Roflumilast: a review of its use in the treatment of COPD

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Abstract: COPD is a progressive condition involving chronic inflammation and parenchymal destruction with resulting airflow limitation. COPD is associated with worsening airflow limitation over time and increased frequency of COPD exacerbations, leading to increased mortality and morbidity. The effects of COPD extend beyond the lungs, as multiple comorbidities may occur with COPD, including cardiovascular disease, diabetes mellitus, osteoporosis, depression, and pneumonia. COPD exacerbations are associated with a rapid worsening of baseline symptoms that requires prompt management and may necessitate hospitalization in the case of a severe episode. Patients with COPD exacerbations require urgent management of symptoms to prevent further worsening, and preventative steps may be taken to help reduce the number and frequency of future exacerbations. Roflumilast is a potent and selective inhibitor of the enzyme phosphodiesterase-4 that targets the systemic inflammation associated with COPD. Roflumilast has a variety of anti-inflammatory effects including decreasing inflammatory mediators and the expression of cell surface markers and inhibition of apoptosis. Several clinical trials evaluating roflumilast in the treatment of COPD have demonstrated significant improvements from baseline versus placebo in lung function, including increases in mean pre- and postbronchodilator forced expiratory volume in 1 second and forced vital capacity. Data suggest that roflumilast reduces moderate to severe exacerbations with the benefit most well established in patients with severe disease. Given this evidence, roflumilast, as part of a combination regimen with long-acting bronchodilators, appears to be a reasonable treatment option for patients with severe to very severe COPD associated with chronic bronchitis and a history of exacerbations.

Keywords: COPD, exacerbations, phosphodiesterase-4 inhibitors, roflumilast, chronic bronchitis

Introduction

COPD is a progressive condition that usually leads to a steady decline in lung function, increased symptoms, and recurrent and worsening exacerbations.1 The progressive airflow limitation that characterizes COPD is a result of chronic airway inflammation in response to the inhalation of noxious stimuli and resulting parenchymal destruction.2 Many systemic inflammatory markers have been associated with COPD health status and its extrapulmonary effects.1,3,4 Inflammatory cells, tissue swelling, and accumulated mucus directly obstruct airways, but also activate innate repair mechanisms that remodel and thicken airway walls over time, leading to parenchymal destruction.5,6 Parenchymal destruction leads to further decreased gas transfer and increased air trapping. Overall, the combined pathological defects of COPD translate to symptoms of breathlessness, coughing, and variable sputum production that greatly impact a patient’s quality of life.3 COPD is associated with an approximate 3.5-fold increase in the risk of death and is linked to multiple comorbidities, including hypertension, heart failure, ischemic heart disease, diabetes mellitus, myocardial infarction, osteoporosis, depression,
Exposure to viral or bacterial pathogens or inhalation of pollutants may be sufficient to precipitate a COPD exacerbation, defined as an acute worsening of a patient’s baseline symptoms. COPD exacerbations are accompanied by marked increases in systemic inflammatory mediators, decreased quality of life, and further elevated risk of morbidity and mortality with each successive exacerbation compared with baseline disease. Some patients with COPD may be more prone to frequent COPD exacerbations (Figure 1) and thus present a greater therapeutic challenge. This recognition is underscored in the guidelines for the management of COPD, which emphasize the importance of minimizing the impact of current exacerbations and preventing the development of subsequent exacerbations.

The purpose of this review is to highlight the pharmacology, clinical efficacy, tolerability, and place in therapy of roflumilast for the treatment of patients with COPD.

**Pharmacology**

**Pharmacodynamics**

Roflumilast, a potent and selective inhibitor of phosphodiesterase-4 (PDE4), is indicated for treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Selective inhibition of PDE4 inhibits the hydrolysis of cyclic adenosine monophosphate (cAMP) in inflammatory cells. Increased intracellular cAMP results in a wide range of anti-inflammatory effects, including decreased release of inflammatory mediators and cytokines, decreased expression of cell surface markers in many cell types, and decreased apoptosis. The suppression of inflammatory mediators and cytokines usually translates into benefits for patients with COPD exacerbations who often have elevated markers of inflammation compared to patients with baseline disease. Roflumilast also reduces allergen-induced inflammation and has been shown to stabilize lipopolysaccharide-induced systemic inflammation.

