

# A Novel Glycopyrrolate Metered Dose Inhaler Formulation Demonstrates Superior Bronchodilator Efficacy Relative to Placebo and Comparable Efficacy and Safety to Spiriva® Handihaler® in Patients with COPD

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## Abstract

**Rationale:** Glycopyrrolate (Robinul® and Robinul Forte®) is an anticholinergic drug that has been approved by the Food and Drug Administration (FDA) for the treatment of peptic ulcer and for use during anesthesia. Glycopyrrolate is not approved for respiratory inhalation. Pearl's novel porous particle based suspension technology allows the formulation of this class of actives in pressurized metered dose inhalers (MDI), and provides better targeting of the drug dose to airways with low oropharyngeal dose. Pearl Glycopyrrolate MDIs (GP MDI) have excellent aerodynamic size distribution, stability, dose uniformity, and product robustness, which have not been achievable with traditional MDIs thus far. Pearl GP MDI is being evaluated for the long-term management of COPD.

**Methods:** Study PT0010801, the first-in-human study of the GP MDI, was a randomized, double-blind, single dose, four-period, six-treatment, placebo-controlled, balanced, incomplete block, cross-over, multi-center, ascending dose study of four doses of GP MDI (18, 36, 72 and 144 µg ex-actuator) in patients with mild to moderate COPD, compared to open label tiotropium (18 µg administered via the Handihaler®) as an active control. Spirometry measures were performed at baseline, 15 and 30 minutes, 1, 2, 4, 6, 8, 10, 12, 16, 22, 23 and 24 hours post-dose.

**Results:** A total of 33 patients were enrolled (19 males, 14 females, mean age: 59 years), 30 of whom completed all 4 treatments within a block. Peak FEV<sub>1</sub> of 0.19, 0.32, 0.37, 0.33, 0.43 and 0.36 L and FEV<sub>1</sub> AUC<sub>0-24hr</sub> of -0.04, 0.09, 0.11, 0.10, 0.16 and 0.16 L/24hr were observed for placebo, GP MDI 18, 36, 72, 144 µg and Spiriva® respectively. All 4 doses of GP MDI demonstrated superior efficacy compared to placebo in terms of Peak FEV<sub>1</sub>, the primary endpoint of the study and FEV<sub>1</sub> AUC<sub>0-24hr</sub> (p<0.003). Furthermore, the GP MDI 72 and 144 µg doses demonstrated non-inferior bronchodilator efficacy relative to Spiriva® for these two parameters. No substantial differences were noted between the GP MDI treatment groups, Spiriva® and placebo in terms of safety.

**Conclusions:** These findings support further development of GP MDI for the management of 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 approved for use as a preoperative antimuscarinic and as an adjunctive therapy for peptic ulcer disease in the United States in oral and parenteral formulations.
- Pearl Therapeutics novel porous particle based suspension technology allows better targeting of drugs to the airways via pressurized metered dose inhaler (MDI), and enables the development of products with improved physical stability and dose content uniformity.
- Pearl Therapeutics is developing GP MDI (PT001) for the long-term management of COPD.

## Objective

- To evaluate the bronchodilatory effect of GP MDI over 12 and 24 hours

## Methods

### Study Design

- Multi-center, randomized, double-blind, six-treatment, placebo controlled, balanced, incomplete block, 4-period crossover, ascending dose study of four doses of GP MDI (18, 36, 72 and 144 µg) in patients with mild to moderate COPD compared to placebo and open-label Spiriva® Handihaler® 18 µg as an active control
- Each patient was randomized to 1 of 6 possible sequences that included 4 of the study treatments.

- There was an interval of ≥ 7 days and no more than 3 weeks between each of the 4 single dose treatments.
- All COPD medications were withheld for at least 6 hours prior to dosing on each treatment day.

### Key Inclusion Criteria

- Current or ex-smokers between 40 to 75 years of age
- Clinical history of COPD with post-ipratropium FEV<sub>1</sub>/FVC ratio ≤ 0.70 and FEV<sub>1</sub> ≥ 50 ≤ 85% of predicted normal and reversibility to ipratropium (> 200 mL; or > 12% and 150 mL)

### Key Exclusion Criteria

- Poorly controlled COPD (hospitalized in last 24 weeks, use of corticosteroids or antibiotics in prior 6 weeks)
- Symptomatic prostatic hypertrophy or bladder neck obstruction
- Known narrow angle glaucoma
- Use of systemic corticosteroids, >1000 µg of fluticasone propionate equivalent, tiotropium, oral/long-acting β-agonists, leukotriene antagonists, theophylline

