

Glycopyrrolate MDI Demonstrates Comparable Efficacy and Safety to Tiotropium Dry Powder Inhaler in a Randomized, Double-Blind, Placebo-Controlled Phase 2b Study in Patients with Moderate to Very Severe Chronic Obstructive Pulmonary Disease

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Abstract

Rationale: Long-acting antimuscarinics (LAMAs) are central to the management of patients with chronic obstructive pulmonary disease (COPD). Tiotropium is a LAMA approved as a dry powder inhaler (DPI) for the maintenance treatment of bronchospasm associated with COPD and for reducing COPD exacerbations. However, an HFA MDI product is not available. The availability of a LAMA administered in an HFA MDI formulation could provide a needed alternative method of administration for this well-characterized class of products. Pearl Therapeutics' (Pearl) proprietary porous particle technology allows the formulation of glycopyrrolate in an MDI format (GP MDI), with stable, robust and aerodynamically efficient drug delivery. In a previous single-dose, Phase 2a study, GP MDI demonstrated comparable efficacy and safety to tiotropium DPI (Spiriva® Handihaler®, 18 µg). Based on these findings, Pearl evaluated GP MDI compared to tiotropium DPI in a chronic dosing study.

Methods: In a randomized, double-blind, customized, unbalanced, incomplete block, crossover study conducted in patients with moderate to very severe COPD, GP MDI 36 µg was compared to placebo MDI and tiotropium DPI (open-label) (NCT01085045). GP MDI and Placebo MDI were administered twice daily for 1 week; tiotropium DPI was administered once daily for 1 week. The primary efficacy endpoint was FEV₁ AUC₀₋₁₂ on Day 7 relative to pre-dose baseline at the start of treatment. Secondary endpoints included peak FEV₁, morning trough FEV₁, inspiratory capacity, and safety assessments.

Results: GP MDI 36 µg and tiotropium DPI were superior to placebo for the primary endpoint (189 and 195 mL respectively, p<0.0001 for all comparisons). GP MDI 36 µg was non-inferior to tiotropium DPI for this endpoint (mean difference = -6 mL, 95% confidence interval (CI): -49, +38 mL). The secondary endpoints confirmed the overall efficacy of the formulations. GP MDI 36 µg was safe and well tolerated with a similar safety profile to tiotropium DPI.

Conclusion: Pearl's formulation of GP MDI 36 µg demonstrated comparable efficacy and safety to marketed tiotropium DPI, supporting the further advancement of this product as another treatment option for patients with COPD.

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 and worldwide in parenteral formulations.
- Pearl Therapeutics is developing GP MDI for the long-term management of COPD.
- In a previous single-dose Phase 2a study, GP MDI demonstrated superior efficacy compared to placebo in terms of peak FEV₁, with a clear dose-response relationship and noninferiority to tiotropium DPI (Spiriva® Handihaler®, 18 µg).

Objective

- To evaluate the bronchodilatory effect of GP MDI 36 µg (ex-actuator) BID compared to placebo BID and tiotropium DPI 18 µg (capsule content) QD after 7 days of treatment.

Methods

Study Design

- Multicenter, randomized, double-blind, chronic dosing (7-days), customized, unbalanced, incomplete block, crossover study in patients with moderate to very severe COPD that evaluated the efficacy and safety of GFF MDI 72/9.6 µg BID, GFF MDI 36/9.6 µg BID, FF MDI 9.6 µg BID, FF MDI 7.2 µg BID, and GP MDI 36 µg BID compared to placebo, Foradil Aerolizer 12 µg BID (open-label), and Spiriva Handihaler 18 µg QD (open-label) as active controls.
- One of the pre-defined assessments of this study, GP MDI compared to tiotropium DPI and placebo, is presented in this poster. Efficacy and safety data only from these treatment arms are presented. The study design and key results from this study were presented at the American Thoracic Society (ATS) Annual Meeting 2011.

