

Fixed Combination of Glycopyrrolate and Formoterol MDI (GFF MDI) Demonstrates Superior Inspiratory Capacity Compared to Tiotropium DPI in a Randomized, Double-Blind, Placebo-Controlled Phase 2b Study in Patients with Moderate to Very Severe COPD

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Abstract

Rationale: In patients with COPD, changes in inspiratory capacity (IC) have shown a higher correlation to patient-focused outcomes, such as dyspnea with exercise, than other standard spirometric measurements. Changes in IC reflect changes in hyperinflation (Celli, 2003). Tiotropium dry powder inhaler (DPI) is a once-daily inhaled anticholinergic, and previous studies have demonstrated improvements in IC following its administration. Pearl Therapeutics' (Pearl) GFF MDI is an inhaled bronchodilator comprised of glycopyrrolate (GP), a long-acting muscarinic antagonist (LAMA) and formoterol fumarate (FF), an established, long-acting beta-2 agonist (LABA), delivered via an HFA 134a MDI. Pearl's proprietary porous particle technology allows the formulation of FF, GP and the combination thereof in MDI format, with highly stable, robust and aerodynamically efficient drug delivery. As part of a large Phase IIb study evaluating the safety and efficacy of GFF MDI, Pearl evaluated improvements in IC following administration of GFF MDI compared to tiotropium DPI and placebo following chronic dosing.

Methods: A randomized, double-blind, customized, unbalanced, incomplete block, crossover study was conducted in patients with moderate to very severe COPD (NCT01085045). This design ensured maximum power for key assessments. Two doses of GFF MDI (72/9.6 and 36/9.6 µg) were compared to tiotropium DPI 18 µg and placebo MDI. All actives and placebo were administered twice daily for 1 week, except tiotropium (open-label), which was administered once daily for 1 week. Changes in peak IC were assessed on Day 1 and on Day 7 relative to average pre-dose baseline at the start of treatment.

Results: 118 patients were randomized into the study. Both doses of GFF MDI (72/9.6 and 36/9.6 µg) and tiotropium DPI were superior to placebo (412 mL, 328 mL and 263 mL respectively; $p < 0.0001$ all comparisons) on Day 1, and on Day 7 (265 mL, 293 mL and 170 mL respectively; $p < 0.0004$ all comparisons). GFF MDI 72/9.6 µg was superior to tiotropium DPI on Day 1 and Day 7 (149 mL and 95 mL improvement respectively; $p < 0.05$ for both comparisons). GFF-MDI 36/9.6 µg demonstrated a numeric advantage compared to tiotropium DPI on Day 1 (65 mL) and was superior on Day 7 (124 mL, $p < 0.01$).

Conclusion: GFF MDI, a novel fixed dose LAMA/LABA combination bronchodilator, demonstrated superiority to placebo and statistically significant (GFF MDI 72/9.6 µg) and numerically greater (GFF MDI 36/9.6 µg) improvements in IC compared to tiotropium DPI. This supports the further development of GFF MDI in patients with COPD and, specifically, a formal evaluation of the effects of GFF MDI on exercise.

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 European Union (EU) and worldwide.
- Formoterol fumarate (FF) is a potent and selective long-acting β -agonist approved in the EU 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) metered dose inhaler (MDI) for the long term management of COPD. GFF MDI is also referred to as PT003.
- GFF MDI has demonstrated significant improvements in forced expiratory volume in one second (FEV₁) compared to placebo and an approved active comparator, tiotropium dry power inhaler (DPI).¹
- While FEV₁ is an important endpoint, measures related to dynamic hyperinflation have been shown to correlate more strongly with exercise tolerance and dyspnea.²
- The extent of dynamic hyperinflation during exercise in COPD has been shown to correlate well with inspiratory capacity (IC).^{3,4}
- Bronchodilators, such as tiotropium DPI, have been shown to improve IC and reduce dynamic hyperinflation with corresponding improvements in exercise endurance time and dyspnea.
- Evaluating the effects of GFF MDI on IC will provide important insight into the potential benefits of GFF MDI on exercise and dyspnea.

Objective

- To evaluate improvements in IC following administration of GFF MDI compared to placebo and tiotropium DPI following chronic administration.

Methods

- This was a randomized, double-blind, customized, unbalanced incomplete block study in patients with moderate to very severe COPD that evaluated the efficacy, safety and pharmacokinetics of GFF MDI [72/9.6 and 36/9.6 µg twice daily (BID)], compared with FF MDI (7.2 and 9.6 µg BID), GP MDI [36 µg BID] compared to placebo MDI (BID), Foradil Aerolizer (12 µg BID) and tiotropium DPI (Spiriva® Handihaler®) [18 µg once daily (QD)] as open-label active controls. Patients took each of their 4 assigned treatments for 1 week followed by at least a 1 week washout between treatments.
- The design/key results for this study were presented at the ATS Annual Meeting 2011.¹
- This poster presents the predefined assessments of IC data between GFF MDI 72/9.6 and 36/9.6 µg BID, placebo MDI BID and tiotropium DPI 18 µg QD.

