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REVIEW

Update on roflumilast, a phosphodiesterase 4 inhibitor for the treatment of chronic obstructive pulmonary disease

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Phosphodiesterase 4 (PDE4) is a member of the PDE enzyme superfamily that inactivates cyclic adenosine monophosphate and cyclic guanosine monophosphate, and is the main PDE isoenzyme occurring in cells involved in inflammatory airway disease such as chronic obstructive pulmonary disease (COPD). COPD is a preventable and treatable disease and is characterized by airflow obstruction that is not fully reversible. Chronic progressive symptoms, particularly dyspnoea, chronic bronchitis and impaired overall health are worse in those who have frequent, acute episodes of symptom exacerbation. Although several experimental PDE4 inhibitors are in clinical development, roflumilast, a highly selective PDE4 inhibitor, is the first in its class to be licensed, and has recently been approved in several countries for oral, once-daily treatment of severe COPD. Clinical trials have demonstrated that roflumilast improves lung function and reduces exacerbation frequency in COPD. Furthermore, its unique mode of action may offer the potential to target the inflammatory processes underlying COPD. Roflumilast is effective when used concomitantly with all forms of bronchodilator and even in patients treated with inhaled corticosteroids. Roflumilast thus represents an important addition to current therapeutic options for COPD patients with chronic bronchitis, including those who remain symptomatic despite treatment. This article reviews the current status of PDE4 inhibitors, focusing on the pharmacokinetics, efficacy and safety of roflumilast. In particular, it provides an overview of the effects of roflumilast on lung function and exacerbations, glucose homoeostasis and weight loss, and the concomitant use of long-acting beta$_2$-adrenergic receptor agonists and short-acting muscarinic receptor antagonists.

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Abbreviations
AUC, area under the concentration–time curve; BMI, body mass index; cAMP, 3′5′-cyclic adenosine monophosphate; cGMP, 3′5′-cyclic guanosine monophosphate; C_{max}, maximum plasma concentrations; COPD, chronic obstructive pulmonary disease; CYP, cytochrome P450; DM2, diabetes mellitus type 2; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GLP-1, glucagon-like peptide-1; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABAs, long-acting beta$_2$-adrenergic receptor agonists; LS mean, least squares mean; PDE4, phosphodiesterase 4; SAMAs, short-acting muscarinic receptor antagonists; SGRQ, St George's Respiratory Questionnaire; $t_{1/2}$, half-life; tPDE4i, total PDE4 inhibitory

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex syndrome that involves airway inflammation and airway limitation, oedema, mucociliary dysfunction and hypoxic vasoconstriction of pulmonary arterioles, which reduces perfusion, and consequent airway structural changes, in addition to significant systemic effects that lead to comorbid conditions (Global Initiative for Chronic Obstructive Lung Disease, 2009). The observation that the functions of

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inflammatory cells could be inhibited by raising their intracellular levels of 3′5′-cyclic adenosine monophosphate (cAMP), and the wide distribution of phosphodiesterase 4 (PDE4) in inflammatory cells and the lung, prompted the exploration of isoenzyme-selective PDE4 inhibitors as a way of reducing inflammation in patients with COPD (Boswell-Smith *et al.*, 2006b; Halpin, 2008).

Phosphodiesterases (PDEs) are a superfamily of enzymes that hydrolyse cAMP and 3′5′-cyclic guanosine monophosphate (cGMP) to their inactive 5′ monophosphates, and thereby regulate the intracellular levels of secondary messengers (Halpin, 2008). One isoenzyme of the PDE family, PDE4, is the major regulator of cAMP levels in leukocytes and other inflammatory cells. As cAMP-specific PDE4 is expressed in all of the inflammatory cells and several other airway cells involved in the pathogenesis of COPD, inhibition of PDE4 should interfere with their function (Torphy and Undem, 1991; Giembycz, 1992; Souness *et al.*, 2000; Burnouf and Pruniaux, 2002; Sanz *et al.*, 2005).

This article will review the current status of PDE4 inhibitors, focusing on the pharmacokinetics, efficacy and safety of roflumilast, the first specific PDE4 inhibitor to be licensed for the treatment of COPD. In particular, it will provide an overview of the effects of roflumilast on lung function and exacerbations, glucose homoeostasis and weight loss and the concomitant use of long-acting beta$_2$-adrenergic receptor agonists (LABAs) and short-acting muscarinic receptor antagonists (SAMAs).