**Pharmacokinetics**

Roflumilast is available in a once-daily oral dosage form (500 μg tablets) with a bioavailability of approximately 80%. Maximum plasma concentrations of roflumilast are achieved in ~1 hour (range: 0.5–2 hours) after a single dose, and maximum concentrations of the active N-oxide metabolite are achieved in ~8 hours (range: 4–13 hours). Roflumilast
and its active metabolite are both highly protein bound in plasma (≥97%). Metabolism occurs by Phase I cytochrome P450 (CYP) reactions (isoenzymes 1A2 and 3A4) and by Phase II conjugation, and the half-life is approximately 17 hours. While roflumilast is three times more potent than its metabolite, the metabolite has approximately ten times greater exposure (plasma area under the curve) than the active drug. Patients with hepatic dysfunction may have impaired elimination, although dose adjustments are not necessary. No dosage adjustments are required for renal impairment. However, roflumilast should not be coadministered with strong inhibitors of CYP3A4 or dual inhibitors of CYP3A4 and CYP1A2 (eg, erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine, or rifampicin). The macrolide azithromycin, which is commonly used in patients with COPD, is only a weak inhibitor of CYP3A4 and is expected to interact with roflumilast to a much lesser degree than erythromycin.

**Clinical efficacy**

The clinical efficacy and safety of roflumilast in the treatment of COPD has been evaluated in nine Phase III/IV randomized double-blind clinical trials, including studies M2-107, M2-111, M2-112, M2-124, M2-125, M2-127, M2-128, ACROSS (ClinicalTrials.gov identifier: NCT01313494), and REACT (Roflumilast in the Prevention of COPD Exacerbations While Taking Appropriate Combination Treatment; NCT01329029) (Table 1). Patients in these studies were required to have at least a 10–20-year pack history of smoking. Studies M2-111, M2-112, M2-124, M2-125, and REACT included only patients with severe to very severe airflow limitation as assessed by Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (ie, forced expiratory volume in 1 second [FEV1] ≤50%).

Across all Phase III studies, active treatment with 500 μg of roflumilast was associated with improvements from baseline in lung function, including increases in mean pre- and postbronchodilator FEV1, ranging from 39 to 88 mL and from 45 to 97 mL, respectively, compared with placebo with all differences statistically significant (P<0.0001). In addition, postbronchodilator forced vital capacity increased 58–114 mL compared with placebo (P<0.05).

While studies M2-111 and M2-112 demonstrated that roflumilast was associated with improved lung function in patients with severe COPD, neither study demonstrated a significant effect on exacerbations, although there was a trend toward lower exacerbations for roflumilast in each study. When results from the two trials were pooled, a significant reduction (14.3%) in moderate to severe exacerbations was observed compared with placebo (P=0.026). Post hoc analyses identified several subgroups of patients that were associated with greater response. In particular, patients receiving concomitant inhaled corticosteroids (ICSs) or short-acting anticholinergics, patients with a history of chronic bronchitis with or without emphysema, and patients with elevated cough or sputum scores at baseline (≥1 average score per day) saw significant reductions in the incidence rate of moderate to severe COPD exacerbations by 18% to 30%.

The identified patient groups most responsive to roflumilast in the M2-111 and M2-112 studies helped to inform the design of the subsequent M2-124 and M2-125 studies. These trials included patients with COPD aged >40 years with severe airflow limitation, bronchitic symptoms, and a history of exacerbations. In these studies, roflumilast was not only associated with improvements in lung function, but the drug was also associated with a 15% reduction in moderate or severe exacerbations (P=0.0278) in study M2-124 and an 18% reduction in M2-125 (P=0.0035). In trials M2-127 and M2-128, roflumilast also significantly improved lung function when combined with salmeterol (M2-127) and tiotropium (M2-128) compared with the use of either agent alone.

