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The bronchodilator effects of extrafine glycopyrronium added to combination treatment with beclometasone dipropionate plus formoterol in COPD: A randomised crossover study (the TRIDENT study)

Dave Singh [a, *], Winfried Schröder-Babo [b], Géraldine Cohuet [c], Annamaria Muraro [d], Françoise Bonnet-Gonod [c], Stefano Petruzzelli [d], Martin Hoffmann [e], Zenon Siergiejko [f], on behalf of the TRIDENT study investigators

[a] University of Manchester, Medicines Evaluation Unit, Manchester, UK
[b] Pulmonology Department, Gelnhausen, Germany
[c] Global Clinical Development, Chiesi S.A., Paris, France
[d] Global Clinical Development, Chiesi Farmaceutici S.p.A., Parma, Italy
[e] Pneumologicum, Practice for Internal Medicine and Pneumology, Hannover, Germany
[f] Respiratory System Diagnostics and Bronchoscopy Department of Medical University in Bialystok, Poland and Private Practice Internal Medicine and Allergology, Bialystok, Poland

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ABSTRACT

This multicentre, double-blind, randomised, placebo-controlled, crossover study aimed to determine the dose-response of the long-acting muscarinic antagonist (LAMA) glycopyrronium bromide (GB) when added to beclometasone dipropionate plus formoterol fumarate (BDP/FF) in patients with COPD.

Patients received extrafine GB 12.5, 25 or 50 μg twice daily (BID) or placebo for 7 days via pressurised metered dose inhaler (pMDI), and extrafine BDP/FF via pMDI throughout the study. The primary objective was to demonstrate superiority of GB plus BDP/FF versus BDP/FF in terms of FEV_1 area under the curve from 0 to 12 h (AUC_{0-12h}) on Day 7. Secondary endpoints included: FEV_1 AUC_{0-12h} on Day 1; peak FEV_1 and FVC on Days 1 and 7; and trough (12 h post-dose) FEV_1, FVC and inspiratory capacity (IC) on Days 1 and 7.

Of 178 patients randomised (mean age 62.7 years, post-bronchodilator FEV_1 48.9%), 172 (96.6%) completed. Mean FEV_1 AUC_{0-12h} on Day 7 was significantly higher ($p < 0.001$) for all GB doses plus BDP/FF compared to BDP/FF alone, with the difference for the 25 and 50 μg BID doses being clinically relevant (i.e., ≥100 mL). The results for the other spirometry endpoints were consistent with the primary endpoint. Adverse events were reported in 7.4, 5.7 and 8.0% of patients receiving GB 12.5, 25 and 50 μg BID, respectively, versus 11.0% of patients receiving BDP/FF alone.

This study confirms the value of adding GB to BDP/FF to improve lung function in COPD patients. The dose of extrafine GB 25 μg BID was associated with the best efficacy/safety profile.

Trial registered at: ClinicalTrials.gov.
Registration number: NCT01476813.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by persistent airflow limitation, with bronchodilators (particularly long-acting) being central to disease management [1]. There are two classes of inhaled long-acting bronchodilators: β_2-agonists (LABAs) and muscarinic antagonists (LAMAs). Long-acting bronchodilators improve lung function, alleviate symptoms, increase exercise performance and reduce exacerbation rates [1,2], and are recommended for use in patients who are symptomatic despite

* Corresponding author.
E-mail address: dsingh@meu.org.uk (D. Singh).

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short acting bronchodilator treatment. Inhaled corticosteroids (ICSs) are used in combination with LABAs in those patients who are at increased risk of exacerbations [1], and such ICS/LABA combinations have been shown to reduce the rate of exacerbations and improve a range of clinically-relevant outcomes compared with ICS or LABA monotherapy [3,4].

Foster® (Chiesi Farmaceutici S.p.A., Parma, Italy) is an extrafine formulation fixed-dose combination (FDC) of the ICS beclometasone dipropionate (BDP) and the LABA formoterol fumarate (FF) delivered via a hydrofluoroalkane (HFA) pressurised metered dose inhaler (pMDI). A 48-week study in COPD patients showed that BDP/FF was superior to FF monotherapy in terms of the rate of exacerbations, lung function and health-related quality of life [4]. Other studies have shown similar clinical benefits with BDP/FF compared to other ICS/LABA FDC commonly used in clinical practice, namely fluticasone propionate/salmeterol and budesonide/formoterol [5,6].

A triple therapy regimen of LABA, LAMA and ICS is a recognised treatment strategy for COPD patients who have a high burden of symptoms and who are at increased risk of exacerbations; these patients are categorised as GOLD category D [1]. In clinical practice it is common for patients with COPD to be 'stepped up' from mono-LAMA or ICS/LABA therapy to such a triple regimen [7], and there is evidence that stepping up treatment in this manner provides significant and clinically important patient benefits such as improved symptoms and reduced exacerbation rates [8,9].

An extrafine formulation of the LAMA glycopyrronium bromide (GB) is in clinical development to be combined with BDP/FF in a single inhaler (a 'fixed triple') for the management of COPD. The aim of this study was to determine the dose-response effects of GB in COPD patients on background BDP/FF treatment. An important aspect of the study design was that we included only patients who were being treated with ICS/LABA FDCs on entry to the study.

