Effect of roflumilast in patients with severe COPD and a history of hospitalisation

To the Editor:

Exacerbations of chronic obstructive pulmonary disease (COPD) are acute events characterised by a worsening of respiratory symptoms that necessitates a change in medication and/or hospital admission [1]. Severe exacerbations (those resulting in hospitalisation and/or death) are associated with a poor prognosis [2], decreased quality of life [3] and higher mortality [2, 4]. Roflumilast is a once-daily, oral, selective phosphodiesterase-4 inhibitor that targets both the systemic and pulmonary inflammation associated with COPD [5]. Previous studies have shown that roflumilast as an add-on to inhaled therapies reduces COPD exacerbations in patients with severe COPD who have chronic bronchitis and a history of exacerbations [6–9]. However, the adverse events associated with systemic therapies such as roflumilast necessitate that these therapies are used to treat specific patient populations in whom they are likely to have the greatest clinical benefit [10].

Recently, the REACT study investigated the effects of roflumilast in a well-defined patient population with severe COPD who experienced exacerbations despite treatment with inhaled corticosteroid/long-acting β_2 -agonist±long-acting muscarinic antagonist (ICS/LABA±LAMA) [11]. The detailed methodology for REACT has been published previously [11]. In brief, it was a double-blind, placebo-controlled, multinational study that included patients with severe airflow limitation (confirmed by a post-bronchodilator forced expiratory volume in 1 s (FEV₁)/forced vital capacity ratio <0.70 and a post-bronchodilator FEV₁ ≤50% predicted), symptoms of chronic bronchitis and a history of at least two exacerbations in the previous year. Patients were randomised (1:1) to receive once-daily roflumilast 500 µg or placebo for 52 weeks, added to ICS/LABA±LAMA (70% of patients used concomitant LAMA).

The primary end-point was the rate of moderate (treated with systemic steroids) or severe (leading to hospitalisation/death) COPD exacerbations per patient per year. When analysed by Poisson regression, the frequency of moderate or severe exacerbations was 13.2% numerically lower in the roflumilast group *versus* placebo, but did not reach statistical significance (rate ratio (RR) 0.868, 95% CI 0.753–1.002; *p*=0.0529), with a statistically significant 14.2% reduction *versus* placebo (RR 0.858, 95% CI 0.740–0.995; *p*=0.0424) when analysed by predefined sensitivity analysis using negative binomial regression [11].

REACT included a large number of patients who had been hospitalised with a severe COPD exacerbation in the year before randomisation [12], a population often excluded from clinical trials. We therefore undertook a *post hoc* analysis of REACT to explore the effect of roflumilast in patients hospitalised for a COPD exacerbation in the previous year. End-points included exacerbation rate, time to first and next severe exacerbation (*i.e.* rehospitalisation), change in post-bronchodilator FEV₁ and change in COPD Assessment Test (CAT) score, as well as adverse events. We used negative binomial regression to estimate exacerbation rates, a Cox proportional hazards regression model to estimate time to first and next severe exacerbation, and an analysis of covariance to calculate the change in post-bronchodilator FEV₁ and total CAT score. All analyses were done in the intention-to-treat (ITT) population. In this exploratory analysis, results are reported as significant at the nominal level of 5%.

Of the 1935 patients recruited, 641 (33%) had been hospitalised with a COPD exacerbation in the previous year (roflumilast *n*=322; placebo *n*=319), while 1294 had not (roflumilast *n*=647; placebo *n*=647). There were more current smokers in the subgroup with a history of hospitalisation than in the subgroup without

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hospitalisation (51.6% and 39.6%, respectively). Other demographic and disease characteristics were similar between the two subgroups, with a mean age of 64.7 years and post-bronchodilator FEV₁ of 34.3% predicted in the prior hospitalisation subgroup.

Among patients with a prior hospitalisation, the rate of moderate or severe exacerbations was 22.9% lower in the roflumilast *versus* placebo group (RR 0.771, 95% CI 0.610–0.974; *p*=0.029) and the rate of severe exacerbations was 34.9% lower (RR 0.651, 95% CI 0.477–0.887; *p*=0.007) (figure 1). In patients without a hospitalisation for COPD exacerbation in the previous year, the reductions in the rate of moderate or severe and severe exacerbations with roflumilast were 8.6% and 7.6%, respectively. Neither was significantly different compared with placebo (figure 1).