Post hoc analyses of these later trials have evaluated the efficacy of roflumilast in select subgroups of patients, for example, the efficacy of roflumilast in patients who were taking concomitant long-acting β2-agonists (LABAs). Moderate to severe exacerbations of COPD were reduced by 20.7% in patients taking roflumilast concomitantly with a LABA (P=0.001) compared with 14.6% in patients taking roflumilast alone (P=0.039) (Figure 2). Roflumilast also prolonged the time to first (P=0.035 with LABA; P=0.300 without LABA) and second COPD exacerbations (P=0.018 with LABA; P=0.049 without LABA). Patients who had frequent COPD exacerbations (≥2) in the year prior to treatment with roflumilast saw the greatest reduction versus placebo in the incidence of exacerbations compared with patients who had infrequent exacerbations (22.3% versus 16.5%, respectively; 95% confidence interval [CI]: 9%–34%).

As frequent COPD exacerbations have been associated with increased morbidity and mortality, an additional analysis looked further into endpoints for the frequent exacerbator population of patients. For patients with GOLD severe airway limitation of 3, treatment with roflumilast may help to shift frequent exacerbator patients at baseline to the more stable infrequent exacerbator type. After 1 year of treatment, only 26.4% of patients treated with roflumilast who were frequent exacerbators at baseline remained frequent exacerbators.
Table 1 Randomized double-blind trials evaluating roflumilast in patients with COPD

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Patient characteristics</th>
<th>Study design</th>
<th>Treatment</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>M2-107</td>
<td>1,157</td>
<td>COPD; &gt;12 mo; 10 y pack history; age &gt;40 y; FEV₁ 80%–80% of predicted FVC &lt;70%</td>
<td>R, MC, DB, PC, PG</td>
<td>ROF 250 µg QD (n=578)</td>
<td>Pre-BD FEV₁ (mL) 64* Post-BD FEV₁ (mL) 74* Post-BD FVC (mL) 71* Moderate/severe exacerbations a</td>
</tr>
<tr>
<td>M2-111</td>
<td>1,514</td>
<td>COPD; 10 y pack history; age &gt;40 y; FEV₁ 50%–50%; FEV₁/FVC ratio &gt;0.7</td>
<td>R, MC, DB, PC, PG</td>
<td>ROF 500 µg QD (n=555)</td>
<td>88*</td>
</tr>
<tr>
<td>M2-124</td>
<td>1,525</td>
<td>COPD; 20 y pack history; age &gt;40 y; FEV₁ 50%–50%; FEV₁/FVC ratio &gt;0.7; chronic cough and sputum production; ≥1 COPD exacerbation in last year</td>
<td>R, MC, DB, PC, PG</td>
<td>ROF 500 µg QD (n=766)</td>
<td>51*</td>
</tr>
<tr>
<td>M2-125</td>
<td>1,571</td>
<td>COPD; 20 y pack history; age &gt;40 y; FEV₁ 50%–50%; FEV₁/FVC ratio &gt;0.7; chronic cough and sputum production; ≥1 COPD exacerbation in last year</td>
<td>R, MC, DB, PC, PG</td>
<td>PLA QD (n=759)</td>
<td>39*</td>
</tr>
<tr>
<td>M2-127</td>
<td>935</td>
<td>COPD; 10 y pack history; FEV₁ 40%–70%; FEV₁/FVC ratio ≤0.7</td>
<td>R, MC, DB, PC, PG</td>
<td>PLA QD (n=798)</td>
<td>58*</td>
</tr>
<tr>
<td>M2-128</td>
<td>744</td>
<td>COPD; 10 y pack history; FEV₁ 40%–70%; FEV₁/FVC ratio ≤0.7; chronic cough and sputum production; frequent (≥28 puffs/week) short-acting β₂-agonist; background tiotropium</td>
<td>R, MC, DB, PC, PG</td>
<td>PLA QD + tiotropium (n=372)</td>
<td>80*</td>
</tr>
<tr>
<td>ACROSS</td>
<td>626</td>
<td>COPD; Chinese, Malay, or Indian ethnicity; ≥10 y pack history; age 40–80 y; FEV₁ 50%; FEV₁/FVC ratio ≤0.7</td>
<td>R, MC, DB, PC, PG</td>
<td>PLA QD + tiotropium (n=372)</td>
<td>49*</td>
</tr>
<tr>
<td>REACT</td>
<td>1,945</td>
<td>COPD; 20 y pack history; age &gt;40 y; FEV₁ 50%; FEV₁/FVC ratio &gt;0.7; symptoms of chronic bronchitis; ≥2 COPD exacerbations in last year</td>
<td>R, MC, DB, PC, PG</td>
<td>PLA QD (n=313)</td>
<td>56*</td>
</tr>
</tbody>
</table>

Notes: *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001 (all versus PLA). bPercent difference versus PLA. cNegative binomial regression analysis. dPoisson regression analysis (P=0.0529).

