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Cardiovascular safety profile of a fixed-dose combination of glycopyrrolate and formoterol fumarate delivered via metered dose inhaler using co-suspension delivery technology

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ABSTRACT

Background: Glycopyrrolate/formoterol fumarate (GFF) metered dose inhaler (MDI) is a fixed-dose combination of the long-acting muscarinic antagonist (LAMA), glycopyrrolate (GP), and the long-acting β_2-agonist (LABA), formoterol fumarate (FF), delivered via metered dose inhaler using innovative co-suspension delivery technology. Here we report the results of two studies that examined the cardiovascular safety of GFF MDI.

Methods: The thorough QT (TQT) study was a Phase I, randomized, double-blind, single-dose, crossover study to assess GFF MDI 18/9.6 (Bevespi Aerosphere®), GFF MDI 144/38.4 and GP MDI 144 µg, compared with placebo MDI and open-label moxifloxacin 400 mg (active control) in healthy volunteers (PT003009). The cardiovascular safety study in patients with chronic obstructive pulmonary disease (COPD) was a Phase IIb, randomized, multicenter, double-blind, 14-day dosing, parallel-group study to evaluate GFF MDI 36/9.6, GP MDI 36 and FF MDI 9.6 µg compared with open-label FF dry powder inhaler (DPI; Foradil® Aerolizer®) 12 µg, in patients with moderate-to-severe COPD (PT003003 [NCT01349803]).

Results: Seventy healthy volunteers were randomized in the TQT study. GFF MDI 144/38.4, GFF MDI 18/9.6 and GP MDI 144 µg all met the confidence interval-based criteria for negative QT prolongation potential. In the study in patients with COPD, 237 subjects were randomized and treated. GFF MDI 36/9.6, GP MDI 36, and FF MDI 9.6 µg did not result in clinically meaningful changes from baseline in 24-h mean heart rate at Day 14 (primary endpoint) or in any of the other Holter monitoring endpoints at Day 14, compared with FF DPI 12 µg.

Conclusions: No clinically significant effects on cardiovascular safety occurred at therapeutic or supratherapeutic doses of GFF MDI, apart from a small and transient increase in heart rate following supratherapeutic dose of GFF MDI 144/38.4 µg. Furthermore, there were no unexpected safety findings reported in either healthy volunteers or patients with COPD.

1. Introduction

Bronchodilator therapy with long-acting muscarinic antagonists (LAMAs) and/or long-acting β_2-agonists (LABAs) is recommended as a maintenance treatment option for patients with chronic obstructive pulmonary disease (COPD) [1–3]. The LAMA, glycopyrrolate (GP), and the LABA, formoterol fumarate (FF), are both approved for the treatment of patients with COPD in countries across the world [4–11]. As a drug class, LABAs have been associated with cardiovascular effects such as tachycardia, increases in blood pressure, as well as

Abbreviations: AE, adverse event; AV, atrioventricular; BID, twice daily; BMI, body mass index; bpm, beats per minute; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; FDA, US Food and Drug Administration; FDC, fixed-dose combination; FF, formoterol fumarate; FEV_1, forced expiratory volume in 1 s; GFF, glycopyrrolate/formoterol fumarate; GP, glycopyrrolate; HFA, hydrofluoroalkane; HR, heart rate; ICH, International Conference on Harmonisation; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LSM, least squares mean; MDI, metered dose inhaler; NA, not applicable; QTcI, QT with individual heart rate correction; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TQT, thorough QT

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electrocardiographic changes [5,8,12]. LAMAs have also been associated with potentially increasing the risk of cardiovascular adverse events (AEs) [12,13].

Glycopyrrolate/formoterol fumarate (GFF) metered dose inhaler (MDI) (Bevespi Aerosphere®), a fixed-dose combination (FDC) of GP 18 µg and FF 9.6 µg (equivalent to glycopyrronium/formoterol fumarate dihydrate 14.4/10 µg [14]) delivered by MDI, is approved in the USA for the long-term maintenance treatment of airflow obstruction in patients with COPD [4]. GFF MDI was the first FDC of GP and FF and the first LAMA/LABA FDC available as an MDI, and it was also the first product using this co-suspension delivery technology platform to be made available. The co-suspension delivery technology formulation combines micronized drug crystals with spray-dried phospholipid porous particles in hydrofluoroalkane (HFA) propellant (reviewed in Ref. [15]). The resulting drug crystal/porous particle complexes provide consistent drug-dose delivery of multiple active ingredients with minimal drug–drug interactions, even in the presence of simulated patient handling errors [16].

A thorough QT (TQT) study in healthy volunteers (PT003009) and a cardiovascular safety study in patients with COPD (PT003003 [NCT01349803]) were conducted as part of the drug development process. This manuscript reports the findings of both of these studies.

2. Methods

Both studies were conducted in accordance with Good Clinical Practice, including the International Conference on Harmonisation (ICH), the US Code of Federal Regulations and the Declaration of Helsinki. Protocols were approved by an independent ethics committee or institutional review board, and written informed consent was obtained from subjects prior to screening.