In patients hospitalised for COPD exacerbation in the previous year, roflumilast significantly prolonged time to first severe exacerbation (hazard ratio (HR) 0.708, 95% CI 0.525–0.949; *p*=0.0218) and median time to rehospitalisation (143 days *versus* 136 days; HR 0.706, 95% CI 0.523–0.948; *p*=0.0214) *versus* placebo. There was no significant difference between roflumilast and placebo in time to a first severe exacerbation in patients not hospitalised for a COPD exacerbation in the previous year (HR 0.963, 95% CI 0.705–1.311; *p*=0.8096).

Additionally, post-bronchodilator FEV₁ increased significantly with roflumilast treatment over the 52 weeks in both hospitalisation subgroups (Δ =47 mL and Δ =60 mL *versus* placebo in patients with and without a prior hospitalisation). Changes in total CAT score were not significantly different between roflumilast and placebo in either hospitalisation subgroup (least squares (LS) mean 0.152, *p*=0.7049 in patients with a prior hospitalisation; LS mean –0.492, *p*=0.0562 in patients with no prior hospitalisation).

The proportion of patients experiencing adverse events was similar across patient groups irrespective of their hospitalisation history. Among those hospitalised for a COPD exacerbation, adverse events were reported by 223 (69.3%) and 220 (69%) patients receiving roflumilast and placebo, respectively, and in the no prior hospitalisation subgroup by 425 (65.8%) and 352 (54.3%) patients, respectively. Serious adverse events were reported by 109 (33.9%) and 137 (42.9%) patients receiving roflumilast and placebo, respectively, within the prior hospitalisation subgroup, while 140 (21.7%) and 148 (22.8%) patients in the no prior hospitalisation subgroup experienced a serious adverse event. The most frequent adverse events associated with roflumilast were diarrhoea, weight loss and nausea, consistent with previous studies [7–9].

Overall, this *post hoc* analysis of REACT has identified a subgroup of patients that derived greater benefit from roflumilast in reducing the rate of moderate or severe exacerbations. This subgroup finding has since been corroborated in the RE²SPOND study, a similarly designed 52-week study [13]. Similar to REACT, 32% (745/2352) of patients in RE²SPOND had been hospitalised for a COPD exacerbation in the previous year. Addition of roflumilast to ICS/LABA±LAMA resulted in an 8.5% reduction in the rate of moderate or severe exacerbations per patient per year (primary end-point), which was not statistically

FIGURE 1 a) Rate of moderate or severe exacerbations per patient per year by history of hospitalisation in the previous year. b) Rate of severe exacerbations per patient per year by history of prior hospitalisation in the previous year. Rate ratios (RR), 95% confidence intervals and *p*-values are based on a negative binomial regression analysis in the intention-to-treat population. Moderate exacerbations were defined as those requiring treatment with systemic steroids. Severe exacerbations were defined as those that led to hospital admission and/or death.

significant (RR 0.92, 95% CI 0.81–1.04, $p=0.163$). However, *post hoc* analyses showed that roflumilast significantly reduced the rate of moderate or severe exacerbations in two patient subgroups: those with >3 exacerbations (39% *versus* placebo (RR 0.61, 95% CI 0.39–0.95; $p=0.030$)) and those with ≥ 1 hospitalisation for a COPD exacerbation (25% *versus* placebo (RR 0.75, 95% CI 0.60–0.93; $p=0.010$)) 1 year prior to randomisation [13].

Although REACT and RE²SPOND were generally similar in design, methodological differences between the two studies included the formulation of roflumilast used (European Medicines Agency-approved enteric film-coated tablets in REACT and US Food and Drug Administration (FDA)-approved uncoated tablets in RE²SPOND), as well as the maximum dose of ICS/LABA allowed in each study (for fluticasone/salmeterol, the maximum approved dose in each participating country, mostly 500/50 µg (one inhalation twice daily) was allowed in REACT and the maximum FDA-approved dose of 250/50 µg (one inhalation twice daily) in RE²SPOND) [13].

Together, the results from REACT and RE²SPOND indicate that roflumilast is most effective at reducing the rate of moderate or severe exacerbations in a subgroup of patients with a hospitalisation for a COPD exacerbation in the previous year. Furthermore, in this COPD phenotype, roflumilast effectively reduced the rate of exacerbations that require hospitalisation, which are the most serious and costly of COPD exacerbations [14], and reduced the risk of re-admission to hospital due to another COPD exacerbation. We speculate that these COPD patients have more pronounced inflammation than those with less advanced disease and that the reduction in exacerbation risk observed with roflumilast may relate to its anti-inflammatory properties. The benefit of reducing the risk of rehospitalisation in the most severe COPD patients is of major significance to patients and payers. These results help to further define the specific COPD patient phenotype that derives the most benefit from roflumilast therapy.

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