Key Inclusion Criteria

- Current or ex-smokers 40 to 80 years of age
- Clinical history of COPD with post-albuterol FEV₁ ≤ 80% of predicted normal and ≥ 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 compared to placebo

Secondary Endpoints Included

- Peak FEV₁ (Day 1 and 7)
- 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 rate (PEFR) during each sequence

Safety Endpoints:

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

Results

- In the study, 118 subjects were included in the intent-to-treat (ITT) population, 104 met criteria for the modified ITT (mITT) population (completed at least two of the four 1-week treatment periods; Table 1).

Table 1: Demographics mITT Population

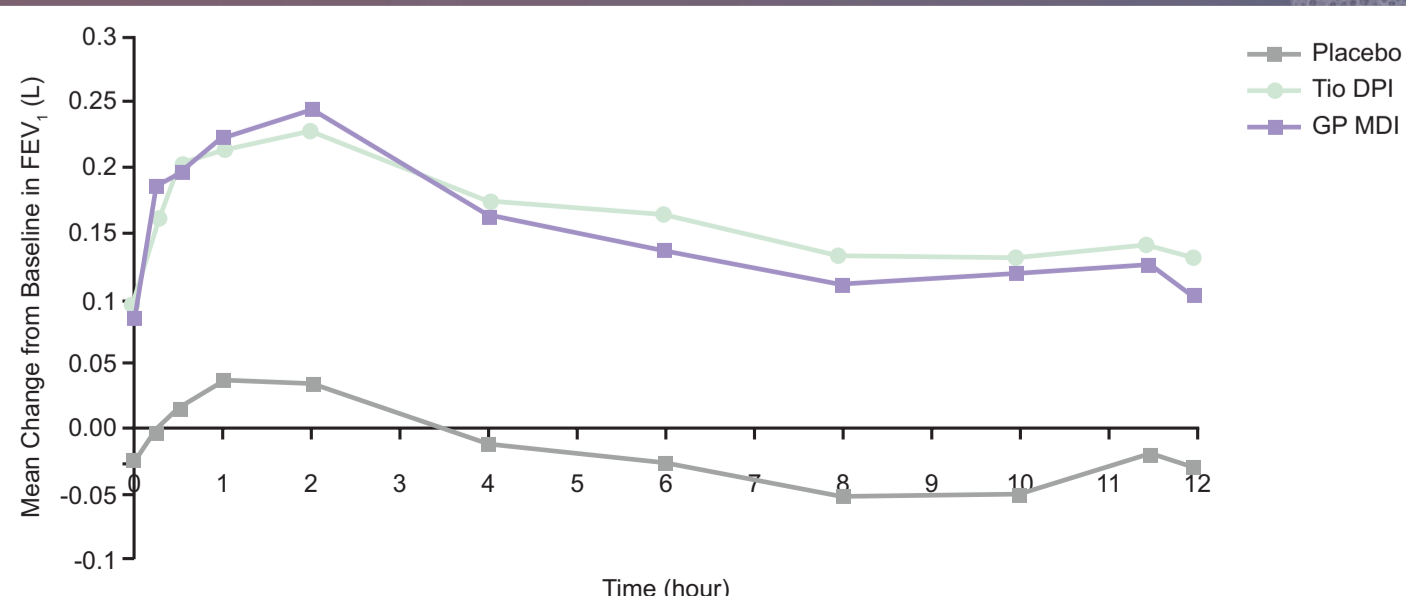
Characteristic	n (%)
Total (Male/Female)	104 (59/45)
Age (years)	63.3 (±8.6)
Smoking history (pack years)	52.3 (±28.7)
Screening FEV ₁ ; Pre-dose L (% predicted)	1.303 (44.4%)
Screening FEV ₁ ; Post-dose L (% predicted)	1.494 (50.9%)
Disease severity (moderate/severe/very severe)	(53%/44%/3%)

- In the mITT population a total of 38, 56 and 47 patients received GP MDI 36 µg, tiotropium DPI 18 µg and placebo, respectively.
- 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 endpoints.

