Respiratory Medicine 120 (2016) 31–35

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Equivalent bronchodilation with budesonide/formoterol combination via Easyhaler and Turbuhaler in patients with asthma

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ARTICLE INFO

Article history:
Received 20 May 2016
Received in revised form
16 August 2016
Accepted 23 September 2016
Available online 25 September 2016

Keywords:
Easyhaler
Asthma
Bronchodilation
Budesonide
Formoterol
Dry powder inhaler

ABSTRACT

Background: Therapeutic equivalence of Budesonide/formoterol Easyhaler compared to Symbicort Turbuhaler has been previously demonstrated with in vitro and pharmacokinetic studies. This study was performed to confirm equivalent bronchodilator efficacy of the products in asthmatic patients.

Methods: A randomised, single-dose, 4-period crossover study was carried out in a double-blind, double-dummy manner in 11 study sites. The studied doses were 320/9 μg and 1280/36 μg of budesonide/formoterol delivered by Easyhaler and Turbuhaler. Spirometry was performed before and 10 min, 20 min and 1, 2, 3, 4, 6, 8, 10 and 12 h after administration of the study treatments. The primary efficacy endpoint was average 12-h forced expiratory volume in 1 s (FEV_1). The secondary efficacy endpoints were maximum FEV_1 and FEV_1 at 12 h post-dose.

Results: 72 asthma patients with reversible airway obstruction were randomised to receive study treatments. 53 patients completed all study periods according to the protocol and had sufficient data available to calculate the primary endpoint. They were included in the per-protocol analyses. The assay sensitivity of the study was shown as the common slope of average 12-h FEV_1 between doses was 0.063 (95% CI 0.032–0.093) and showed statistical significance ($p < 0.001$). In equivalence testing, the difference in average 12-h FEV_1 between the treatments (Easyhaler-Turbuhaler) was 0.013 l at the lower dose and −0.028 l at the higher dose, and their 95% confidence intervals (CIs) (−0.047 to 0.073 and −0.087 to 0.032, respectively) fell within the range of a clinically non-relevant difference. The results of the secondary efficacy endpoints were in line with the results of the primary endpoint. All treatments were well tolerated.

Conclusions: The results confirm equivalent bronchodilator efficacy of Budesonide/formoterol Easyhaler compared to Symbicort Turbuhaler.

Trial registration: This trial was registered on ClinicalTrials.gov, Identifier: NCT02308098.

1. Introduction

Dry powder inhalers (DPIs) containing the corticosteroid budesonide and the rapid- and long-acting β2-agonist formoterol have been used for several years for maintenance treatment of patients with moderate-to-severe asthma or chronic obstructive pulmonary disease (COPD). In some countries, budesonide/formoterol combination has also been approved for as-needed treatment in addition to regular maintenance therapy because of the rapid onset of dose-dependent bronchodilation with formoterol [1–3]. The bronchodilating effect of the budesonide/formoterol combination inhaler is more rapid than that of the combination inhaler containing salmeterol and fluticasone propionate [4].

The Easyhaler DPI products containing salbutamol, formoterol, beclomethasone dipropionate and budesonide have already been

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http://dx.doi.org/10.1016/j.rmed.2016.09.016

available for many years. Easyhaler is a reservoir type multi-dose DPI designed to be simple and easy for different asthma and COPD patients to use [5]. The appearance of Easyhaler is fairly similar to that of metered dose inhalers (MDIs) but no hand to mouth coordination in synchronizing the actuation and inhalation is required. Compared to Turbuhaler the size of the Easyhaler is quite similar and both inhalers have a dose counter. Where Turbuhaler operation is based on opening, twisting and inhaling, Easyhaler operational sequence is shake, click and inhale. Easyhaler also provides dosing feedback to the patient with the taste of lactose.

Recently, the budesonide/formoterol combination Easyhaler has been developed and introduced to the market in order to complement the Easyhaler product portfolio. The product has the same qualitative composition in terms of active substances and the same pharmaceutical form as the originator product Symbicort® Turbuhaler®. Based on in vitro studies and in vivo pharmacokinetic (PK) studies, Budesonide/formoterol Easyhaler products, 80/4.5, 160/4.5 and 320/9 μg per inhalation, were found to be therapeutically equivalent with the originator products [6–8].

In this study, we sought to confirm equivalent bronchodilator efficacy of budesonide/formoterol combination delivered via Easyhaler and Turbuhaler by testing the products at two dose levels in stable but less than optimally controlled patients with asthma.