### Primary Endpoint

- Peak improvement in FEV<sub>1</sub> relative to test day baseline for each dose of GP MDI (18, 36, 72 and 144 µg) compared to placebo

### Secondary Endpoints

- Trough FEV<sub>1</sub> at 12 and 24 hours, time to onset of action, time to peak FEV<sub>1</sub>, FEV<sub>1</sub> AUC<sub>0-12</sub>, FEV<sub>1</sub> AUC<sub>12-24</sub> and FEV<sub>1</sub> AUC<sub>0-24</sub>, peak expiratory flow rate (PEFR), inspiratory capacity (IC) and forced vital capacity (FVC)

### Safety

- Adverse events (AEs), vital signs, serial ECGs, laboratory testing, symptoms of dry mouth and monitoring for paradoxical bronchospasm

### Pharmacokinetics (PK)

- PK was evaluated in all patients through 24 hours post-dose.

### Statistical Methods

- Safety analyzed in ITT population, efficacy and PK analyzed in a modified ITT population (randomized, received ≥ one dose of study treatment and no major protocol violations)
- Primary efficacy analysis included pairwise differences and estimates of 95% CI for GP MDI doses vs. placebo. Specific contrasts included GP MDI doses to placebo, GP MDI doses to active control, linear and quadratic trend contrasts among GP MDI doses and comparison among adjacent doses. Contrasts were estimated using a mixed model analysis of variance for repeated measures and longitudinal data approaches. Descriptive analysis of pairwise differences and mixed effects analyses were performed for secondary endpoints.

## Results

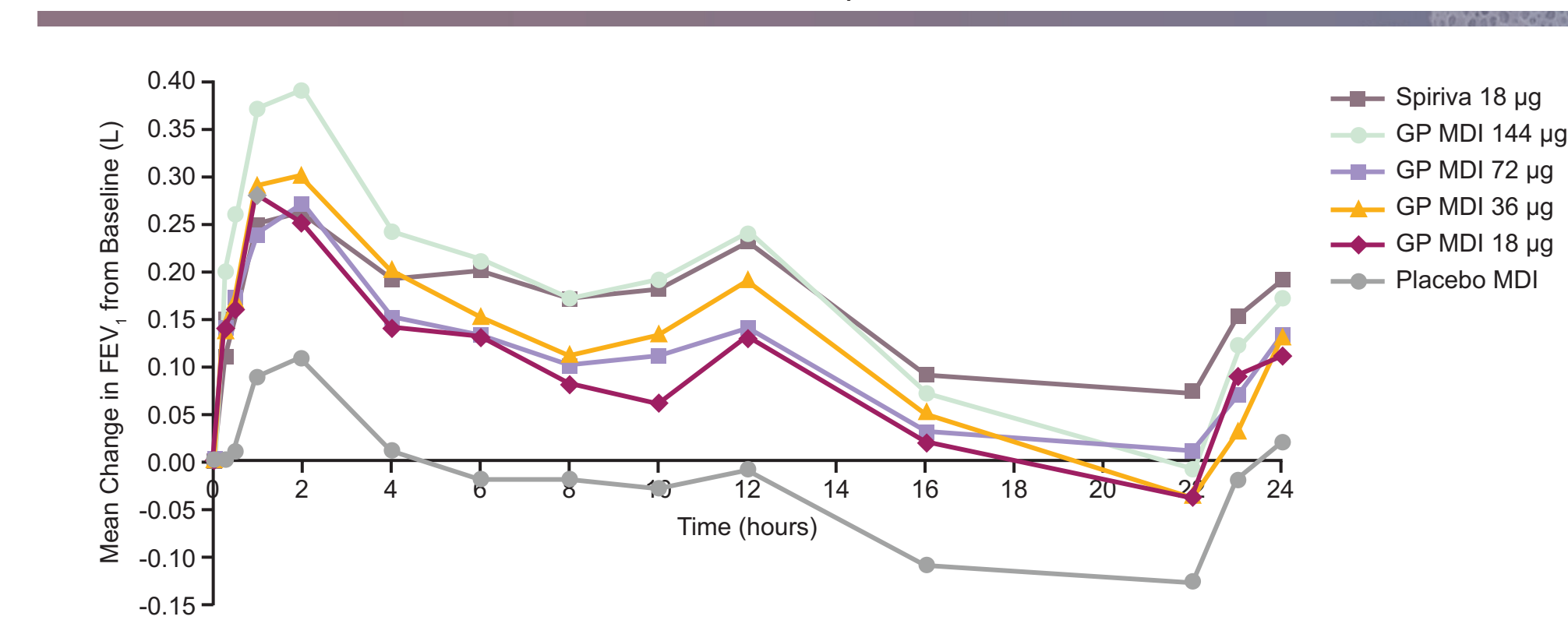
### Study Population, Demographics and Screening Lung Function