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 or will enter pulmonary rehabilitation during the study

Pre-defined Secondary Endpoints and Exploratory Endpoints

- Peak improvement in IC (mean of 1 and 2 hour post-dose) on Day 1 and Day 7
- Morning pre-dose IC (mean of -60 and -30 minutes pre-dose) on Day 7

Measurement of IC

- IC measurements were performed in accordance with ATS criteria and standardized across sites. Patients were instructed on performance of IC maneuver and tested in seated position with nose clip. Patients were relaxed/breathed regularly for a minimum of 5 breaths until end-expiratory lung volume (FRC) was stable. They were urged to take a deep breath to total lung capacity (TLC) without hesitation. From at least 3 acceptable trials, the 2 largest IC measurements should agree within 5% or 100 mL.

Results

- In the study, 118 subjects were included in the ITT Population, 104 met criteria for MITT (completed at least two of the four 1-week treatment periods; Table 1)
- A total of 38, 40, 56 and 47 patients received GFF MDI 72/9.6 µg, GFF MDI 36/9.6 µg, tiotropium DPI 18 µg and placebo, respectively.

Table 1: Demographics mITT Population

Characteristic	Value
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%)
Baseline pre-dose IC (Day 1)	2.283 L

Efficacy

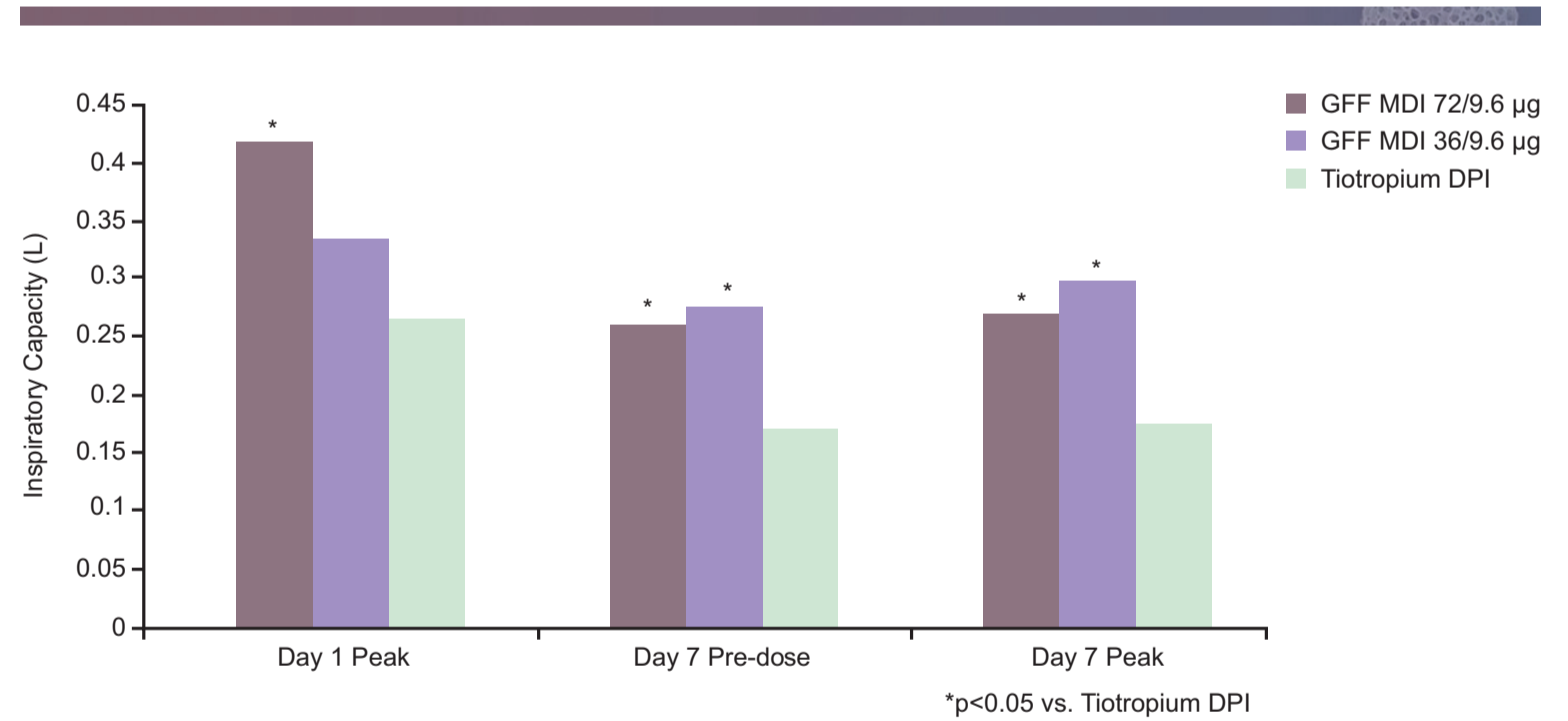
- The study met its primary endpoint (FEV₁ AUC₀₋₁₂ at Day 7). Both GFF MDI 72/9.6 and 36/9.6 µg were significantly greater than GP MDI and FF MDI, placebo and tiotropium DPI ($p < 0.0001$) allowing for further analysis of the secondary and exploratory endpoints.
- The change from baseline in peak IC on Day 1, change from baseline in morning pre-dose IC and peak IC on Day 7 are presented in Table 2.

