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Initial assessment of single and repeat doses of inhaled umeclidinium in patients with chronic obstructive pulmonary disease: Two randomised studies

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ABSTRACT

To characterise the safety, tolerability, pharmacodynamics (bronchodilatory effect) and pharmacokinetics of inhaled umeclidinium in patients with chronic obstructive pulmonary disease (COPD).

The first investigation was a single dose, randomised, double-blind, placebo-controlled study (clinicaltrials.gov: NCT00515502) in which ipratropium bromide-sensitive patients received umeclidinium (250 μg, 500 μg, and 1000 μg), tiotropium bromide 18 μg or placebo. Patients were randomised to receive four out of five possible treatments as an incomplete block four-way cross-over. A subsequent study (clinicaltrials.gov: NCT700732472) was focused on assessment of safety, tolerability and pharmacokinetics of umeclidinium (250 μg and 1000 μg) administered once-daily for 7 days in a randomised, double-blind, placebo-controlled, parallel-group design.

Of the 24 patients randomised for the single dose study, 20 completed; 31 out of 38 patients completed the repeat dose study. Most adverse events were mild-to-moderate and transient. Examination of heart rate, QTc interval, blood pressure and clinical laboratory assessments raised no concern over the safety of umeclidinium. Evidence of pharmacology was demonstrated in first study by statistically significant increases in specific airway conductance (sGaw) for up to 24 h for all active treatments compared with placebo. Increases in forced expiratory volume in 1 s were also observed. Pharmacokinetic analysis demonstrated that maximum observed plasma umeclidinium concentration (C_{max}) was reached rapidly (time to C_{max}: ~5–15 min) after single and repeat doses; 1.5–1.9-fold accumulation was observed after repeat-dosing.

Single and repeat doses of umeclidinium were well tolerated and produced clinically relevant lung function improvements over 24 h in patients with COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterised by increasing airflow obstruction that places a significant burden on a patient's quality of life. Chronic obstructive pulmonary disease is often associated with diabetes and co-morbid cardiovascular illnesses, such as ischaemic heart disease, hypertension and arrhythmias (Sin and Man, 2005; Halpin, 2008). Given the progressive nature of COPD, additional targeted pharmacological therapies are required that provide symptom control and broaden treatment options for clinicians and patients.

The blockade of acetylcholine muscarinic receptors (M_1, M_2 and M_3) is an established mechanism for the treatment of COPD as these receptors play an important role in maintenance of airway tone, mucus secretion and regulation of release of acetylcholine (Eglen et al., 1996). The long acting muscarinic receptor antagonist tiotropium bromide is known to provide a bronchodilator effect in COPD patients which lasts over 24 h. Its therapeutic index is considered acceptable because it dissociates more slowly from the M_1 and M_3 receptors, which are located in the smooth muscle of the airways, than from the M_2 receptor, which is located in the heart (Haddad et al., 1994; Barr et al., 2005).

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Blockade of the cardiac M_2 receptor can result in tachycardia, which is a reported adverse effect associated with antimuscarinic agents (DiFrancesco et al., 1989; Kesten et al., 2006). Umeclidinium (GSK573719) is a potent long acting muscarinic receptor antagonist in development for the treatment of COPD. *In vitro*, umeclidinium demonstrated slow reversibility at the M_3 receptor; *in vivo*, umeclidinium displayed a long duration of action when administered directly to the lungs in pre-clinical models (Lainé et al., 2011). Single doses of umeclidinium administered to healthy volunteers responsive to an inhaled short acting anticholinergic (ipratropium bromide) were well tolerated, and had a sustained duration of action up to 24 h as demonstrated by increases in specific airway conductance (sGaw) and forced expiratory volume (FEV_1) in 1 s relative to placebo (Cahn et al., 2011). The pharmacokinetic and tolerability profiles were confirmed in a repeat dose study in healthy volunteers (Mehta et al., 2011). The efficacy of umeclidinium as a bronchodilator in a 14-day dose ranging study in COPD patients was recently reported (Donohue et al., 2012). This study showed that once-daily dosing with umeclidinium provided clinically significant and sustained improvements in lung function over 24 h with similar efficacy to twice-daily dosing (Donohue et al., 2012). These results are supported by another study in 285 COPD patients who received umeclidinium once-daily during 28 days (Decramer et al., 2013). In this report, we describe the results of two early phase studies with umeclidinium that aimed to assess its potential as a treatment for COPD by investigating the safety, tolerability, pharmacokinetics and pharmacodynamics (defined as 24-h bronchodilator effect) of umeclidinium administered in two different devices: the Diskus® and a novel proprietary device.

