Pulmonary Pharmacology & Therapeutics 29 (2014) 49–57

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

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

# A randomized, placebo- and moxifloxacin-controlled thorough QT study of umeclidinium monotherapy and umeclidinium/vilanterol combination in healthy subjects

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ARTICLE INFO

*Article history:*
Received 3 December 2013
Received in revised form
24 June 2014
Accepted 6 July 2014
Available online 12 July 2014

*Keywords:*
Chronic obstructive pulmonary disease
GSK573719
QT interval
Umeclidinium
Vilanterol

ABSTRACT

*Introduction:* The long-acting muscarinic antagonist umeclidinium (UMEC) and the combination of UMEC with the long-acting beta$_2$ agonist vilanterol (VI) are approved maintenance treatments for chronic obstructive pulmonary disease in the US and EU.
*Objectives:* This study investigated the effect of UMEC and UMEC/VI on the QT interval corrected using Fridericia's correction (QTcF) following a 10-day treatment period.
*Methods:* Randomized, placebo- and moxifloxacin-controlled, 4-period incomplete block crossover study of healthy non-smokers ($n$ = 103). All treatments were double blind, except for moxifloxacin/moxifloxacin placebo controls which were single blinded. Subjects were randomized to a treatment sequence which consisted of 4 of 5 regimens. Each regimen consisted of once-daily doses on Days 1–10 via the ELLIPTA™ dry powder inhaler and a single tablet on Day 10 of the following: placebo + placebo; placebo + moxifloxacin; UMEC 500 μg + placebo; UMEC/VI 125/25 μg (delivered dose: 113/22 μg) + placebo; UMEC/VI 500/100 μg + placebo. QT interval, additional cardiac parameters, pharmacokinetics, pharmacodynamics and safety were assessed.
*Results:* No clinically significant changes from baseline in QTcF occurred with UMEC 500 μg and UMEC/VI 125/25 μg compared with placebo, however, there was a change in QTcF from baseline of 6.4 ms (90% confidence interval [CI]: 4.3, 8.5) at 10 min and 8.2 ms (90%: 6.2, 10.2) at 30 min post dose following UMEC/VI 500/100 μg compared with placebo. On Day 10, categorical analysis demonstrated absolute QTcF values >450–480 ms for UMEC/VI 125/25 μg (1 subject) and moxifloxacin (3 subjects), and a change from baseline QTcF of >30–60 ms for UMEC/VI 125/25 μg, UMEC 500/100 μg and placebo (1 subject each) and moxifloxacin (2 subjects). On Day 10, the mean change from baseline in heart rate was increased with UMEC/VI 125/25 μg and UMEC 500/100 μg compared with placebo with the maximum increase occurring at 10 min post dose (8.4 bpm [90% CI: 7.0, 9.8] for UMEC/VI 125/25 μg; 20.3 bpm [90% CI: 18.9, 21.7] for UMEC/VI 500/100 μg); after this timepoint, heart rate rapidly returned to normal levels. UMEC and VI systemic exposures following UMEC/VI 500/100 μg were >4-fold higher than those following UMEC/VI 125/25 μg. All treatments were generally well tolerated in terms of adverse events, laboratory, vital signs and electrocardiogram data; the proportion of subjects with any adverse event was similar across treatments arms (39–59%)..
*Conclusion:* There was no clinically significant effect on QTcF observed following 10-days' treatment with inhaled UMEC/VI 125/25 μg or UMEC 500 μg compared with placebo. The supratherapeutic dose of UMEC/VI 500/100 μg prolonged QTcF by 6.4 ms (90% CI: 4.3, 8.5) at 10 min and 8.2 ms (90% CI: 6.2, 10.2) at 30 min compared with placebo, following which QTcF interval difference from placebo declined rapidly..
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## 1. Introduction

Certain non-antiarrhythmic drugs have been associated with 'QT liability' – the potential to prolong the QT interval of the

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http://dx.doi.org/10.1016/j.pupt.2014.07.002
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**Abbreviations**

| | |
|---|---|
| AE | adverse events |
| $AUC_{(0-\tau)}$ | area under the concentration-time curve over the dosing interval |
| bpm | beats per minutes |
| CI | confidence interval |
| CL/F | oral clearance |
| $C_{max}$ | maximum observed plasma concentration |
| COPD | chronic obstructive pulmonary disease |
| CVb | between-subject coefficient of variation |
| ECG | electrocardiogram |
| FDA | Food and Drug Administration |
| FF | fluticasone furoate |
| hERG | human ether A-Go-Go-related gene |
| HR | heart rate |
| $IC_{50}$ | half-maximal inhibitory concentration |
| LABA | long-acting $beta_2$ agonists |
| LAMA | long-acting muscarinic antagonists |
| Moxi | moxifloxacin |
| PK | pharmacokinetic |
| QTcB | QT interval corrected for HR using Bazett's formula |
| QTcF | QT interval corrected using Fridericia's correction |
| QTcI | QT interval corrected for heart rate of the individual subject |
| $t_{½}$ | terminal phase half life |
| TdP | Torsades de Pointes |
| $t_{max}$ | time to $C_{max}$ |
| UMEC/VI | umeclidinium/vilanterol |
| UMEC | umeclidinium |
| VI | vilanterol |