Efficacy

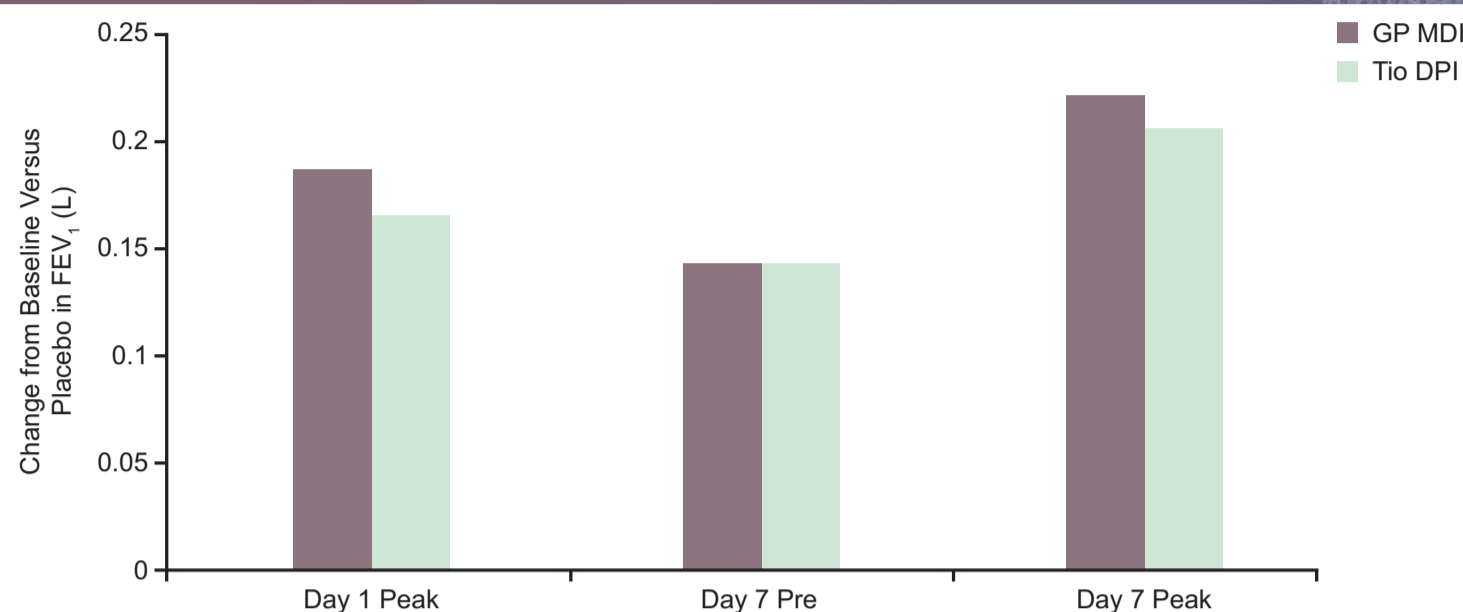
- For the primary endpoint, FEV₁ AUC₀₋₁₂ relative to baseline following chronic dosing, GP MDI (36 µg, BID) and tiotropium DPI (18 µg, QD) were superior to placebo (GP MDI: 0.189 L ± 0.028 [n=35]; tiotropium DPI: 0.195 L ± 0.02 [n=53]; p<0.0001 for all comparisons).
- GP MDI was non-inferior to tiotropium DPI (Difference = -6 mL, 95% CI: -0.049, 0.038)
- The mean change from baseline on treatment day 7 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 By Treatment on Treatment Day 7