- 33 patients were randomized, two patients withdrew (1 due to major protocol violations and the other due to the Investigator considering it in the best interest of the patient)
- Mean age 59 years (range 44 to 71 years), 60% males and 40% females, at screening mean pre-dose FEV<sub>1</sub> was 1.6 L (50.5% of predicted normal) with mean post-ipratropium FEV<sub>1</sub> of 1.93 L (60.6% of predicted normal)

### Efficacy

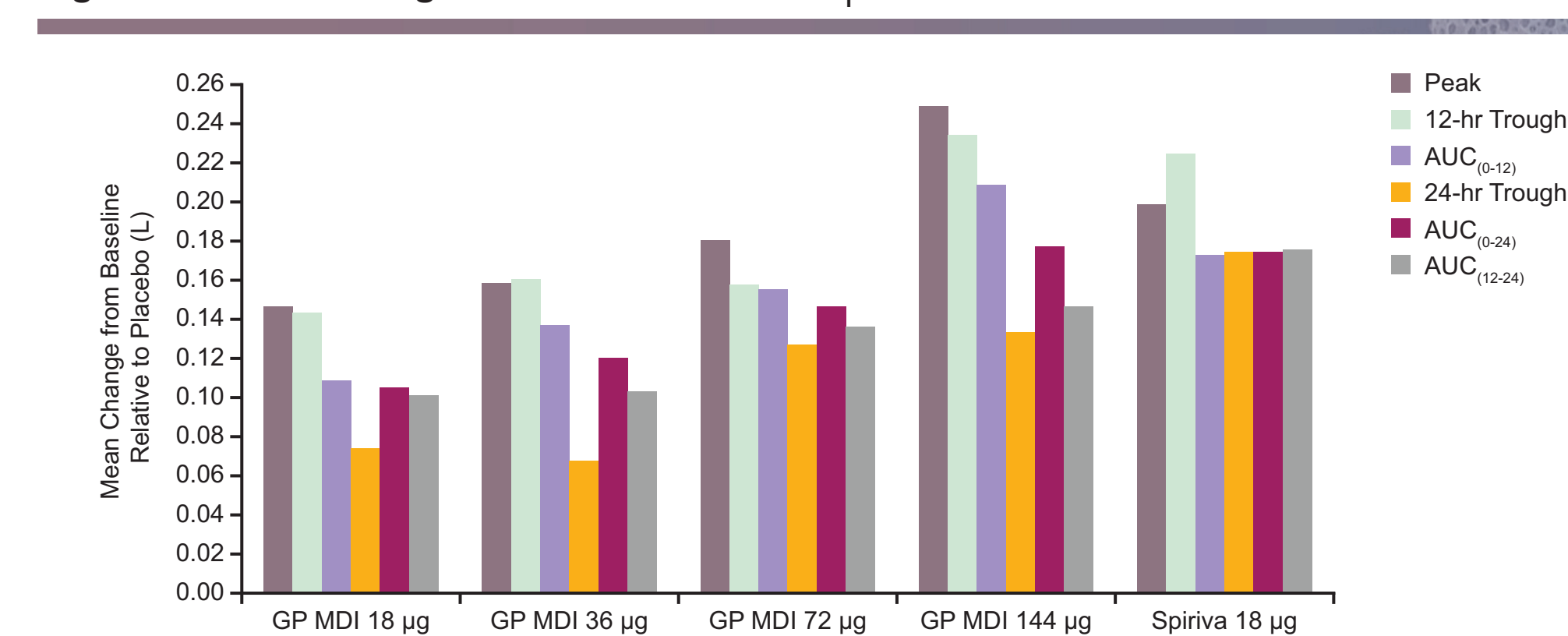
- For the primary endpoint, peak improvement in FEV<sub>1</sub>, each dose of GP MDI showed statistically significant improvements relative to placebo (p<0.001) with a clear dose response relationship.
- The mean change from baseline over the 24-hour test period for each treatment arm is presented in Figure 1.

