Assessment of Pharmacokinetic and Pharmacoepidemiological Impact of a Novel Fixed Combination of Glycopyrrolate and Formoterol Fumarate HFA in Healthy Volunteers


Abstract

Objective: To evaluate the safety of a single-dose of GPP/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, at-home, crossover study. 16 healthy volunteers completed 4 treatment periods: 1. placebo MDI (4 puffs), 2. fixed combination (PT005) or fixed combination (PT003), 3. GT loose combination (n=15), 4. GT fixed combination (n=15). The study was randomized in blocks of 6 with volunteers balanced across blocks.
- There was an interval of at least 7 days and no more than 21 days between each of the 4 treatments. Spirometry (pre-dose, 30 minutes, 2, 6 and 12 hours post-dose) including monitoring for paradoxical upper respiratory tract infection (URTI) was performed. ECG (pre-dose, 30 minutes, 2, 6 and 12 hours post-dose) was performed with the use of a 12-lead system.
- Vitals (SBP, DBP, HR) were monitored pre-dose and 2 hours post-dose. Pulse oximetry was performed pre-dose and post-dose. Tension readings were taken pre-dose and 2 hours post-dose.

Results

Subject Disposition

- 13 subjects completing all treatment periods. No important safety trends or signals were noted for GP/FF clinical chemistry, vital signs, 12-lead electrocardiograms (ECG), spirometry, physical examinations, or treatments. Evaluations included adverse events (AEs), dry mouth and tremor assessments, hematology, clinical chemistry, urinalysis, 12-lead electrocardiograms (ECG), spirometry, physical examination, and PAN parameters.
- Sixteen subjects (11 females, 5 males), average age 27 years (range 19 to 47), were enrolled with 104 8 12. Any AE: Placebo (n=13), FT loose combination (n=15), PT005 (n=15), PT003 (n=15). 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 treatments.

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 (GPP/FF MDI) and as a combination from two separate MDIs was safe and well-tolerated, with a safety profile similar to that of GP MDI and FF MDI administered alone.

- A fixed combination resulted in similar PK profiles for GP; similar (n=13), FT loose combination (n=15), PT005 (n=15), PT003 (n=15). 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 treatments.
- There were no notable changes over time or differences among treatments in any laboratory values or spirometry assessment. There were no evidence of paradoxical bronchoconstriction. Changes in HR, SBP and DBP were small and no important trends were noted between treatments. Across all treatments, mean change in HR, SBP and DBP did not exceed ± 5, ± 4.4 mmHg and ± 6.3 mmHg respectively at any time point.

References
