Assessment of Safety and Pharmacokinetic Profile of a Novel Fixed Combination of Glycopyrrolate and Formoterol HFA MDI in Healthy Volunteers

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Abstract

Rationale: This first-in-human study provided safety and pharmacokinetic (PK) data on a novel fixed dose combination of Glycopyrrolate and Formoterol Fumarate metered dose inhaler (MDI). Pearl's 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 combination products with improved physical stability, content uniformity, and aerodynamic size distribution similarity across the combination drug components. The objective of this study was to provide safety and PK evidence in support of further clinical studies in patients with COPD.

Methods: Study PT0030901 was a randomized, double-blind, single-dose, 4-period crossover, single-center study in healthy subjects that evaluated a single administration of 4 inhaled treatments: glycopyrrolate 72 µg (GP), formoterol fumarate 9.6 µg (FF), the fixed combination GP/FF from a single MDI, and the loose combination of GP + FF administered from two separate MDIs. At each treatment visit, subjects were assessed for 12 hours after dosing. There was a minimum 7 day washout period between treatments. Evaluations included adverse events (AEs), dry mouth and tremor assessments, hematology, clinical chemistry, vital signs, 12-lead electrocardiograms (ECG), spirometry, physical examinations, and PK parameters.

Results: Sixteen subjects (11 females, 5 males), average age 27 years (range 19 to 47), were enrolled with 13 subjects completing all treatment periods. No important safety trends or signals were noted for GP/FF MDI fixed dose combination in terms of AEs, changes in serum potassium or other laboratory values, vital signs, ECGs, or spirometry parameters.

Conclusions: The novel GP/FF MDI fixed dose combination was safe and well-tolerated, with a safety profile similar to that observed with the components administered individually or at the same time as a loose combination. These safety findings support further evaluation of GP/FF MDI in patients with COPD.

Introduction

- Bronchodilator medications are central to the symptomatic management of chronic obstructive pulmonary disease (COPD).
- Combining bronchodilators of different classes may improve efficacy and reduce the risk of side effects compared to increasing the dose of a single bronchodilator.[1]
- Glycopyrrolate (GP) is a well established anticholinergic drug that is approved in the United States and worldwide in oral and parenteral formulations.
- Formoterol fumarate (FF) is a potent and selective long-acting β-agonist approved in the U.S. and worldwide for use in patients with COPD.
- 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 combination products with improved physical stability, content uniformity, and aerodynamic size distribution similarity across the combination drug components.
- Pearl Therapeutics is developing Glycopyrrolate (PT001), Formoterol Fumarate (PT005) and combination (GP/FF) MDI (PT003) for the long term management of COPD.

Objective

- To evaluate the safety of a single dose of GP/FF MDI compared to single doses of GP MDI, FF MDI and the combination of GP MDI + FF MDI delivered consecutively from two separate inhalers in healthy subjects

Methods

Study Design

- Single-center, randomized, double-blind, single-dose, 4-period, 4-treatment, crossover study
- Single administration of 4-inhaled treatments:
  - GP MDI 72 µg (4 puffs 18 µg/puff) + Placebo MDI (4 puffs)
  - FF MDI 9.6 µg (4 puffs 2.4 µg/puff) + Placebo MDI (4 puffs)
  - GP MDI 72 µg (4 puffs 18 µg/puff) + FF MDI 9.6 µg (4 puffs 2.4 µg/puff) (referred to as "loose combination")
  - GP/FF MDI 72 µg of glycopyrrolate and 9.6 µg of formoterol fumarate (4 puffs, 18 µg glycopyrrolate and 2.4 µg formoterol fumarate/puff) (referred to as "fixed combination") + Placebo MDI (4 puffs)
- Planned enrollment was 16 healthy subjects:
  - Four sentinel subjects were planned. Each of these four subjects received one of the 4 possible treatments and were monitored for 24 hours after dosing. Their safety data were evaluated by the Principal Investigator in consultation with the Pearl Therapeutics Chief Medical Officer to determine whether the remaining subjects should be dosed.
- There was an interval of at least 7 days and no more than 21 days between each of the 4 treatments.

Main Criteria for Inclusion

Eligible subjects met the following criteria:

- 18 to 55 years of age
- Healthy
- Agreed to contraception requirements during the study (women of childbearing potential)
- Body mass index (BMI) between 18.5 and 30 kg/m^2 (inclusive)
- Non-smokers for at least 6 months prior to screening
- Pulmonary function tests within normal limits at screening
- Willing to remain at the study center for 12 to 24 hours on each test day

Pharmacokinetics (PK)

- PK was evaluated in all subjects through 12 hours post-dose

Safety Endpoints

- Adverse events (AEs)
- Symptoms of dry mouth and tremor assessments
- Electrocardiograms (ECG) (pre-dose, 30 minutes, 2 and 12 hours post-dose)
- Vital signs [heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), oxygen saturation (SPO_2)]
- Spirometry (pre-dose, 30 minutes, 2, 6 and 12 hours post-dose) including monitoring for paradoxical bronchospasm
- Clinical laboratory evaluations (chemistry and hematology; pre-dose and at the end of each treatment visit with only potassium collected at 30 minutes and 2 hours post-dose)

Statistical Methods

- AEs, dry mouth and tremor assessments were summarized by treatment. For clinical laboratory variables, vital signs, ECG and spirometry parameters summary statistics for raw data and for change from baseline values (pre-dose values at the same treatment period) were provided.

