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Randomized study of the effects of Aerochamber Plus® Flow-Vu® on the efficacy, pharmacokinetics and safety of glycopyrronium/formoterol fumarate dihydrate metered dose inhaler in patients with chronic obstructive pulmonary disease

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ABSTRACT

Objectives: This study compared the efficacy, pharmacokinetics (PK), and safety of GFF MDI (Bevespi Aerosphere®), a fixed-dose combination of glycopyrronium and formoterol fumarate dihydrate (14.4/10 μg) delivered by a metered dose inhaler (MDI) formulated using innovative co-suspension delivery technology, in patients with moderate-to-very severe chronic obstructive pulmonary disease (COPD) with and without the Aerochamber Plus® Flow-Vu® valved holding chamber (VHC).

Methods: In this multicenter, open-label, crossover, Phase III study (NCT02454959), patients were randomized to receive GFF MDI 14.4/10 μg (equivalent to glycopyrrolate/formoterol fumarate 18/9.6 μg) twice daily for 7 days with and without the VHC. The primary endpoint was forced expiratory volume in 1 s area under the curve from 0 to 12 h (FEV_1 $AUC_{0\text{-}12}$) on Day 8. Steady state PK parameters for glycopyrronium and formoterol ($AUC_{0\text{-}12}$, peak concentration [C_{max}] and time to peak concentration [t_{max}]) were estimated from 12-h plasma concentration time data on Day 8. Safety and tolerability were also assessed throughout.

Results: Eighty patients were randomized. On Day 8, the ratio (90% confidence interval [CI]) of least squares mean (LSM) FEV_1 $AUC_{0\text{-}12}$ for GFF MDI with VHC (LSM = 1538 mL; n = 67) versus without VHC (LSM = 1516 mL; n = 68) was 101.4% (100.1, 102.7). PK parameters were comparable overall with a slightly higher exposure to glycopyrronium with the VHC. The $AUC_{0\text{-}12}$ geometric LSM ratio (90% CI) for GFF MDI with versus without VHC was 115.99% (99.74, 134.89) for glycopyrronium and 96.66% (86.69, 107.78) for formoterol. GFF MDI with and without VHC were well tolerated with a similar adverse event profile.

Conclusions: The magnitude of bronchodilatory effect was similar with and without a VHC following GFF MDI treatment. This, together with the PK and safety profiles, supports the use of the VHC with GFF MDI for the maintenance treatment of COPD, which could be particularly useful for patients who have difficulty with the coordination of an MDI.

Abbreviations: AE, adverse event; ANOVA, analysis of variance; $AUC_{0–12}$, area under the curve from 0 to 12 h; BMI, body mass index; CFC, chlorofluorocarbon; CI, confidence interval; C_{max}, maximum observed plasma concentration; C_{min}, lowest concentration in the dosing interval; COPD, chronic obstructive pulmonary disease; CV, coefficient of variation; FDC, fixed-dose combination; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GFF, glycopyrronium/formoterol fumarate dihydrate; GI, gastrointestinal; HFA, hydrofluoroalkanes; ICS, inhaled corticosteroid; ITT, intent-to-treat; IWRS, Interactive Web-based Response System; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LLQ, lower limit of quantification; LSM, least squares mean; MDI, metered dose inhaler; mITT, modified intent-to-treat; NA, not available; PEFR, peak expiratory flow rate; PK, pharmacokinetics; R, randomization; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event; t_{max}, time to reach maximum observed plasma concentration; VHC, valved holding chamber

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1. Introduction

Spacers are attachments that can be used in combination with metered dose inhalers (MDIs) to reduce difficulties with the coordination of inhaler actuation and inhalation [1], and thereby may improve the therapeutic effect of inhaled medications in patients unable to use a MDI correctly [2]. The use of an MDI with a spacer is particularly recommended for patients who have poor inhalation technique [3], and can result in decreased oropharyngeal deposition and increased lung deposition [1]. Spacer devices were first introduced when MDIs were formulated using chlorofluorocarbons (CFCs) [1,4]. Hydrofluoroalkane (HFA) MDIs generally deliver a less forceful plume than CFC MDIs, which can result in lower drug deposition in the spacer [4]. Valved holding chambers (VHCs) are a type of spacer containing a one-way valve that regulates inspiratory flow. A VHC further reduces the need for coordination of actuation with inhalation by capturing the aerosol and releasing it in a breath-actuated manner [1,5].

The Aerochamber Plus® Flow-Vu® VHC (Trudell Medical International, Ontario, Canada) is a VHC that incorporates an inspiratory flow indicator, allowing visual inhalation feedback during use [6,7]. Studies with the inhaled corticosteroid (ICS) ciclesonide and an ICS/long-acting β_2-agonist (LABA) fixed-dose combination (FDC) of mometasone furoate/formoterol fumarate have shown that drug efficacy and safety were unaffected by the addition of this VHC [8,9]. However, as active compounds delivered by a specific MDI may perform differently when delivered through a spacer, it is recommended that any MDI in development should be tested in combination with a specific spacer to confirm whether or not the spacer affects drug delivery, efficacy, and safety [3].

