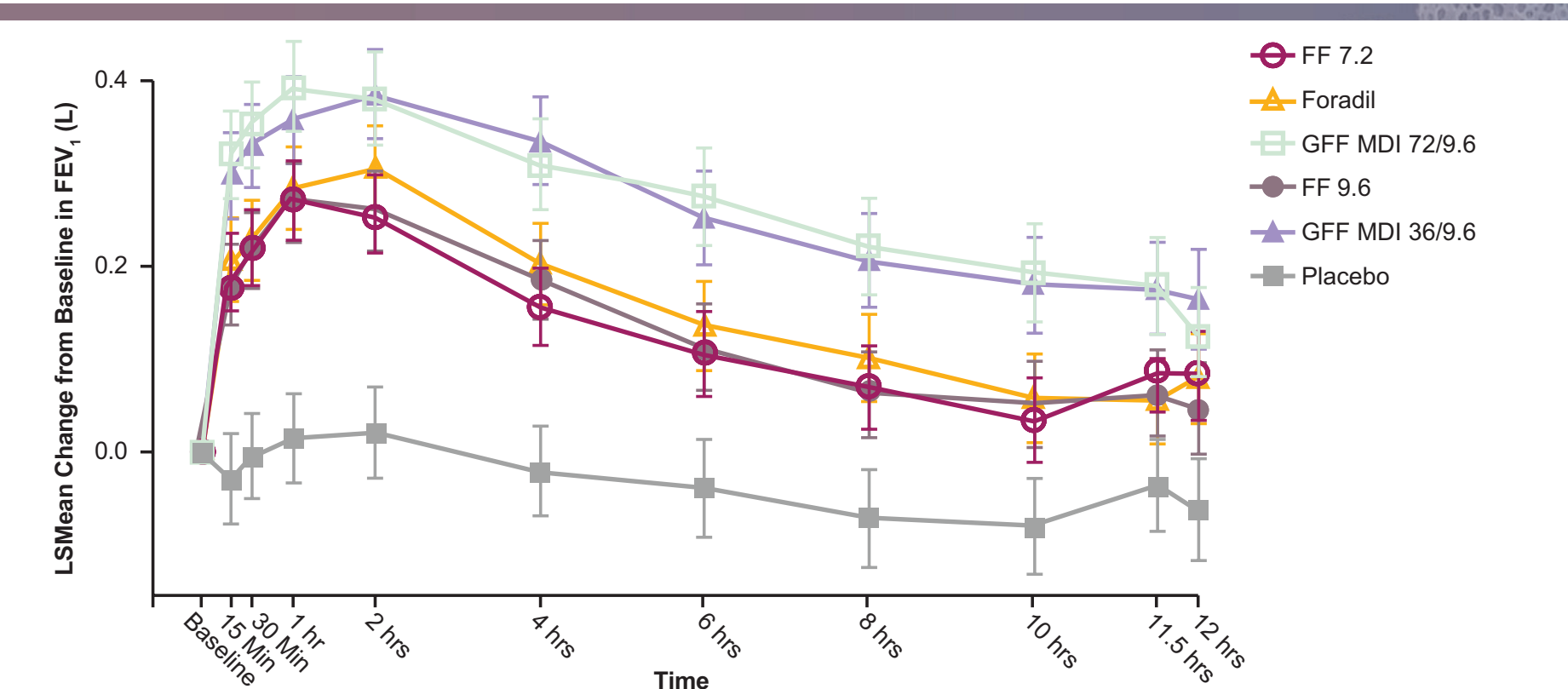