Results

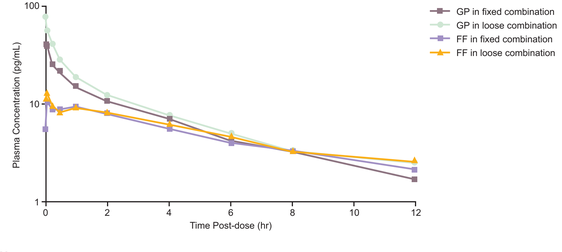
Subject Disposition

- 4 sentinel subjects were enrolled. There were no clinically relevant changes in vital signs, ECGs, spirometry tests or any AEs of clinical concern. Dosing was opened for the remaining subjects.
- 16 subjects were enrolled (5 males, 11 females; mean age 27), 13 of whom completed.
- Three subjects were discontinued due to Investigators decision: 1 due to moderate first degree heart block on pre-dose ECG, (later determined a pre-existing condition); 1 due to poor venous access; and one due to an upper respiratory tract infection (URI).

Pharmacokinetics

- Figure 1 shows the mean plasma concentration-time profiles for GP and FF delivered as loose (PT005+PT001) or fixed combination (PT003).
- Administration of drug as a loose or fixed combination resulted in similar PK profiles for GP.
- Administration of drug as a loose or fixed combination resulted in similar PK profiles for FF.

Figure 1. Mean Plasma Concentration-time Profiles for GP and FF Delivered as Loose (PT005+PT001) or Fixed Combination (PT003)



Safety

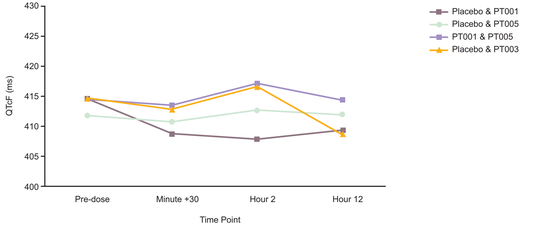
- Table 1 summarizes AEs occurring in more than 1 subject.
- There were no deaths or SAEs during the study.
- One patient was discontinued by the Investigator due to an intermittent URI. This AE was considered moderate, not related to study treatment and resolved after ~16 days.

Table 1. Adverse Events Reported in More Than One Subject Across Treatment Groups

Preferred Term	GP MDI (n=15)	FF MDI (n=13)	GP MDI +FF MDI (n=16)	GP/FF MDI (n=15)	Total
Any AE	7 (47%)	6 (46%)	8 (50%)	9 (60%)	13 (81%)
Headache	2 (13%)	1 (8%)	1 (6%)	5 (33%)	8 (50%)
Dry mouth	2 (13%)	3 (23%)	4 (25%)	4 (27%)	6 (38%)
Upper respiratory tract infection	0	1 (8%)	1 (6%)	1 (7%)	3 (19%)
Dizziness	1 (7%)	1 (8%)	1 (6%)	1 (7%)	3 (19%)
Tremor	0	1 (8%)	2 (13%)	1 (7%)	3 (19%)
Rhinitis allergic	2 (13%)	0	0	1 (7%)	2 (13%)

- Three subjects reported tremor. One had mild bilateral hand tremors after the fixed and loose combination. The second had mild bilateral hand tremor 4 hours after FF MDI and the third had mild tremor 2 and 4 hours after the loose combination. All events resolved and were considered probably related to study treatment.
- Three subjects had dry mouth post-dose (not seen pre-dose). One after fixed combination; the second after FF MDI, fixed and loose combination; and third after fixed and loose combination.
- There were no notable changes over time or differences among treatments in any laboratory values or spirometry assessments. There were no instances of paradoxical bronchospasm.
- Changes in HR, DBP, SBP and SPO_2 were small and no important trends were noted between treatments. Across all treatments, mean change in HR, SBP and DBP did not exceed ± 5 bpm, ± 4.4 mmHg and ± 6.3 mmHg respectively at any time point.
- Three subjects had abnormal ECG findings that were considered clinically significant (2 occurred pre-dose, 1 post-dose at a single time-point). Repeat ECGs were normal in all subjects.
- Mean changes in QTcF values from pre-dose were small at all time points post-dose following each treatment. Across all treatments the mean change in QTcF did not exceed ± 6.7msec at any time point post-dose.
- Figure 2 shows the mean QTcF over time by treatment.

Figure 2. Mean QTcF by Treatment Over Time



Conclusions

- In this healthy volunteer study, the combination of 72 µg of glycopyrrolate and 9.6 µg of formoterol fumarate [administered as a fixed combination (GP/FF MDI) and as a loose combination from two separate inhalers (GP MDI + FF MDI)] was observed to be safe and well tolerated with a similar safety profile to that of GP MDI and FF MDI administered alone.
- Administration of drug as a loose or fixed combination resulted in similar PK profiles for GP; similar findings were observed for FF.
- The data from this study support the further evaluation of GP/FF MDI in patients with COPD.

References

1. GOLD. Global Initiative for Chronic Obstructive Lung Disease. Workshop report: global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. National Institutes of Health, updated 2007. Available at: www.goldcopd.com. Accessed April 17, 2008.
2. ClinicalTrials.gov Identifier: NCT00893971.