2. Materials and methods

2.1. Participants

This was a multicentre, double-blind, randomised, active- and placebo-controlled, 4-way crossover study, that recruited males and females from 40 to 80 years of age, who had a diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document. To be eligible, patients were required to have a post-bronchodilator forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio <0.7, a post-bronchodilator FEV_1 between 30 and 60% of the predicted value, and an increase in FEV_1 of at least 60 mL at 30 min after inhalation of 80 μg ipratropium. All patients were to be receiving an ICS/LABA combination on entry to the study (ICS/LABA plus tiotropium was acceptable providing this was taken for no longer than 1 month prior to study entry; tiotropium was not to be taken from 24 h prior to screening and for the duration of the study). Current or ex-smokers with a smoking history of at least 10 pack-years were eligible.

The key exclusion criteria were: a diagnosis of asthma, or history of allergic rhinitis or atopy; hospitalisation for COPD or pneumonia within 3 months prior to screening; a COPD exacerbation requiring systemic steroids and/or antibiotics in the 4 weeks prior to screening, or during the run-in period; and hypersensitivity to any of the study drugs or excipients. Patients were also excluded if they had clinically significant abnormal electrocardiograms (ECG), QTc (Fridericia's formula) > 450 ms for males or >470 ms for females, clinically significant laboratory abnormalities that could impact the feasibility of the results, or unstable concurrent disease, or required long-term (at least 12 h daily) oxygen therapy for chronic hypoxaemia.

2.2. Trial design

The study was conducted at a mixture of primary, secondary and tertiary care, and specialised research institutions. It comprised four 7-day treatment periods with 7-day washout periods between treatments (Fig. 1). At the screening visit (Visit 1), inclusion and exclusion criteria were checked, with spirometry assessed pre- and 30-min post ipratropium 80 μg. There was a 4-week run-in period between Visits 1 and 2, during which all patients received BDP/FF 100/6 μg, two inhalations (i.e., 200/12 μg) twice daily (BID) via pressurised metered dose inhaler (pMDI). At the baseline visit (Visit 2), after confirming eligibility, patients were randomised equally to one of four treatment sequences. On Day 1 of each treatment period (Visits 2, 4, 6 and 8), pre- and post-dose spirometry (FEV_1, FVC and inspiratory capacity [IC]) were measured (at −45, −10, 15, 30 and 45 min, and 1, 2, 4, 6, 8, 10 and 12 h, and 12 h 30 min). The evening dose of study medication was inhaled after the 12 h 30 min spirometry assessments. On Day 7 of each treatment period (Visits 3, 5, 7 and 9), pre- and post-dose spirometry (FEV_1, FVC and IC) were measured at the same timepoints as Day 1, and also at 14 h, 23 h 30 min and 24 h. As with the Day 1 visit, the evening dose of study medication was inhaled after the 12 h 30 min spirometry assessments, and so the 14 h, 23 h 30 min and 24 h spirometry assessments were therefore effectively obtained at 1 h 30 min, 11 h and 11 h 30 min after the evening dose of medication.

The study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the Independent Ethics Committees or Independent Review Boards at all sites prior to initiation. All patients provided written informed consent at a prescreening visit before any study procedure was performed. There were no amendments to the protocol.

2.3. Interventions

Over the four treatment periods, patients were to receive GB 12.5, 25 and 50 μg BID (i.e., total daily doses of 25, 50 or 100 μg), and matching placebo, delivered via HFA pMDI. All patients also received BDP/FF 200/12 μg BID via HFA pMDI for the duration of the study (including the run-in, treatment and washout periods).

Patients were randomised to one of four treatment sequences using a balanced block randomisation scheme generated by Bilcare Global Clinical Supplies, Phoenixville, PA, USA. Patient numbers were centrally assigned via interactive response technology (voice and/or web), with treatment kits corresponding to the treatment regimen dispensed at the start of each treatment period. All study site personnel and employees of the sponsor (and their representatives) were blinded to treatment, as were the patients.

2.4. Outcomes and assessments

The primary objective was to evaluate the effect of GB 12.5, 25 and 50 μg BID (i.e., total daily doses of 25, 50 and 100 μg) plus BDP/FF compared with BDP/FF alone in terms of FEV_1 time-normalised area under the curve from 0 to 12 h (AUC_{0-12h}) on Day 7. Secondary objectives included the evaluation of GB plus BDP/FF compared with BDP/FF alone in terms of: FEV_1 AUC_{0-12h} on Day 1; peak FEV_1 and FVC on Days 1 and 7; trough FEV_1, FVC and IC at 12 h on Days 1 and 7 (where trough was the mean of the assessments at 12 and 12.5 h post-dose); trough FEV_1, FVC and IC assessed on the morning of Day 8 (the mean of the assessments at 23.5 h and 24 h after the time of dosing on the morning of Day 7); individual timepoint FEV_1, FVC and IC on Days 1 and 7; and rescue medication use across the