Abbreviations: BD, bronchodilator; DB, double-blind; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonists; MC, multicenter; mo, month; PC, placebo-controlled; PG, parallel group; PLA, placebo; QD, once daily; R, randomized; ROF, roflumilast; y, year.
compared with 38.9% of patients randomized to placebo ($P=0.0042$). An additional analysis of studies M2-124 and M2-125 demonstrated that roflumilast reduced the rate of severe COPD exacerbations leading to hospitalization compared with placebo (rate ratio [RR] 0.78; 95% CI: 0.62–0.90; $P=0.044$).

A post hoc analysis of study M2-128 indicated that roflumilast shows efficacy in patients with highly symptomatic COPD. Using the modified Medical Research Council questionnaire, which evaluates the severity of breathlessness, the efficacy of roflumilast in patients with moderate to severe COPD and Grade 2 or higher breathlessness was evaluated. Mean pre- and postbronchodilator FEV$_1$ increased by 79 mL and 78 mL, respectively, compared with placebo ($P=0.0002$). Roflumilast was associated with a 45.5% reduction in moderate to severe exacerbations compared with placebo ($P=0.0338$). The reduction observed in this subgroup of patients with highly symptomatic COPD was greater than the 27% reduction in exacerbations observed in the overall study population.

The most recent study was REACT, a Phase III/IV randomized, double-blind, multicenter study designed to investigate whether roflumilast further reduces exacerbations when added to inhaled combination therapy (LABA/ICS) in patients still suffering from frequent exacerbations. Patients were randomized to receive roflumilast 500 µg or placebo once daily in combination with a fixed ICS/LABA combination. The rate of moderate to severe COPD exacerbations in the intention-to-treat population (primary endpoint) was 13.2% lower in the roflumilast group versus the placebo group in the Poisson regression analysis (RR 0.868; 95% CI: 0.753–1.002; $P=0.0529$) and was 14.2% lower in the negative binomial regression analysis (RR 0.858; 95% CI: 0.740–0.995; $P=0.0424$). The benefit was evident irrespective of concomitant use of long-acting antimuscarinic agents. Roflumilast was also superior to placebo for reducing severe events (RR 0.757; 95% CI: 0.601–0.952; $P=0.0175$) and for reducing exacerbations requiring hospitalization (RR 0.761; 95% CI: 0.604–0.960; $P=0.0209$) (Figure 3).

Quality of life

In the DACOTA (Daxas for COPD therapy; NCT01285167) study, the effects of roflumilast on the quality of life of patients with COPD (N=3,597) were investigated in a non-interventional, real-life cohort study for 6 months. Patients were divided into frequent and infrequent exacerbator subpopulations based on their exacerbation history over the 12 months leading up to treatment with roflumilast. Clinical COPD Questionnaire (CCQ) scores (1-week version) and COPD Assessment Test (CAT) scores were used to assess improvements in quality of life. The minimal clinically important difference thresholds for CCQ and CAT scores were...
demonstrating improvement in quality of life are 0.41 and 2.0, respectively. At the end of 12 months, both subpopulations showed significant improvements from baseline in mean CCQ scores with roflumilast treatment (\(P<0.001\)), with greater improvements seen for frequent exacerbators compared with infrequent exacerbators (−1.00 versus −0.73, respectively; \(P<0.001\)). Similar results were shown for CAT scores, with significant improvements from baseline scores observed in both subpopulations (\(P<0.001\)) and significantly greater improvements in frequent exacerbators compared with infrequent exacerbators (−6.62 versus −4.91; \(P<0.001\)). An earlier study also demonstrated that treatment with roflumilast improved health-related quality of life as assessed by the St George’s Respiratory Questionnaire total score. In this study, roflumilast showed greater improvement in health-related quality of life than placebo, although the difference was not statistically significant.