Figure 1. Mean Change from Baseline in FEV<sub>1</sub> Over Time



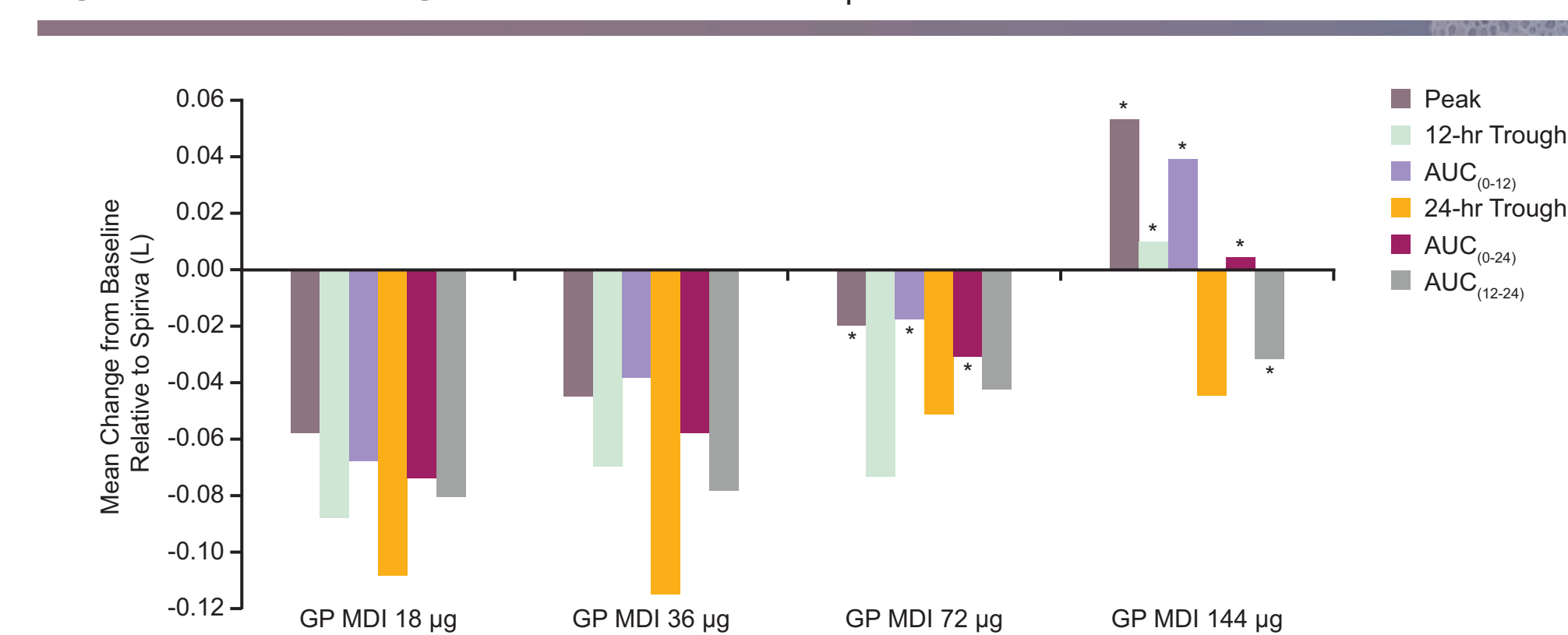
- The secondary endpoints based on FEV<sub>1</sub> parameters generally confirmed the findings for the primary with superior efficacy versus placebo (p<0.05, Figure 2). The only endpoint that did not achieve statistical significance was 24 hour trough FEV<sub>1</sub> for GP MDI 36 µg.

Figure 2. Mean Change from Baseline in FEV<sub>1</sub> Parameters vs. Placebo



- GP MDI 72 and 144 µg were non-inferior (bound of 100 mL) to Spiriva® Handihaler® for peak FEV<sub>1</sub>, AUC<sub>0-12</sub> and AUC<sub>0-24</sub> (Figure 3).

Figure 3. Mean Change from Baseline in FEV<sub>1</sub> Parameters vs. Spiriva® Handihaler®



\*Non-inferior to Spiriva® Handihaler® based on 100 mL non-inferiority bound.

### Safety

- Table 2 summarizes AEs reported by > 1 patient.
- Dry mouth was the most frequently reported AE, there did not appear to be a dose relationship between the incidence of dry mouth and GP MDI dose.
- There were no deaths, SAEs or withdrawals due to AEs during the study.
- One patient who completed the study died outside of the study reporting period (defined as > 30 days post last treatment day), due to complications of COPD. This event was considered not related to study drug by the Investigator.