2. Methods

2.1. Single dose study (GlaxoSmithKline protocol: AC4108123; NCT#00515502)

This was a multicentre, randomised, double-blind, placebo-controlled, double-dummy, dose-ascending, crossover study conducted from 11 June to 6 November 2007 at three centres in Germany. Twenty-four COPD patients were randomised to receive four of the following five treatments: umeclidinium (250 μg, 500 μg and 1000 μg), tiotropium bromide 18 μg (as a positive control) or placebo. Patients were randomised as an incomplete block four-way cross-over. Patients received a unique randomisation number and were assigned to each treatment using the randomisation schedule provided by GlaxoSmithKline. Each single dose treatment period was separated by a washout of at least 14 days and a follow-up visit occurred within 10 days after the last treatment period.

2.2. Repeat dose study (GlaxoSmithKline protocol: AC4105211; NCT#00732472)

This was a multicentre, randomised, dose-ascending, double-blind, placebo-controlled, parallel group study with three cohorts conducted from 20 October 2008 to 10 August 2009 at seven centres in the United Kingdom. The study was originally planned as a two-cohort study with Cohort I scheduled to receive umeclidinium 250 μg and Cohort II scheduled to receive 1000 μg. A dosing error occurred and the cohort that was planned to receive 1000 μg received 250 μg. As both cohorts received 250 μg, a third cohort was recruited to receive umeclidinium 1000 μg. Each cohort consisted of 12 patients randomised to receive active treatment ($n=9$) or placebo ($n=3$) once-daily for 7 days. Patients received a unique randomisation number and were assigned to treatment as above. A follow-up assessment was completed at least 5 days after the last dose of study medication. Lung function (FEV_1) was only assessed as a safety measurement at single time-points to check for paradoxical bronchospasm; assessments were performed at screening, Day 1 and Day 7 from pre-dose to 4 h post-dose, and at follow-up.

2.3. Population

Male and female patients diagnosed with moderate to severe COPD (defined at that time using Global Initiative for Chronic Obstructive Lung Disease criteria (GOLD, 2007), with a $FEV_1 \geq 40\%$ and $\leq 80\%$ of predicted normal following inhalation of salbutamol 400 μg and a FEV_1/forced vital capacity ratio of ≤ 0.7 at screening, aged 40–75 years, current or ex-smokers with at least a 10 pack year history and a body mass index of 18.0–32.0 kg/m^{2}were eligible to enrol in these studies. For safety purposes, a lower limit for predicted FEV_1 of 40% was chosen. In the single dose study, patients were eligible if they demonstrated reversibility to anticholinergics as defined by an increase in sGaw $\geq 25\%$ compared with pre-dose 2 h after inhalation of ipratropium bromide 80 μg (Borrill et al., 2008) at or within 3 months of screening.

Key exclusion criteria for both studies included diagnosis of lung cancer, clinically overt bronchiectasis, allergic rhinitis or asthma, poorly controlled COPD, participation in a pulmonary rehabilitation programme, respiratory tract infection within 4 weeks of screening, current congestive heart failure, elevated resting blood pressure, mean heart rate outside 50–100 bpm or a history of clinically significant cardiac arrhythmia. With the exception of the third cohort in the repeat dose study, those with a CYP2D6 poor metaboliser genotype as defined by a genetic screen were excluded. Genotyping was determined using the extensive CYP2D6 polymorphism panel contained on the Roche AmpliChip CYP450 test. This test identifies 26 possible polymorphisms on each of the two alleles. Patients were not permitted to take medications known to be CYP2D6 inhibitors or substrates.

Patients could continue regular inhaled steroid medication if required but other medications for COPD were stopped for the duration of the study. If patients were taking inhaled steroid/long-acting bronchodilator combination treatments, the long-acting bronchodilator component was stopped. In both studies, patients experiencing an exacerbation requiring oral corticosteroids during either study were withdrawn.

2.4. Ethics

All patients provided signed informed consent prior to screening and subsequent amendments were approved by Local and Regional Ethics Review Committees; the studies were conducted in accordance with Good Clinical Practice and the guiding principles of the Declaration of Helsinki (World Medical Association, 2011).

2.5. Inhalers

In the single dose study, umeclidinium and matching placebo were administered using a Diskus/Accuhaler® (GlaxoSmithKline, Ware, United Kingdom) dry powder inhaler in a lactose and cellobiose octaacetate (1%) formulation. Tiotropium and tiotropium placebo were administered using a Handihaler® (Boehringer Ingelheim, Bracknell, United Kingdom) dry powder inhaler. Due to feasibility, the tiotropium arm was single-blinded. In the repeat dose study, umeclidinium was administered as a 0.4% magnesium