Overview of the field

The first generation of PDE4 inhibitors (e.g. rolipram) were shown to be effective in inhibiting inflammatory cell functions, but their use was limited by side effects, particularly those affecting the gastrointestinal tract (Barnette and Underwood, 2000). There remained a need for a molecule with more specific anti-inflammatory activity and an improved safety profile. Development of such a molecule was potentially achievable as the PDE4 family is highly complex, with four genes (A, B, C and D) coding for the enzyme and each gene having several splice variants (Muller *et al.*, 1996). Indeed, more than 20 isoforms of PDE4 have been identified and there are significant differences in the tissue distribution of the mRNA for each of these isoforms.

Several experimental PDE4 inhibitors are in clinical development, but only cilomilast and roflumilast have reached Phase III clinical trials. Data from Phase I and II studies showed that cilomilast significantly improved lung function and reduced exacerbation rates in COPD (Giembycz, 2006). However, because of its greater selectivity for the PDE4D subtype, cilomilast is associated with gastrointestinal disturbances, such as emesis and nausea (Boswell-Smith and Spina, 2007), and drug development for COPD was terminated (Field, 2008; Rennard *et al.*, 2008). Current investigational drugs include oglemilast (GRC 3886), an oral PDE4 inhibitor under investigation in inflammatory airway diseases. In animal models *in vitro* and *in vivo*, oglemilast inhibited pulmonary cell infiltration, including eosinophilia and neutrophilia (Vakkalanka *et al.*, 2004; Giembycz, 2008). Tetomilast is a once-daily oral PDE4 inhibitor that is currently in development for COPD and ulcerative colitis (O'Mahony, 2005; Schreiber *et al.*, 2007); two recent multicentre Phase III studies in ulcerative colitis reported that efficacy was generally numerically better with tetomilast than placebo, but statistically significant improvement was not demonstrated (Keshavarzian *et al.*, 2007). ONO-6126 has been tested in healthy subjects (Furuie *et al.*, 2003; Giembycz, 2008) and is believed to be in Phase II development, while ELB353 has exhibited a good efficacy profile in animal models of pulmonary neutrophilia (Pages *et al.*, 2009), and a further Phase I trial is underway to study its safety and pharmacokinetics in healthy subjects. Several inhaled PDE4 inhibitors are in the early stages of development: GSK256066, SCH900182 and ibudilast (Knowles *et al.*, 2009; Chapman *et al.*, 2010; Etsuko *et al.*, 2010), while several more have been discontinued due to a lack of efficacy: AWD 12–281, UK-500,001 and tofimilast (CP 325366) (Giembycz, 2008).

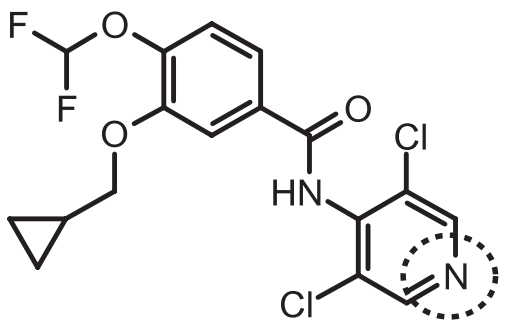
Pharmacodynamics, pharmacokinetics and metabolism

Roflumilast (3-cyclopropylmethoxy-4-difluoromethoxy-*N*-[3,5-dichloropyrid-4-yl]-benzamide) is an oral PDE4 inhibitor for the treatment of COPD (Figure 1) (Boswell-Smith *et al.*, 2006b). Roflumilast was identified in 1993 from a series of benzamides in a comprehensive screening programme (Amschler, 1995). The high potency and selectivity of roflumilast for competitive inhibition of PDE4, without affecting PDE1, 2, 3 or 5 isoenzymes, within various cells and tissues indicated its potential as a therapeutic agent (Hatzelmann *et al.*, 2010).