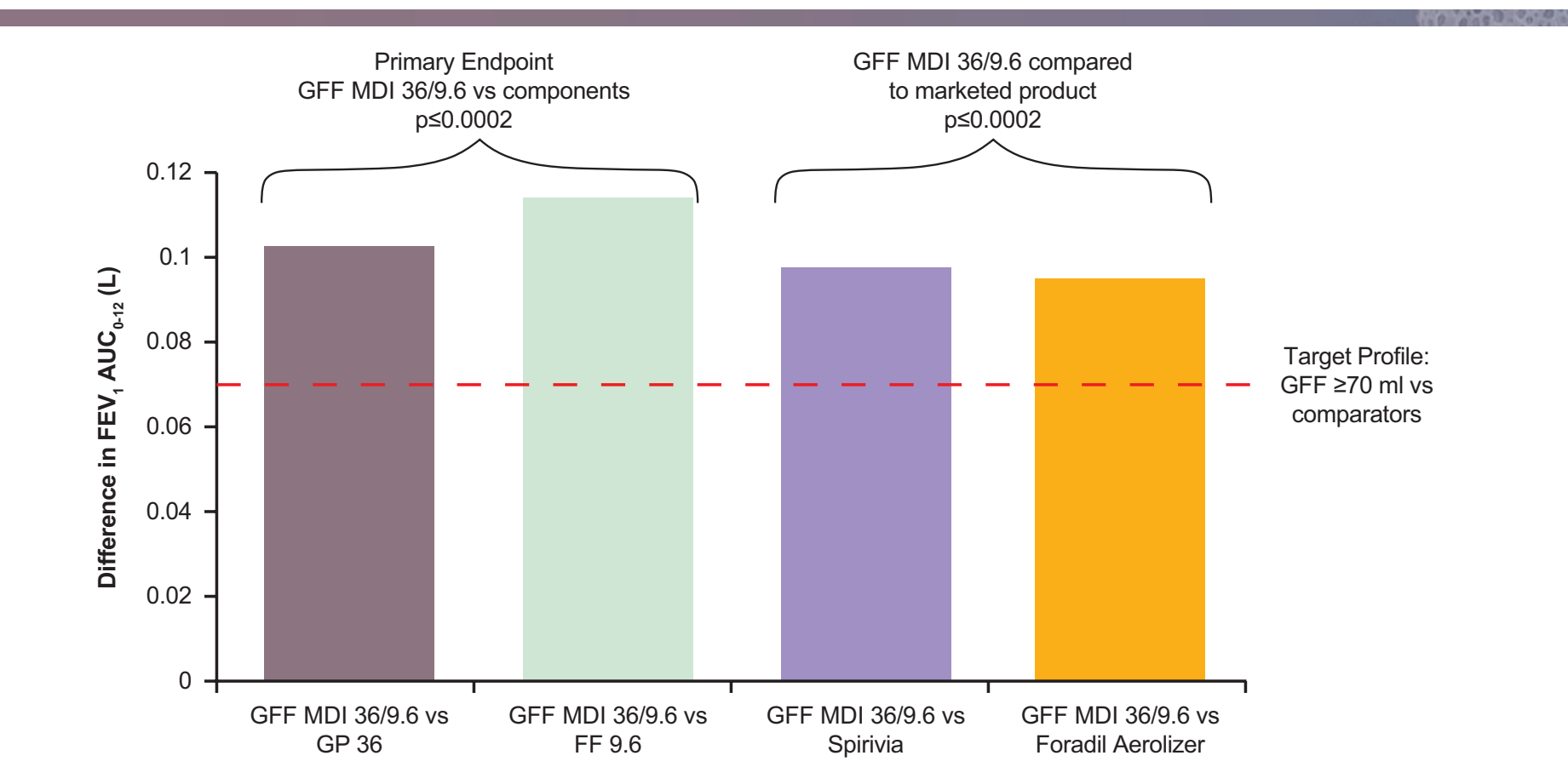