Table 2: Change from Baseline in IC on Day 1 and Day 7

	Placebo (n=45)	GFF MDI 72/9.6 µg (n=38)	GFF MDI 36/9.6 µg (n=39)	Tiotropium DPI (n=53)
Pre-dose IC on Day 1, Baseline (SD)	2.110 (0.5225)	2.273 (0.6395)	2.186 (0.5634)	2.215 (0.6104)
Mean change from baseline in peak IC on Day 1 (SD)	0.104 (0.2331)	0.482 (0.3300)	0.412 (0.2666)	0.318 (0.2946)
Mean change from baseline in pre-dose IC on Day 7 (SD)	-0.039 (0.2246)	0.188 (0.1818)	0.175 (0.2260)	0.089 (0.2018)
Mean change from baseline in peak IC on Day 7 (SD)	0.101 (0.2348)	0.396 (0.2925)	0.422 (0.3673)	0.300 (0.2614)

- The IC compared to placebo was significantly greater for both GFF MDI treatment groups compared to tiotropium DPI on Day 1 (post-dose) and Day 7 (pre and post-dose) (Figure 1).
- GFF MDI 72/9.6 µg was superior to tiotropium DPI for peak IC on Day 1.
- Both GFF MDI 72/9.6 µg and GFF MDI 36/9.6 µg were superior to tiotropium DPI on pre-dose IC and peak IC on Day 7.

Figure 1: Inspiratory Capacity: LS Mean Change from Baseline Compared to Placebo



Conclusions

- It has recently been shown that the progressive reduction of resting IC with worsening airflow obstruction and hyperinflation is associated with the development of an increasingly shallow, rapid breathing pattern and worsening dyspnea at progressively lower levels of ventilation during exercise.⁶ It has also been shown that resting FEV₁ and IC are the best correlates of peak incremental work rate in patients with COPD.⁶ Improvement in IC also correlates well with improvement in dyspnea at rest and with exercise, as well as overall exercise endurance.⁵
- GFF MDI (PT003) has demonstrated significant improvements in FEV₁ AUC₀₋₁₂ (primary endpoint) compared to tiotropium DPI (Spiriva® Handihaler®).¹
- GFF MDI (PT003) provided substantial improvement in IC relative to tiotropium DPI after the initial dose, with further improvements following chronic dosing.
- These data suggest that GFF MDI (PT003) may provide significant improvements in symptomatic benefits and exercise performance compared to tiotropium DPI (Spiriva® Handihaler®) and supports further evaluation.

References

- C Reisner, C Fogarty, S Spangenthal, L Dunn, EM Kerwin, D Quinn, JP Seale, M Thomas, E St. Rose, CJ Orevillo. 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. [abstract] American Journal of Respiratory and Critical Care Medicine 2011:A6435
- F Di Marco, J Milic-Emilli, B Boveri, P Carlucci, P Santus, F.Casanova, M.Cazzolaz, S Centanni. Effect of inhaled bronchodilators on inspiratory capacity and dyspnoea at rest in COPD. European Respiratory Journal 2003; 21:86-94
- JM Marin, SJ Carrizo, M Gascon, A Sanchezm BA Gallego, BR Celli. Inspiratory Capacity, Dynamic Hyperinflation, Breathlessness, and Exercise Performance during the 6-Minute-Walk Test in Chronic Obstructive Pulmonary Disease. American Journal of Respiratory and Critical Care Medicine 2001; 163:1395-1399
- DE O'Donnell, SM Revill, KA Webb. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 2001; 164:770-777
- O'Donnell DE, Flüge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnea and exercise tolerance in COPD. Eur Respir J. 2004;23:832-40
- O'Donnell DE, Guenette JA, Maltais F, Webb KA. Decline of resting inspiratory capacity during exercise in COPD: The impact of breathing pattern, dyspnea and ventilatory capacity during exercise. Chest 2011; prepublished online August 18, 2011