The potency and selectivity of roflumilast and its active metabolite have been studied for PDE1–11 (Table 1) (Hatzelmann *et al.*, 2010). Roflumilast does not affect PDE enzymes apart from PDE4, and is a subnanomolar inhibitor of most PDE4 splicing variants tested. It showed no PDE4 subtype selectivity apart from PDE4C, which is inhibited with a slightly lower potency. Roflumilast N-oxide is only twofold to threefold less potent than roflumilast, with respect to PDE4 inhibition, maintains high selectivity to other PDE isoenzymes and shows no selectivity for PDE4 subtypes. In contrast, cilomilast shows some subtype selectivity for PDE4D (Table 1).

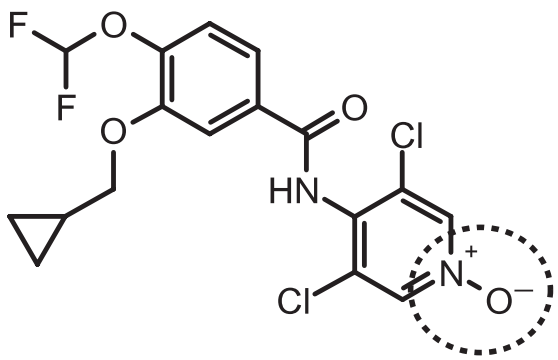
Inhibitors of PDE4, such as roflumilast, interfere with the breakdown of cAMP, leading to its intracellular accumulation. In turn, an elevated concentration of intracellular cAMP activates protein kinase A, which enhances phosphorylation of proteins (Figure 2) (Torphy and Undem, 1991; Giembycz, 1992; Souness *et al.*, 2000; Burnouf and Pruniaux, 2002; Conti *et al.*, 2003; Sanz *et al.*, 2005). *In vitro*, inhibition of PDE4 results in a wide range of effects, including decreased apoptosis (which may result in the clearance of sputum) and release of inflammatory mediators in neutrophils (a reduction in influx resulting in a reduction of neutrophils in the airways), decreased expression of cell surface markers in many cell types (e.g. adhesion molecules in T-cells), and decreased release of cytokines in many cell types (such as tumour necrosis factor alpha, interleukin-1β and interleukin-10 in macrophages) (Hatzelmann *et al.*, 2010). *In vivo*, inhibition of PDE4 leads to a broad spectrum of effects,

A



3-cyclopropylmethoxy-4-difluoromethoxy-N-[3,5-dichloropyrid-4-yl]-benzamide
$C_{17}H_{14}Cl_2F_2N_2O_3$

B



N-(3,5-dichloro-1-oxypyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide

Figure 1

The chemical structure of (A) roflumilast and (B) roflumilast N-oxide.

such as the inhibition of cell trafficking, and cytokine and chemokine release from inflammatory cells such as neutrophils, eosinophils, macrophages and T-cells (Sanz *et al.*, 2005).

Animal studies with roflumilast demonstrated that it reduced the accumulation of neutrophils in bronchoalveolar lavage fluid following short-term exposure of guinea pigs, mice or rats to tobacco smoke, and following exposure of rats to a combination of tobacco smoke and bacterial lipopolysaccharide, and abolished the lung parenchymal influx of inflammatory cells seen in rats exposed to tobacco smoke for 7 months (Fitzgerald, 2001; Martorana *et al.*, 2005; 2008; Fitzgerald *et al.*, 2006; Le Quement *et al.*, 2008; Weidenbach *et al.*, 2008; Carnini *et al.*, 2009; Hardaker *et al.*, 2009; 2010; Stevenson *et al.*, 2009). Similarly, roflumilast was able to prevent bleomycin-induced lung infiltration of neutrophils and macrophages in mice (Cortijo *et al.*, 2009). Furthermore, roflumilast was not only able to reduce smoke-induced emphysema in mice exposed to tobacco smoke for 7 months

Table 1

Phosphodiesterase (PDE) selectivities of roflumilast, roflumilast N-oxide and cilomilast. (Adapted with permission from Hatzelmann *et al.*, 2010)