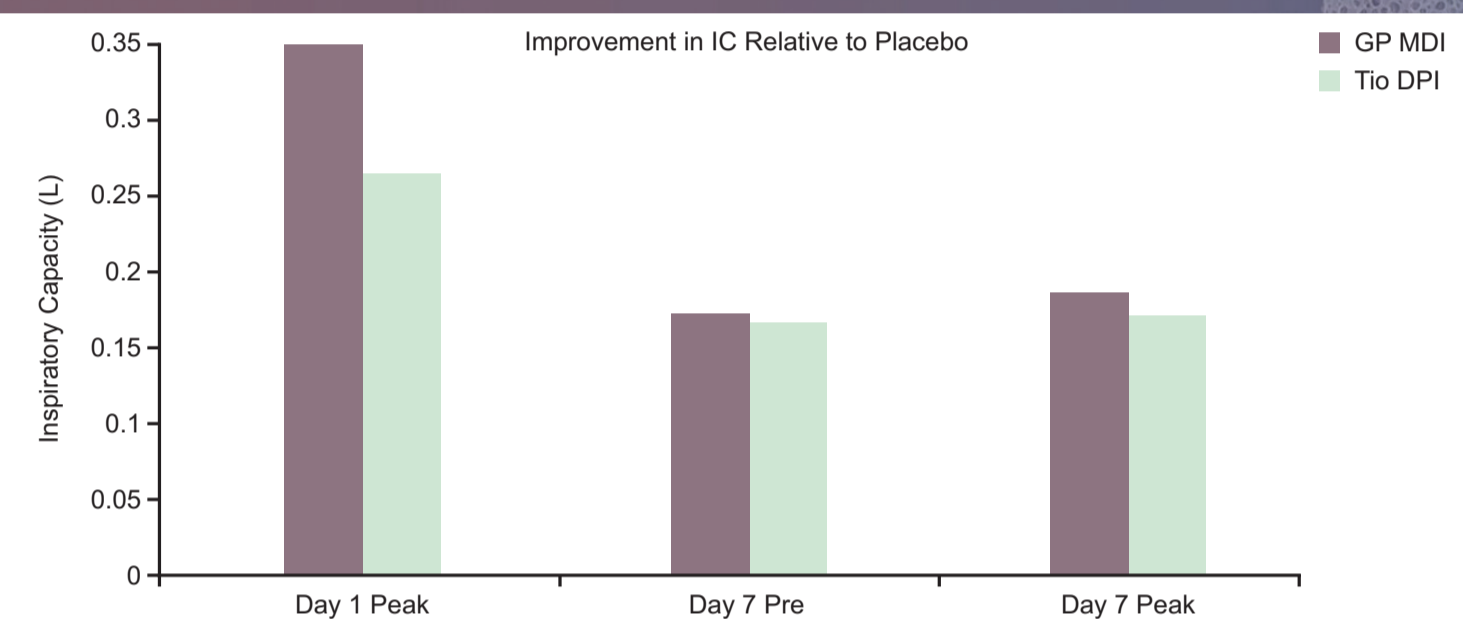
- In general, the secondary endpoints confirmed the findings for the primary endpoint with superior efficacy versus placebo (p<0.0001, Figure 2) and comparability between GP MDI and tiotropium DPI.

Figure 2: Peak FEV₁ on Day 1, Peak and Morning Trough FEV₁ on Day 7 Versus Placebo