Table 2. Adverse Events Reported in More than 1 Patient

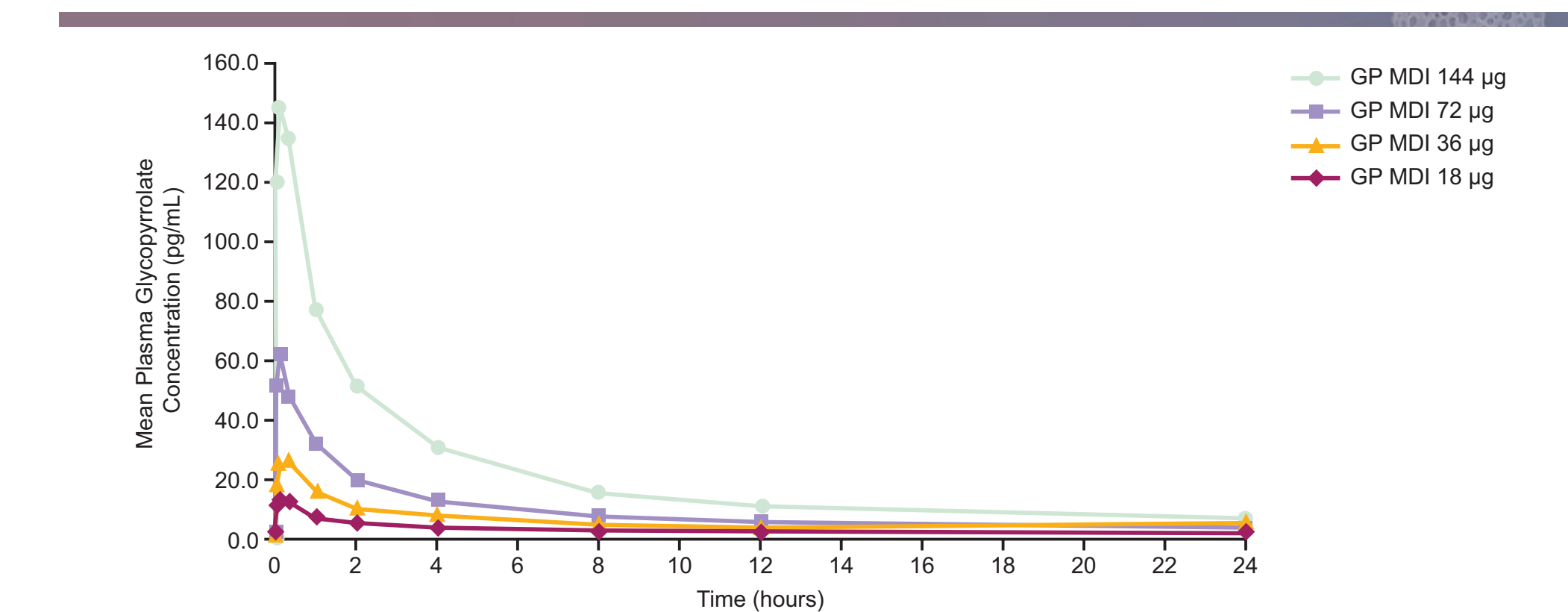
Preferred Term	Placebo MDI	GP MDI 18 µg	GP MDI 36 µg	GP MDI 72 µg	GP MDI 144 µg	Spiriva® Handihaler®
Number of Patients Exposed	21	21	23	21	21	22
One or more AEs	4 (19%)	3 (14%)	3 (13%)	5 (24%)	3 (14%)	4 (18%)
Dry Mouth	2 (10%)	1 (5%)	0	3 (14%)	1 (5%)	2 (9%)
Oropharyngeal Pain	0	1 (5%)	0	0	1 (5%)	0
Vessel puncture site hematoma	0	0	1 (4%)	0	0	1 (4%)

- Changes in laboratory values, vital signs, and serial ECG parameters were generally small and no important trends were noted between GP MDI doses, placebo and Spiriva® Handihaler®.

### Pharmacokinetics

- Exposure to GP increased in a dose proportional manner within the 18 to 144 µg dose range (Figure 4).

Figure 4. Glycopyrrolate Concentration-Time Plots by Treatment



## Conclusions

- All four doses of GP MDI demonstrated superior efficacy compared to placebo in terms of peak FEV<sub>1</sub> with a clear dose response relationship.
- The secondary endpoints based on FEV<sub>1</sub> parameters generally confirmed the findings for the primary endpoint.
- GP MDI 72 and 144 µg demonstrated statistically non-inferior bronchodilator efficacy for peak FEV<sub>1</sub>, FEV<sub>1</sub> AUC<sub>0-12</sub> and FEV<sub>1</sub> AUC<sub>0-24</sub> relative to Spiriva® Handihaler®.
- All doses of GP MDI were safe and well tolerated in this study.
- Plasma GP concentrations increased in a dose proportional manner within the 18 to 144 µg dose range.
- The data from this study support the further evaluation of GP MDI in patients with COPD.

## References

- ClinicalTrials.gov Identifier: NCT00871182.