		4A1	4A4	4B1	4B2	4C1	4C2	4Cshort	4D2	4D3	4D4	4D5	1A3	1B1	1C1	2A3	3A1	5A1	6 (bovine)	7A1	8B	9A3	10A	11A4
Roflumilast	nM	0.7	0.9	0.7	0.2	3	4.3	3.5	0.3	0.4	0.2	0.4	>10 000	>10 000	>10 000	>10 000	>10 000	4500	4200	>10 000	>10 000	>10 000	>10 000	>10 000
Roflumilast N-oxide	nM	1.4	2.3	0.95	1.1	5.9	7.8	3.9	0.4	0.8	0.5	0.8	>10 000	>10 000	>10 000	>10 000	>10 000	>10 000	6300	>10 000	>10 000	>10 000	>10 000	>10 000
Cilomilast	µM	0.11	0.16	0.14	0.09	0.47	0.63	0.65	0.018	0.02	0.02	0.025	48	>100	74	84	>100	>100	24	>100	21	>100	>100	92

Selectivity was assessed using human recombinant enzymes except PDE6, which is from a bovine source.
Values given are IC_{50} for inhibition of PDE catalysis; these are nM values for roflumilast and its N-oxide and µM-values for cilomilast.

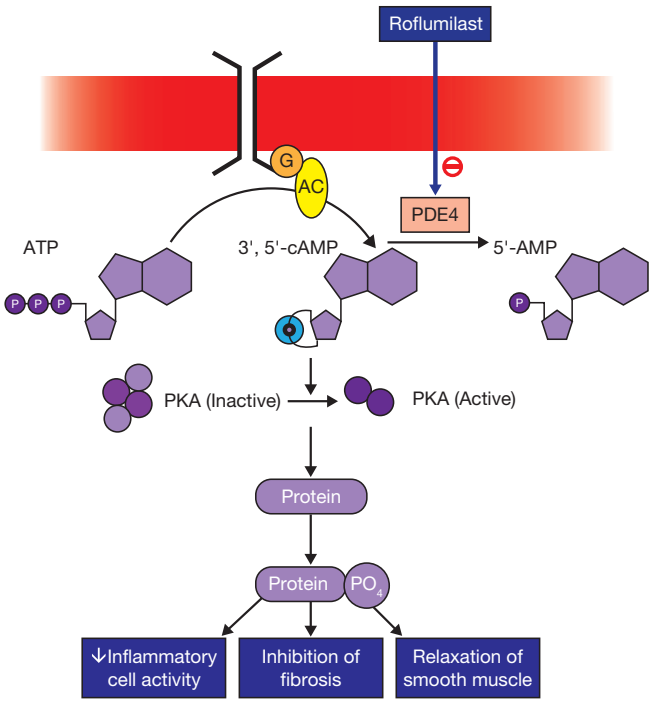


Figure 2

PDE4 inhibitors increase levels of cyclic adenosine monophosphate (cAMP) through inhibition of its metabolism. The resulting increase in protein kinase A (PKA) activation stimulates increased protein phosphorylation, with subsequent inhibition of pro-inflammatory cells and mediators and inhibition of fibrosis. Although increased cAMP levels generally have smooth muscle relaxant effects, roflumilast does not have acute bronchodilator effects (Grootendorst *et al.*, 2003), which are not a property of selective PDE4 inhibitors. It may be speculated that smooth muscle has several PDE isoenzymes, and that selective inhibition of PDE4 is insufficient to afford an acute dilator effect.

but also to prevent progression of emphysema when given to mice after exposure for 4 months (Martorana *et al.*, 2005).

Following oral dosing, roflumilast is rapidly converted by cytochrome P450 (CYP) 3A4 and 1A2 to its active metabolite roflumilast N-oxide (Bethke *et al.*, 2007). This metabolite has similar potency and specificity to the parent compound, and has been estimated to contribute ~90% of the total PDE4 inhibitory (tPDE4i) activity of roflumilast (Hatzelmann and Schudt, 2001; Hauns *et al.*, 2006; Hermann *et al.*, 2006; Bethke *et al.*, 2007; Lahu *et al.*, 2009). Roflumilast N-oxide is primarily cleared by CYP3A4, with some contribution from CYP2C19 and extrahepatic CYP1A1. A number of covariates, including age, gender and smoking, can affect the activity of CYP3A4 and CYP1A2 (Bebia *et al.*, 2004; Mangoni and Jackson, 2004; Cotreau *et al.*, 2005; Funck-Brentano *et al.*, 2006). However, a recent modelling study that analysed the effects of a range of covariates on tPDE4i activity of roflumilast found them to have a limited impact on this parameter (Lahu *et al.*, 2010c).