2.1. TQT study

This Phase I, randomized, double-blind, placebo- and moxifloxacin-controlled, five-arm, single-dose, crossover study in male and female healthy volunteers (18–45 years of age) assessed the cardiovascular safety of GFF MDI 18/9.6, GFF MDI 144/38.4 and GP MDI 144 µg, compared with placebo MDI, according to ICH E14 regulatory requirements [17]. The primary endpoint was the change from baseline in QT with individual heart rate (HR) correction (QTcI). Details of the inclusion criteria, assessments, endpoints and statistical analyses from the TQT study are provided in the supplementary material.

2.2. Cardiovascular safety study in patients with COPD

2.2.1. Study design

This Phase IIb, randomized, multicenter, double-blind, 14-day dosing, parallel-group study assessed the safety of GFF MDI 36/9.6, GP MDI 36 and FF MDI 9.6 µg compared with open-label FF dry powder inhaler (DPI; Foradil® Aerolizer®; 12 µg FF dihydrate, equivalent to approximately 11.5 µg formoterol fumarate; all administered twice daily [BID]) in patients with moderate-to-severe COPD (NCT01349803). The FF DPI 12 µg delivers 10 µg FF dihydrate from the mouthpiece, comparable to the 9.6 µg FF MDI dose. At screening Visit 1, patients who met all entry criteria had their inhaled bronchodilator medication switched to ipratropium bromide (Atrovent® HFA) four times a day and albuterol sulfate as needed as rescue medication for a period of 1–3 weeks (≥2 weeks if taking tiotropium or phosphodiesterase inhibitors) prior to the first Holter assessment (Visit 2). At Visit 3, eligible patients were randomized to one of four treatment groups using an interactive web-based response system. The study design is summarized in Fig. 1.

2.2.2. Subjects

Patients who were 40–80 years of age with an established clinical history of COPD, as defined by the American Thoracic Society/European Respiratory Society [18], and a smoking history of at least 10 pack-years were eligible for inclusion. Patients were also required to have pre- and post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity ratio < 0.7, post-bronchodilator FEV_1 ≥30% and < 80% of the predicted value and ≥750 mL at screening (Visit 1), and a pre-bronchodilator FEV_1 < 80% of the predicted value at baseline (Visit 3) [19,20].

Overall, the exclusion criteria were similar to those described for other studies of GFF MDI [14]. Briefly, patients were excluded if they had poorly controlled COPD or if they had clinically significant medical conditions, including – but not limited to – cardiovascular conditions. Details of the cardiovascular exclusion criteria are shown in the supplementary material.

2.2.3. Assessments and endpoints

At Visit 2, patients underwent 24-h Holter monitoring to provide a baseline assessment. Electrocardiograms (ECGs) were conducted on Days 1, 7 and 14 of the treatment period, with 24-h Holter monitoring performed on Days 1 and 14. The primary cardiac safety endpoint was the change from baseline in mean HR averaged over 24 h post-dose

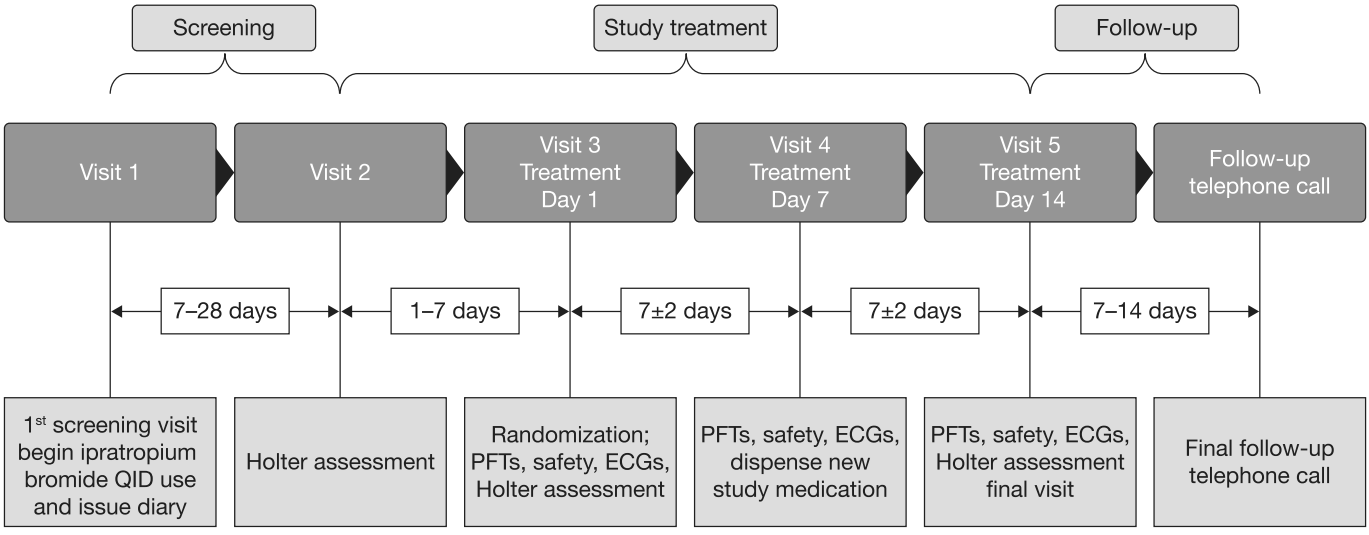

Fig. 1. Design of the cardiovascular safety study in patients with COPD.
COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; PFT = pulmonary function test; QID = four times a day.