electrocardiogram (ECG) and cause cardiac arrhythmias [1]. This prolongation is due to the delayed ventricular repolarization primarily caused by blocking human ether a-go-go-related gene (hERG) potassium channels [2]. Torsades de pointes (TdP) is a potentially fatal ventricular tachyarrhythmia that can be triggered following a prolonged QT interval. QT prolongation with or without TdP, along with hepatotoxicity, have accounted for >60% of drug withdrawals from major markets over the past 2 decades [3]. In addition, upwards of 60% of new molecular entities are discontinued early in the developmental process due to positive hERG assays. As such, regulatory agencies have mandated thorough QT studies for all non-cardiac entities in development even when their anticipated indication is not cardiovascular or anti-arrhythmic in nature [4,5].

Long-acting muscarinic antagonists (LAMAs) and long-acting $beta_2$ agonists (LABAs) are currently recommended as maintenance bronchodilator therapy for chronic obstructive pulmonary disease (COPD) [6]. Combination therapy with bronchodilators of different drug classes may be beneficial over monotherapy alone in the treatment of COPD [6–8].

The LAMA umeclidinium (GSK573719; UMEC) as an inhaled monotherapy [9–13] and in combination with the LABA vilanterol (GW642444, VI) [14,15] are approved maintenance treatments for COPD in the US and EU; they are not indicated for the treatment of asthma. VI in combination with the inhaled corticosteroid fluticasone furoate (FF) is approved in the United States and European Union for long-term, once-daily maintenance treatment of airflow obstruction and for reducing exacerbations in patients with COPD [16].

A QT study of the FF/VI combination demonstrated no prolongation of the QT interval corrected using Fridericia's correction (QTcF) or QT interval corrected for heart rate of the individual subject (QTcI) at a dose of 200/25 μg [17]. However, at a supratherapeutic dose (800/100 μg), there was a brief transient prolongation of time-matched QTcF, while QTcI was not prolonged. In the supportive study of FF alone, no prolongation of the QT interval was demonstrated at a supratherapeutic dose of FF (4000 μg). Thus, the brief transient increase observed with the FF/VI combination (800/100 μg) is likely attributed to the supratherapeutic dose of VI in the combination.

*In vitro* receptor binding studies in human embryonic kidney 293 cells showed that UMEC inhibited the hERG channel tail current in a concentration dependent manner, with a half-maximal inhibitory concentration ($IC_{50}$) of 9.4 μM [18]. A population pharmacokinetic model predicted the UMEC maximum plasma concentration ($C_{max}$) geometric mean (95% confidence interval [CI]) to be 68.5 (65.2–71.9) pg/mL (i.e. 0.135 nM) in a phase III clinical study in patients with COPD treated with UMEC/VI at the therapeutic dose of 62.5/25 μg [19]; which is several orders of magnitude lower than the in-vitro UMEC $IC_{50}$ of hERG channel tail current. Although QT prolongation is typically linked to inhibition of the hERG potassium channel in the heart and not believed to be related to blockade of muscarinic receptors, these findings along with the Food and Drug Administration (FDA) requirement for all new non-cardiac entities [5], warranted further QT studies of UMEC and UMEC/VI in humans. No preclinical QT prolongation studies were conducted with the combination UMEC/VI.

Previous clinical studies of UMEC (15.6–1000 μg once daily or 15.6–250 μg twice daily) and UMEC/VI (500/25 μg to 500/50 μg) in healthy subjects [15] and patients with COPD [10–12,14] demonstrated no clinically significant 12-lead ECG or 24-h Holter ECG abnormalities or significant episodes of arrhythmia. Although there were some minor elevations in heart rate (HR) and ECG parameters, these findings were not considered clinically relevant.

The aim of the current study was to investigate the effect of UMEC monotherapy and UMEC/VI combination therapy on the QTcF interval. UMEC was assessed at a supratherapeutic dose (500 μg) and the UMEC/VI combination was assessed at the higher nominal UMEC dose of the 2 doses investigated in phase III clinical studies (125/25 μg) and at a supratherapeutic dose (500/100 μg; representing 4 times the dose of the individual components). The approved therapeutic dose of UMEC/VI worldwide is 62.5/25 μg nominal dose, the lower of the 2 UMEC doses investigated in the phase III trials. Moxifloxacin was included as a positive control due to its established effects on QTc prolongation [20] Preliminary results have been presented at the American Thoracic Society annual meeting [21]. The study design was externally reviewed by the United States FDA inter-department QT-study review panel, and the study was conducted in accordance with the International Conference on Harmonization [4,5].

## 2. Methods

### 2.1. Subjects

Eligible male and female subjects were healthy non-smokers, aged 18–65 years, with body weight ≥45 kg and a body mass index of 18–29.5 $kg/m^2$. Subjects had no significant abnormalities on 12-lead ECG or 24-h Holter ECG and had normal spirometry. Subjects were excluded if they had a family history of QT prolongation, early or sudden cardiac death or early cardiovascular disease, or a history of symptomatic arrhythmias.

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