Figure 3: GFF MDI 36/9.6 μ g Exceeded Target for Clinical Meaningful Improvement of 70 mL*



*Results for GFF 72/9.6 μ g comparisons were numerically higher (p<0.0001 for comparisons shown above)

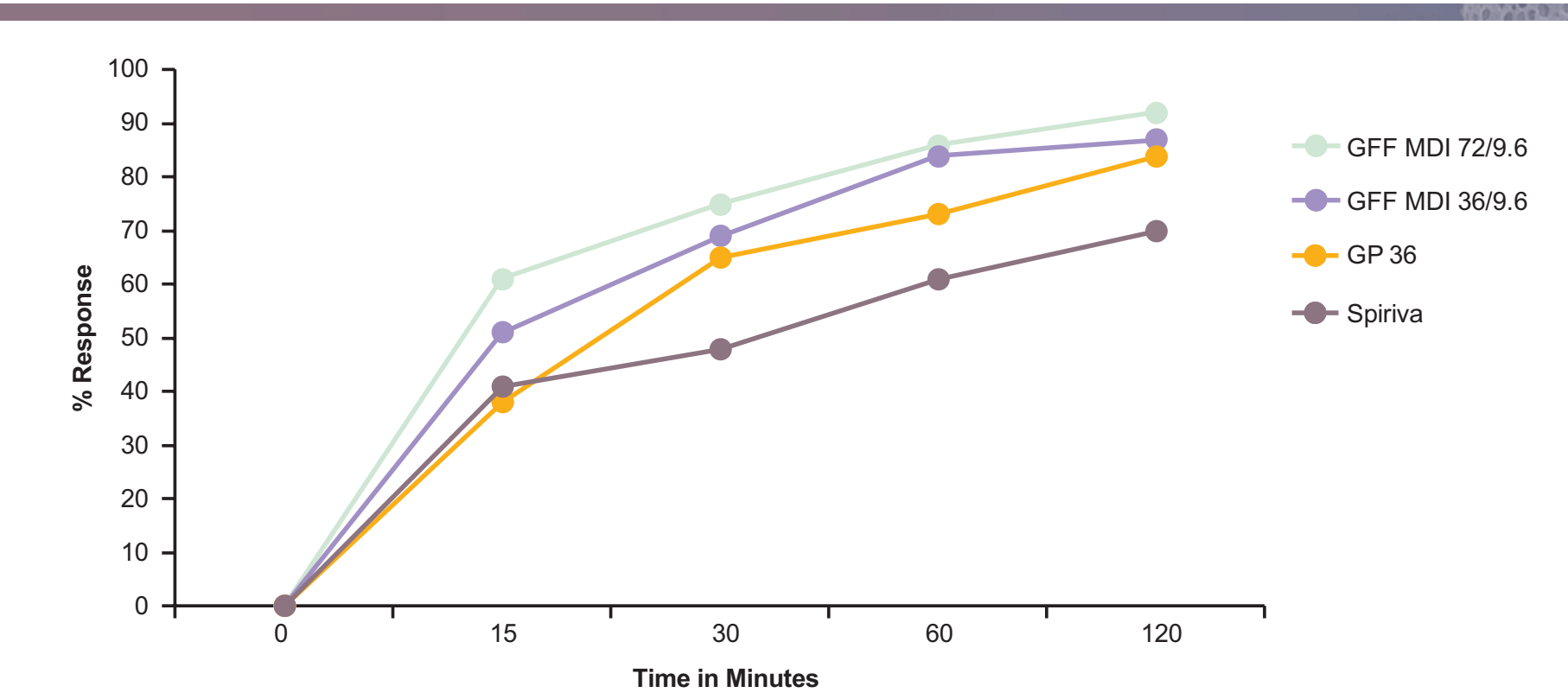
- In general, the secondary endpoints confirmed the findings of the primary endpoint, with GFF MDI 36/9.6 μ g and GFF MDI 72/9.6 μ g demonstrating superiority to components and active comparators, and comparability between each other.