**Cost effectiveness**
Both COPD treatment and COPD exacerbations have an economic impact on health care systems. The total direct costs related to COPD in the USA and Europe are 53.7 billion dollars ($) (COPD/asthma combined) and 23 billion euros (£), respectively. Using claims data from the United Kingdom National Health Service, a Markov cohort model was developed to evaluate the total costs, life-years, and quality-adjusted life-years of COPD exacerbations related to different COPD regimens. Roflumilast was found to be generally cost effective when added on to standard-of-care therapy. Roflumilast added on to a regimen of tiotropium and salmeterol resulted in an incremental cost-effectiveness ratio of £13,764/quality-adjusted life-year gained. When added on to a regimen of tiotropium and salmeterol/fluticasone, the result was £16,566/quality-adjusted life-year gained. Similar findings were observed for a cost-effectiveness analysis comparing roflumilast added on to tiotropium versus tiotropium alone. Roflumilast was found to be cost effective as add-on therapy over a period of 5 years ($15,815/quality-adjusted life-year). Economic analyses of data from the REACT study will provide additional data on the cost effectiveness of roflumilast when used in combination with LABA/ICS.
Tolerability

Roflumilast is generally well tolerated with adverse events (AEs) consistent with those expected for PDE4 inhibitors. Combining the data from several 1-year and 6-month clinical trials of roflumilast (N=8,630), the most common AEs were gastrointestinal disorders (diarrhea and nausea) and weight loss (Table 2). Other AEs that occurred with greater frequency compared with placebo were back pain, insomnia, and decreased appetite. In another pooled safety analysis that included data from 14 intermediate- and long-term placebo-controlled clinical trials of roflumilast (N=12,054), the rates of AEs (67.2% versus 62.8%) and severe AEs (13.5% versus 14.2%) were found to be near similar compared with placebo. Rates of infection (25.9% versus 27.5%), pneumonia (1.8% versus 2.0%), and cardiovascular AEs (5.2% versus 5.7%) were also similar. In the REACT trial, AEs were reported by 67% of those receiving roflumilast compared with 59% of the placebo group, with serious AEs reported in 26% and 30%, respectively. However, there were more discontinuations due to AEs among those receiving roflumilast (n=82) versus placebo (n=29). A common systemic effect of COPD is weight loss, which can be seen in patients with severe COPD. Both selective and nonselective PDE inhibitors have been associated with weight loss, which may be related to the effects of increased cAMP on signaling pathways that regulate lipolysis. Weight loss in one pooled analysis was found to be 2.14 kg greater with roflumilast treatment compared with placebo (P<0.0001). The extent of weight loss was mostly realized within the first 4 weeks of treatment and was shown to occur in patients with greater fat mass. After discontinuing roflumilast, patients regained one-half of their lost weight within 3 months. Animal models suggest that PDE4 inhibitors may also increase glucagon-like peptide-1 levels. Glucagon-like peptide-1 receptor agonists are used in the treatment of diabetes and are also associated with weight loss. This may serve as another possible explanation for the weight loss seen in patients with COPD treated with roflumilast and could also explain favorable effects on glycemic parameters as well as the gastrointestinal AEs (nausea and diarrhea) associated with the drug. In a 12-week, placebo-controlled trial in patients with newly diagnosed type 2 diabetes mellitus, roflumilast increased insulin sensitivity and was associated with a significantly greater change in glycated hemoglobin than placebo (least-square mean =−0.45%; P<0.0001) (Figure 4).

Cardiovascular safety

Patients diagnosed with COPD are approximately 3 and 3.5 times more likely to experience a stroke and acute myocardial infarction, respectively. Thus, the effect of COPD treatment on cardiovascular safety is a concern for both clinicians and patients. Using the same pooled safety data for previous analyses described (N=12,054), the potential major adverse cardiovascular events (eg, composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) were assessed in patients randomized to receive roflumilast (Figure 5). Roflumilast was associated with a significantly lower risk of major adverse cardiovascular events versus placebo-treated patients: 14.3 per 1,000 versus 22.3 per 1,000 patient-years, respectively (hazard ratio 0.65; 95% CI: 0.45–0.93; P=0.019).

