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Pneumonia risk with inhaled fluticasone furoate and vilanterol in COPD patients with moderate airflow limitation: The SUMMIT trial

Courtney Crim [a, *], Peter M.A. Calverley [b], Julie A. Anderson [c], Andrew P. Holmes [d], Sally Kilbride [c], Fernando J. Martinez [e], Robert D. Brook [f], David E. Newby [g], Julie C. Yates [a], Bartolomé R. Celli [h], Jørgen Vestbo [i], on behalf of the SUMMIT investigators

[a] GlaxoSmithKline, Research Triangle Park, USA
[b] University Hospital Aintree, Liverpool, UK
[c] GSK R&D, Stockley Park, UK
[d] Veramed Limited, Twickenham, UK
[e] NewYork-Presbyterian Hospital/Weill Cornell Medical Center, New York, USA
[f] University of Michigan Health System, Ann Arbor, USA
[g] University of Edinburgh, Edinburgh, UK
[h] Brigham and Women's Hospital, Harvard Medical School, Boston, USA
[i] University of Manchester and University Hospital South Manchester NHS Foundation Trust, Manchester, UK

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ABSTRACT

Rationale: Pneumonia risk with inhaled corticosteroid use in chronic obstructive pulmonary disease (COPD) has not been thoroughly assessed in patients with moderate airflow limitation.
Objectives: To determine the incidence of pneumonia and risk factors in COPD patients with moderate airflow limitation who had, or were at high risk for cardiovascular disease.
Methods: In the Study to Understand Mortality and MorbidITy in COPD (SUMMIT), 16,590 subjects with moderate airflow limitation (50% $\leq$ FEV_1 $\leq$ 70% predicted) and heightened cardiovascular risk were randomized double-blind 1:1:1:1 to inhaled once-daily vilanterol 25 μg (VI), fluticasone furoate 100 μg (FF), vilanterol 25 μg combined with 100 μg fluticasone furoate (FF/VI), or matched placebo. In a pre-specified analysis, we assessed investigator-reported adverse pneumonia events, and independently-adjudicated fatal events.
Measurements and main results: The safety population comprised 16,568 subjects who actually received study medication. There were 1017 pneumonia events reported from 842 subjects. For placebo, FF, VI and FF/VI, reported pneumonia incidence was 5%, 5%, 4% and 6%, respectively. When adjusted for time on treatment, event rates were similar in the placebo, FF and FF/VI containing arms (3.84, 4.24 and 3.95/100 treatment years, respectively) but lower in the VI group (2.77/100 treatment years). Risk factors for pneumonia risk included: greater degree of airflow limitation (i.e. FEV_1 <60% predicted), prior exacerbation history, and BMI <25 kg/m^2.
Conclusions: In contrast to previous studies in patients with severe disease, increased pneumonia risk with inhaled corticosteroid use was not evident in COPD subjects with moderate airflow limitation and heightened cardiovascular risk.

According to the World Health Organization in 2014, lower respiratory tract infections and chronic obstructive pulmonary disease (COPD) represented the third and fourth leading causes of death worldwide [1]. Furthermore, COPD itself is a known risk factor for pneumonia [2,3]. We and others have previously reported that the chronic use of inhaled corticosteroid (ICS)-containing regimens further increase adverse events of pneumonia in COPD patients [4–7] and both the United States Food and Drug Administration and European Medicines Agency require labeling of such products to highlight this risk [8–10].

Mechanisms to explain this increased pneumonia risk in COPD

* Corresponding author. Respiratory Therapeutic Area Unit, GlaxoSmithKline, Five Moore Dr., 5.3317.3A, Research Triangle Park, NC 27709-3398, USA.
E-mail address: Courtney.c.crim@gsk.com (C. Crim).

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patients are unclear but are undoubtedly multifactorial. In addition to impaired mucociliary clearance of inhaled pathogens, potential mechanisms are likely to be in part related to recognized defects in both innate and acquired immunity [11–17]. A history of COPD exacerbations is not only an additional risk factor for pneumonia, possibly related to the acquisition of new strains of bacteria [18], but such exacerbation-prone individuals might also have impaired innate immunity. For example, Berenson and colleagues reported that compared with those without prior recent exacerbations, alveolar macrophages recovered from exacerbation-prone COPD subjects elicited a lower cytokine (e.g. interleukin (IL)-8, tumor necrosis factor (TNF)-α) response in the presence of *H. influenzae, M. catarrhalis* and *S. pneumoniae* when induced with Toll-like receptor (TLR)-2 and TLR4 ligands [13]. Furthermore, although the induction of TLR4 on alveolar macrophages did not differ between exacerbation-prone and non-exacerbators following exposure to any of these bacteria, TLR2 expression following exposure to *M. catarrhalis* and *S. pneumoniae* was reduced [13].