GFF MDI (Bevespi Aerosphere®), an FDC of the long-acting muscarinic antagonist (LAMA) glycopyrronium and the LABA formoterol fumarate dihydrate delivered by an MDI using innovative co-suspension delivery technology [10,11], has been shown to be efficacious and well tolerated in patients with moderate-to-very severe chronic obstructive pulmonary disease (COPD) in Phase III clinical studies with a duration of up to 52 weeks [12–14]. The co-suspension delivery technology provides consistent dose delivery of GFF MDI *in vitro* even after simulated handling errors [15], and also provides consistent delivery of drug particles throughout the whole lung *in vivo* [16]. GFF MDI is the first LAMA/LABA FDC that is available as an MDI, and has been approved for the long-term maintenance treatment of airflow obstruction in patients with COPD in the USA [17].

This study evaluated the efficacy, pharmacokinetics (PK), and safety of GFF MDI with and without the addition of the Aerochamber Plus Flow-Vu VHC in patients with moderate-to-very severe COPD. The primary objective of this study was to compare the lung function effects of GFF MDI with VHC to GFF MDI without VHC, and the secondary objective was to assess glycopyrronium and formoterol PK parameters following 7 days of dosing with and without VHC.

2. Methods

2.1. Study design

In this randomized, two-period, open-label, chronic-dosing, multicenter Phase III study, patients with moderate-to-very severe COPD received treatment with GFF MDI 14.4/10 μg twice daily (delivered dose), administered as two actuations of the MDI (7.2/5 μg per actuation), both with and without the Aerochamber Plus Flow-Vu VHC for 7 days in crossover fashion. GFF MDI 14.4/10 μg is also known as, and equivalent to, glycopyrrolate/formoterol fumarate 18/9.6 μg. The study was conducted between 8 June 2015 and 22 March 2016 across eight sites in the USA (ClinicalTrials.gov identifier: NCT02454959; Fig. 1). This study was conducted in accordance with Good Clinical Practice, including the International Council on Harmonization guidelines, the US Code of Federal Regulations, and the Declaration of Helsinki. The protocol and the informed consent form were approved by an Institutional Review Board prior to initiation of the study, and written informed consent was obtained from all patients prior to study entry.

Patients were randomized to one of two treatment sequences through an Interactive Web-based Response System (IWRS), receiving 7 days of study treatment with or without the VHC for two separate treatment periods. Study personnel had access to the IWRS to allocate patients and distribute treatments. Washout periods of 7–28 days took place between screening and the first treatment period, and of 7–14 days between the two treatment periods. Patients were required to discontinue any previously prescribed inhaled bronchodilators, and were provided with ipratropium bromide inhalation aerosol administered four times daily as COPD maintenance therapy during the screening and washout periods, as well as albuterol (salbutamol) inhalation aerosol to use as needed for symptom relief. The use of previously prescribed ICS as maintenance therapy was permitted throughout. Patients reported to the study site before 10 a.m. on Day 1 and Day 8 of each treatment period, and were required to stay in the clinic until all protocol-defined assessments had been completed.

2.2. Patient populations

Patients enrolled in this study were 40–80 years of age, with a smoking history of ≥10 pack-years. To be eligible for inclusion, patients were required to have an established clinical history of COPD as defined by American Thoracic Society/European Respiratory Society guidelines [18] with a screening post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio of < 0.70; and a screening post-bronchodilator FEV_1 < 80% of the predicted normal value, and ≥750 mL if < 30% of the predicted normal value (calculated using reference equations from NHANES III, the third National Health and Nutritional Examination Survey). The average of the −60 and −30 min pre-dose FEV_1 assessments on Day 1 of treatment period 1 must also have been < 80% predicted normal value. Additionally, patients needed to have a stable baseline FEV_1, i.e. a baseline FEV_1 on Day 1 of the second treatment period within ± 20% or 200 mL of the pre-dose FEV_1 obtained on Day 1 of the first treatment period. If a patient did not meet this criterion, they may have been rescheduled or discontinued at the Investigator's discretion.

Patients were not eligible for inclusion in this study if they had poorly controlled COPD (defined as acute worsening of COPD that required treatment with oral corticosteroids or antibiotics within 6 weeks prior to or during the screening period), had been hospitalized due to poorly controlled COPD within 3 months prior to or during the screening period, or if they required long-term oxygen therapy for > 12 h/day. Patients with a change in smoking status (i.e. starting or stopping smoking) within 6 weeks prior to or during the screening period were excluded. Patients with poor hand-to-breath coordination were also excluded.

2.3. Assessments

2.3.1. Lung function

The primary efficacy endpoint of this study was FEV_1 area under the curve from 0 to 12 h ($AUC_{0–12}$) on Day 8. Other efficacy endpoints included FVC $AUC_{0–12}$ and peak expiratory flow rate (PEFR) $AUC_{0–12}$ on Day 8; peak change from baseline in FEV_1, FVC, and PEFR on Day 1 and Day 8; and change from baseline in morning pre-dose trough FEV_1, FVC, and PEFR on Day 8.

Spirometry assessments were performed on Day 1 of each treatment period 60 and 30 min prior to dosing, 15 and 30 min post-dose, and 1 and 2 h post-dose. Further spirometry assessments were performed on Day 8 of each treatment period 60 and 30 min prior to dosing, 15 and 30 min post-dose, and 1, 2, 4, 8, 10, 11.5, and 12 h post-dose.