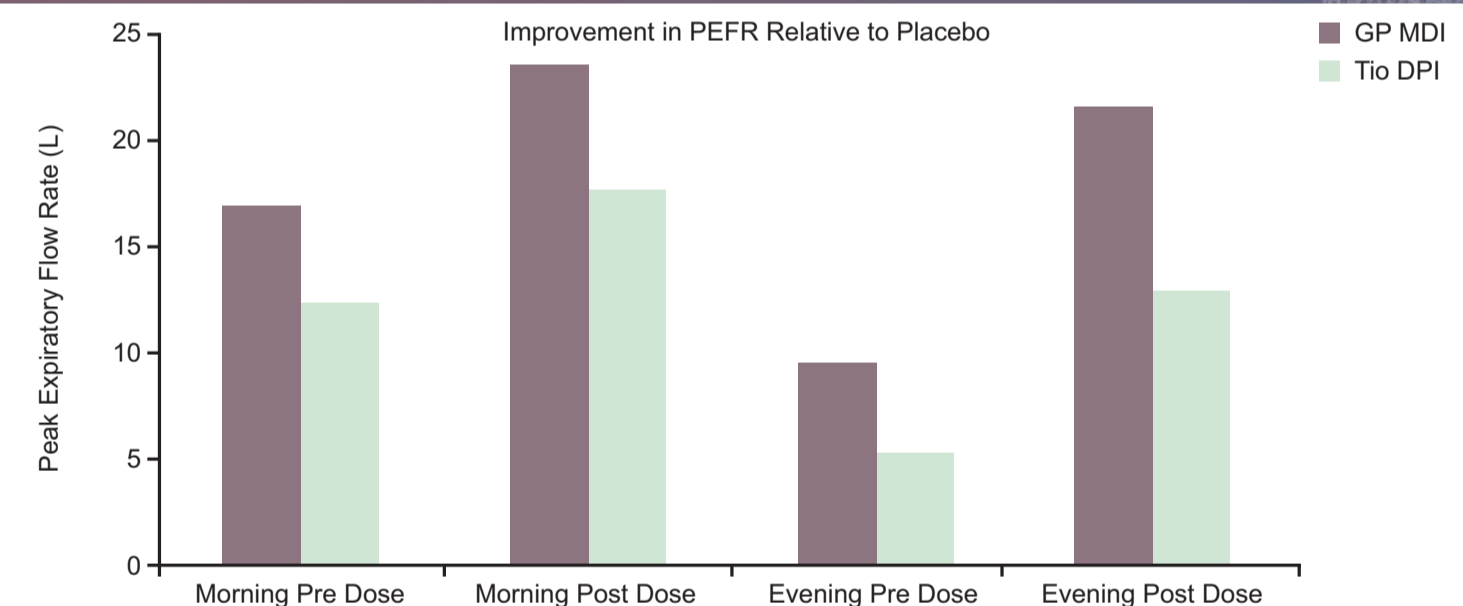
- GP MDI was non-inferior to tiotropium DPI for inspiratory capacity (Figure 3).

Figure 3: Inspiratory Capacity: GP MDI Provides Comparable Improvement to Tiotropium DPI



- The Mean change in PEFR (L) obtained morning pre- and post-dose and evening pre- and post dose was consistently greater for GP MDI than tiotropium DPI.

Figure 4: Mean Change in PEFR Pre- and Post-Dose, Morning and Evening



Safety

Both treatments were well tolerated. The most commonly reported AEs are presented in Table 2.

Table 2: Treatment-Emergent Adverse Events Reported in ≥2 Subjects

Preferred Term	GP MDI 36 µg (n=41)	Tio DPI 18 µg (n=58)	Placebo (n=52)
Any TEAE	11 (26.8%)	22 (37.9%)	9 (17.3%)
Dry Mouth	6 (14.6%)	5 (8.6%)	1 (1.9%)
Nausea	0	2 (3.4%)	0
Nasopharyngitis	0	0	1 (1.9%)
Headache	2 (4.9%)	1 (1.7%)	1 (1.9%)
Tremor	1 (2.4%)	1 (1.7%)	0
Cough	1 (2.4%)	2 (3.4%)	2 (3.8%)
Oropharyngeal Pain	2 (4.9%)	1 (1.7%)	0
Dysphonia	0	0	0
COPD	0	0	1 (1.9%)
Hypertension	0	2 (3.4%)	0

- Two patients on tiotropium DPI experienced a treatment-emergent SAE, no patients in the GP MDI or placebo treatment groups experienced treatment-emergent SAEs.
- Across all treatment groups, mean changes in QTcF were small with no important trends noted between groups.

Conclusions

- GP MDI (PT001) demonstrated superior efficacy to placebo and comparable efficacy to tiotropium DPI for the primary endpoint and key secondary endpoints including IC, peak FEV₁, and morning trough FEV₁.
- The improvement in the morning and evening PEFR suggests that BID dosing of GP MDI (PT001) is associated with a dual peak effect, and this second peak may provide an additional benefit in patients with COPD.
- No safety concerns were identified in this study.
- The data from this study are reassuring and support the further evaluation of GP MDI in patients with COPD.

References

1. 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 183:2011:A6435.