Table 2: Peak FEV₁ on Day 1, Peak and morning trough FEV₁ on Day 7 Versus Placebo

	GFF MDI 72/9.6 μ g	GFF MDI 36/9.6 μ g	FF MDI 9.6 μ g	FF MDI 7.2 μ g	FA 12 μ g	GP MDI 36 μ g	Spiriva 18 μ g
Peak FEV ₁ Day 1	227 mL	216 mL	163 mL	166 mL	152 mL	152 mL	124 mL
Peak FEV ₁ Day 7	328 mL	330 mL	230 mL	218 mL	241 mL	207 mL	188 mL
A. M. Trough FEV ₁ Day 7	234 mL	211 mL	105 mL	114 mL	143 mL	139 mL	139 mL

- All comparisons to placebo statistically significant (p<0.0001)
- GFF MDI 72/9.6 and GFF MDI 36/9.6 were superior to individual components, Spiriva Handihaler and Foradil Aerolizer for above listed assessments (p<0.03)

Figure 4: Cumulative Response Over Time on Day 1 (>10% Improvement in FEV₁ from Baseline)



- GFF MDI had a faster onset of action than Spiriva Handihaler (75% higher probability of onset in GFF MDI group than in the Spiriva Handihaler group at any time point during the first 2 hours post-dose) (p<0.0003)
- GP MDI had a faster onset of action than Spiriva Handihaler (32% higher probability of onset in GP MDI group than in the Spiriva Handihaler group at any time point during the first 2 hours post-dose) (p=0.055)
- No meaningful differences noted for GFF MDI when compared to formoterol containing treatments

Safety

Table 3: Treatment Emergent Adverse Events (TEAE) Occurring in \geq 3 Patients in Any Treatment Group

	GFF MDI 72/9.6 μ g (n=41)	GFF MDI 36/9.6 μ g (n=43)	GP MDI 36 μ g (n=41)	FF MDI 9.6 μ g (n=64)	FF MDI 7.2 μ g (n=64)	FA 12 μ g (n=55)	Spiriva 18 μ g (n=58)	Placebo (n=52)
Any TEAE	17 (42%)	18 (42%)	11 (27%)	24 (38%)	16 (25%)	17 (31%)	22 (38%)	9 (17%)
Dry Mouth	8 (20%)	3 (7%)	6 (15%)	3 (5%)	3 (5%)	3 (6%)	6 (15%)	5 (9%)
Headache	5 (12%)	5 (12%)	2 (5%)	1 (2%)	0	3 (6%)	1 (2%)	1 (2%)
Tremor	1 (2%)	6 (14%)	1 (2%)	0	1 (2%)	0	1 (2%)	0
COPD	1 (2%)	0	1 (2%)	3 (5%)	3 (5%)	0	0	1 (2%)
Cough	0	3 (7%)	1 (2%)	1 (2%)	0	1 (2%)	2 (3%)	2 (4%)

- Five patients reported a total of 6 treatment-emergent SAEs, none attributed to treatment: 2 patients-Spiriva Handihaler, 2 patients-FF MDI 7.2 μ g, 1 patient-GFF MDI 36/9.6 μ g and 1 patient FF MDI 9.6 μ g.
- No patient had a post-baseline serum potassium level <3.0 mmol/L and only one patient with <3.5 mmol/L and 0.5 mmol/L change (isolated event).
- Ten patients had glucose values >11.1 mmol/L (>200 mg/dL) post-baseline during the study. Six of the ten had prior history of diabetes; with the exception of two patients, elevated values were seen at a single time point.
- Across all treatments, mean changes in QTcF were small with no important trends noted between groups.
- A total of 5 patients met the QTcF threshold criteria [$>$ 30 msec increase in QTcF over baseline with an absolute QTcF >450 (males) or 470 msec in (females)]; 2 patients-Foradil Aerolizer, 2 patients-Spiriva Handihaler, and 1 patient-GP MDI 36 μ g. Per the reviewing cardiologist (blinded to treatment), these changes were of no clinical significance.

Conclusions

- GFF MDI (PT003) demonstrated superior bronchodilation compared to Spiriva Handihaler, Foradil Aerolizer, and its individual components
- GFF MDI (PT003) demonstrated significantly more rapid onset of action than Spiriva Handihaler
- No safety concerns identified
- Data support the further development of GFF MDI (PT003) in patients with COPD