Severe airflow limitation appears to increase pneumonia risk in COPD patients [4,7]. However, in our report with the ICS/long-acting beta-2-agonist (LABA) regimen of fluticasone furoate/vilanterol (FF/VI) in an exacerbating COPD population, we were unable to demonstrate an increased pneumonia risk in the subgroup of subjects with an FEV_1 $\geq$50% of predicted [7]. The Study to Understand Mortality and MorbidITy in COPD (SUMMIT) investigated whether FF/VI could improve survival in patients with moderate COPD who had, or were at high risk for, cardiovascular disease (CVD) [19,20]. The risk of pneumonia in these patients with COPD and moderate airflow limitation receiving FF, VI, or the combination was assessed as a safety endpoint in SUMMIT. In the pre-specified analysis reported here, we investigated the hypothesis that in this population, the incidence of pneumonia with an FF-containing treatment regimen would not be increased compared with placebo.

1. Methods

1.1. Study design and subjects

This was a pre-specified analysis of the SUMMIT trial, for which the design and primary result have been previously published [19,20]. Briefly, in this prospective, double-blind, parallel-group, placebo-controlled, event-driven trial, subjects were randomized to receive one of the following (once daily) from the ELLIPTA™ dry powder inhaler (GSK, UK; ELLIPTA is a trademark of the GSK group of companies): FF/VI 100/25 μg, FF 100 μg, VI 25 μg, or placebo. All treatment groups were allowed to continue short-acting bronchodilators and/or theophylline; use of inhaled corticosteroids and long-acting bronchodilators was discontinued at least 48 h before study entry. Participants were current or former smokers aged 40–80 years, with a diagnosis of COPD and a post-bronchodilator FEV_1 $\geq$50 and $\leq$70% of the predicted value, a post-bronchodilator FEV_1/forced vital capacity $\leq$0.70, and $\geq$2 on the modified Medical Research Council dyspnea scale.

At screening, eligible subjects were required to have a history of CVD (coronary artery disease, peripheral arterial disease, prior stroke or myocardial infarction, or diabetes mellitus with target organ disease) or increased cardiovascular risk ($\geq$60 years and receiving medications for $\geq$2 of the following: hypercholesterolemia, hypertension, diabetes mellitus, or peripheral vascular disease). For the assessment of the primary endpoint of all-cause mortality for the comparison of FF/VI 100/25 μg with placebo, this event-driven study concluded at a common end date when approximately 1000 deaths were predicted to have occurred. Secondary objectives evaluated the effect of FF/VI compared with placebo on the rate of FEV_1 decline, and the effect of FF/VI compared with placebo on a cardiovascular composite endpoint comprised of on-treatment CV death, myocardial infarction, stroke, unstable angina and transient ischemic attack (TIA). COPD exacerbations were collected as an efficacy endpoint. The risk of pneumonia in the active treatment arms was assessed as a safety endpoint of special interest and included on-treatment events reported after the common end date until closure of the site.

1.2. Pneumonia adverse events (AEs) and serious AEs

There was no *a priori* definition of pneumonia, nor were chest x-rays, sputum cultures or laboratory evaluations required to confirm the clinical diagnosis. Pneumonia as an adverse event (AE) or serious AE (SAE) was reported by the investigator using available clinical information and coded using the Medical Dictionary for Regulatory Activities (MedDRA® Version 18.0; International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), Geneva, Switzerland). All MedDRA preferred terms that could relate to pneumonia (see Table E1 in the online supplement) were counted to provide a more complete assessment of all physician-reported pneumonias (defined as pneumonia AE of special interest, AESI).

All deaths were categorized by an independent clinical endpoints committee (CEC), blind to treatment allocation, based on additional source documents (e.g. medical records, chest x-rays, autopsy reports, death certificates) regardless of the investigator-reported fatal SAE term [21]. Fatal pneumonia events reported by the investigator were those present at the time of death; fatal pneumonia events adjudicated by the CEC were those deemed to be the actual cause of death regardless of the reported AE term. The CEC adjudicated deaths therefore provided a consistent classification of deaths across the study.

1.3. Statistical analysis

Subjects were included in the analysis if they took at least one dose of study medication and analyzed according to the treatment they took for the majority of the treatment period. Apart from one subject, this was the treatment to which they were randomized. Pneumonia and COPD exacerbations were included in the analysis if they started between treatment start and the day after treatment stop date, inclusive. Deaths were considered on-treatment if they occurred between treatment start and seven days after treatment stop date, inclusive. The number and proportion of subjects who were reported as having any of the above grouped pneumonia terms as an AE or SAE was summarized by treatment group. Due to differential treatment exposure between the treatment groups, the rate of pneumonia events per 100 treatment-years was calculated by dividing the number of AEs by the number of years subjects were exposed to study treatment, then multiplying by 100.

The time to first pneumonia and time to first composite of pneumonia or moderate/severe COPD exacerbation was compared between treatment groups using Kaplan–Meier estimates and the Cox Proportional Hazards model (PH) including covariates of age and gender; for the analysis of the composite endpoint a covariate of previous exacerbations (exacerbations in the year prior to the study as 0, 1, $\geq$2) was also included. This was repeated for time to serious pneumonia and the composite of serious pneumonia or severe COPD exacerbation. Kaplan–Meier cumulative incidence curves were also produced. A similar Cox PH analysis was performed *post-hoc* for the on-treatment deaths adjudicated as pneumonia accounting for the non-pneumonia deaths as competing risks. The numbers of subjects who died within 30 days of their last on-treatment pneumonia were summarized by treatment group.