2. Methods

2.1. Patients

Asthmatic male and female patients aged 18–70 years were recruited to the study in Bulgaria and Hungary between December 2014 and May 2015. The patients were eligible for inclusion if they had asthma diagnosed in accordance with recommendations provided by the Global Initiative for Asthma [9] for at least 6 months and if their asthma had been stable with the same regular treatment (e.g. inhaled corticosteroid) for at least 4 weeks prior to screening. Prebronchodilator forced expiratory volume in 1 s (FEV_1) of the patients had to be 45–90% of the predicted value based on GLI-2012 reference values [10] and they had to demonstrate reversible airway function with increase of at least 12% and 200 ml in FEV_1 after inhalation of short-acting β2-agonist (SABA). In addition, eligible patients showed step-wise reversibility of airway function with formoterol [11].

The key exclusion criteria were respiratory infection within 4 weeks prior to the screening visit, abnormal serum potassium value, current smoking and smoking history of more than 10 pack-years. Corticosteroids other than inhaled corticosteroids, long-acting β2-agonists (LABAs), xanthine derivatives, and β-blockers were not allowed within 4 weeks prior to the screening.

To assure stable asthma throughout the study, the pre-dose (baseline) FEV_1 on study treatment day was not to differ more than 12% compared to the screening prebronchodilator FEV_1.

The study was conducted in compliance with the protocol, ICH-GCP guidelines and the applicable local regulatory requirements. The study was approved by the central ethics committees of Bulgaria and Hungary. All patients provided written informed consent to take part in the study.

2.2. Study design

The study was a randomised, single-dose, 4-period crossover study carried out in a double-blind, double-dummy manner. Patients were randomised before first study drug administration to receive all 4 study treatments in random order with 3–14 days wash-out between the administrations. The randomisation was performed according to 4-treatment 4-period William's design.

The study treatments were 1 and 4 inhalation(s) of Budesonide/formoterol Easyhaler® 320/9 μg/inhalation (Orion Pharma, Finland) and Symbicort® Turbuhaler® 320/9 μg/inhalation (AstraZeneca, UK); the formoterol doses were 9 μg and 36 μg. Corresponding number of placebo inhalation(s) were given from Easyhaler or Turbuhaler. The study treatment administrations took place at the study centres and the trained staff instructed the patients on correct inhalation technique, which was practised with placebo inhalers.

During the study, the patients continued the use of their regular asthma medication with a constant dose. Inhaled SABA and anticholinergics, oral sympathomimetics, cough medicines containing salbutamol or ephedrine, and pseudoephedrine-containing antihistamines were not allowed before spirometry. If additional bronchodilating relief was needed during a study treatment day, salbutamol inhalation aerosol was given as a rescue medication.

Serial spirometry was performed up to 12 h after dosing using a KoKo® spirometer in combination with eSP™ Spirometry Systems (nSpire Health, US). Lung function tests were performed using current joint ERS/ATS spirometry recommendations [12] and were quality controlled centrally. At least 3 successive manoeuvres at baseline and at least 2 successive manoeuvres after the study treatment administration at each time point were performed. Up to 5 manoeuvres were carried out per time point and the highest acceptable FEV_1 value was used for analysis.

The safety of the study drugs was evaluated based on adverse events (AEs). Other safety assessments consisting of physical examination, vital signs, electrocardiogram [ECG] and laboratory tests were carried out at screening and end-of-study visits.

2.3. Endpoints

Spirometry was performed before and 10 min, 20 min and 1, 2, 3, 4, 6, 8, 10 and 12 h after administration of the study treatment. The primary efficacy endpoint was the average 12-h FEV_1 determined from serial spirometry and calculated on the basis of area under curve (AUC) of FEV_1 (AUC divided by observation time). Single missing FEV_1 values were imputed by weighted mean of FEV_1 values right before and after the missing value. Missing baseline FEV_1 values could not be estimated. The secondary efficacy endpoints were maximum FEV_1 over the 12-h serial assessments and FEV_1 at 12 h post-dose (i.e. FEV_1 at the trough of the effect).

The number of patients using rescue medication during each study treatment day was recorded. AEs were collected and reported per study treatment. Changes in physical examination, vital signs, ECG and laboratory tests between screening and end-of-study were evaluated.

2.4. Statistics

The sample size calculation was based on showing the higher dose to be statistically significantly superior to the lower dose. Significance level was 0.05, average 12-h FEV_1 for the higher dose was assumed to be 3.33% higher than for the lower dose, and power was 80%. The sample size calculation resulted in 72 patients.

In primary efficacy analyses (per-protocol [PP] analyses) only the patients who completed all 4 study periods without protocol violations and without the use of rescue medication, were included. Intention-to-treat (ITT) analyses included all patients who had data from at least one period.

Firstly, it was tested with the common slope model if the average 12-h FEV_1 is the same for both of the doses [13]. It was tested if the slope of log of dose is statistically significantly different from zero, i.e. if the study is sensitive enough to separate the doses from each other. Secondly, the equivalence of study treatments