Table 2 Adverse reactions (%≥2%) associated with roflumilast from four 1-year placebo-controlled trials and four 6-month trials

<table>
<thead>
<tr>
<th>Adverse reaction, % (n)</th>
<th>Roflumilast (n=4,438)</th>
<th>Placebo (n=4,192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>9.5 (420)</td>
<td>2.7 (113)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>7.5 (331)</td>
<td>2.1 (89)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.7 (209)</td>
<td>1.4 (60)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3.2 (142)</td>
<td>2.2 (92)</td>
</tr>
<tr>
<td>Influenza</td>
<td>2.8 (124)</td>
<td>2.7 (112)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2.4 (105)</td>
<td>1.0 (41)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2.1 (91)</td>
<td>0.4 (15)</td>
</tr>
</tbody>
</table>


Figure 4 Changes in mean glycated hemoglobin (HbA1c) levels over 12 weeks in patients with newly diagnosed, treatment-naive type 2 diabetes mellitus.

There appear to be differences between ICS for the risk of pneumonia, with a 73% higher rate of pneumonia among patients receiving fluticasone/salmeterol compared with those receiving budesonide/formoterol.61

Roflumilast is a PDE4 inhibitor with demonstrated efficacy for improving lung function and decreasing exacerbations in patients with severe to very severe COPD associated with chronic bronchitis. This includes decreasing the incidence of exacerbations in frequent exacerbators and also of hospitalization.31,32,34,35 Thus, roflumilast in combination with a LABA with or without an ICS or a long-acting muscarinic antagonist appears to be a reasonable alternative choice for patients with severe to very severe COPD associated with chronic bronchitis and a history of COPD exacerbations. As of now, the benefits of roflumilast are most well established in those with severe disease. A recent benefit/harm analysis of the use of roflumilast in patients with COPD found that only patients with a high risk of severe exacerbations achieved a net benefit from roflumilast therapy.62

Extrapulmonary manifestations of COPD also need to be taken into consideration when managing patients. Recent evidence suggests that COPD has manifestations beyond the respiratory tract, including an increased risk of cardiovascular disease, osteoporosis, diabetes, and anxiety/depression.6,63 One of the key mechanisms underlying these systemic manifestations is low-grade, chronic systemic inflammation, and it is possible that these represent a common pathophysiology or at least shared risk factors. Data supporting this include the observation that roflumilast decreases the risk of cardiovascular events in patients with COPD57 and that the drug improves glucose homeostasis in patients with type 2 diabetes mellitus.6,56 Thus, the current target population for the use of roflumilast is patients at high risk who have a higher risk for exacerbations, COPD hospitalization, and death.64

Additional trials are underway to further define the role of roflumilast for targeting the underlying systemic inflammation associated with COPD. Another ongoing trial (Trial to Assess the Anti-inflammatory Effects of Roflumilast in COPD; NCT01509677) is evaluating the effect of roflumilast 500 µg versus placebo on inflammation parameters in bronchial biopsy tissue specimens in patients with moderate to severe COPD associated with chronic bronchitis.65

In summary, clinical efficacy, quality of life, and cost-effectiveness data suggest that roflumilast can be an important and cost-effective alternative to ICS in the prevention of exacerbations, particularly for patients with severe to very severe COPD.
severe COPD associated with chronic bronchitis and a history of exacerbations.

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Disclosure

JAW has participated in advisory board meetings and/or spoken at meetings for GlaxoSmithKline, Pfizer, Takeda, Boehringer Ingelheim, AstraZeneca, Johnson & Johnson, Napp Pharmaceuticals Limited, Vifor Pharma, and Novartis. PMAC has advised on study conduct and spoken at meetings sponsored by GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Novartis, and Takeda. KFR has received research support for serving as an investigator from Altana Pharma, Novartis, AstraZeneca, Merck Sharp & Dohme, and Nycomed. The authors report no other conflicts of interest in this work.

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