Roflumilast is rapidly and almost completely absorbed after oral administration, with maximum plasma concentrations (C_{max}) reached within ~1 h in healthy volunteers (Bethke *et al.*, 2007). Absolute bioavailability is ~80% when administered as an immediate-release tablet (David *et al.*, 2004). The pharmacokinetic profile of roflumilast is linear and predictable over the dose range of 250–1000 μg (Bethke *et al.*, 2007). The therapeutic dose is 500 μg, taken once daily (which can be either in the morning or the evening). On repeated oral dosing with roflumilast 500 μg once daily in healthy subjects, the free drug concentration of roflumilast N-oxide in plasma over 24 h was estimated to be about 1–2 nM, following the measurement of plasma protein binding of roflumilast N-oxide of approximately 97% (Bethke *et al.*, 2007). The apparent effective plasma half-life ($t_{1/2}$) of roflumilast ranges from 8 to 31 h (median 17 h) and steady-state plasma concentrations are achieved after 3–4 days of oral, once-daily dosing (Lahu *et al.*, 2010c). The C_{max} for roflumilast N-oxide is reached ~8 h after drug intake (Bethke *et al.*, 2007; Hermann *et al.*, 2007a,b; Nassr *et al.*, 2007a; von Richter *et al.*, 2007), and the $t_{1/2}$ is ~30 h (Bethke *et al.*, 2007; Hermann *et al.*, 2007a,b; von Richter *et al.*, 2007). Steady-state plasma concentrations of roflumilast N-oxide are achieved within 6 days of oral, once-daily dosing (Bethke *et al.*, 2007). There is no effect of food on the pharmacokinetics of roflumilast or roflumilast N-oxide (Hauns *et al.*, 2006).

The pharmacokinetics of roflumilast 500 μg once daily in patients with severe renal impairment and roflumilast 250 μg once daily in patients with mild/moderate hepatic impairment were assessed (Drollmann *et al.*, 2002). In patients with severe renal impairment, the area under the concentration–time curve (AUC) was 21% and 7% lower for roflumilast and roflumilast N-oxide, respectively, compared with healthy subjects. A decrease of 16% and 12% in the C_{max} of roflumilast and roflumilast N-oxide was also observed in the renally impaired group. In patients with severe renal impairment, tPDE4i was decreased by 9% compared with healthy controls (Bethke *et al.*, unpublished data). In patients with mild hepatic impairment, the AUC of roflumilast increased by 51% (roflumilast N-oxide increased by 24%), and the C_{max} increased by 3% (roflumilast N-oxide increased by 26%), compared with healthy controls. For those patients with moderate hepatic impairment, the AUC of roflumilast increased by 92% (roflumilast N-oxide increased by 41%), while the C_{max} of roflumilast increased by 26% (roflumilast N-oxide increased by 40%), compared with healthy controls. Relative to healthy subjects, mean increases in tPDE4i were 26% and 46% in patients with mild or moderate hepatic impairment respectively (Hermann *et al.*, 2007a).

Drug interaction studies have shown that no dose adjustment of roflumilast 500 μg was required when co-administered with erythromycin (Lahu *et al.*, 2009), ketoconazole (Lahu *et al.*, 2008), midazolam (Nassr *et al.*, 2007b), digoxin (Lahu *et al.*, 2010a) and Maalox®, an antacid containing magnesium hydroxide and aluminium hydroxide (Nassr *et al.*, 2007a). Furthermore, no interaction was noted between roflumilast and cigarette smoke (Nycomed GmbH, 2010b). However, co-administration of rifampicin 600 mg, a potent CYP3A4 inducer, and roflumilast led to a reduction of 58% in tPDE4i activity of roflumilast, suggesting that co-administration may have reduced the therapeutic effect of roflumilast (Nassr *et al.*, 2009). In addition, co-administration with the antidepressant fluvoxamine 50 mg, a strong multiple pathway inhibitor blocking more than one relevant CYP

isoenzyme, led to an increase of 59% in tPDE4i activity of roflumilast. This increase would not be expected when co-administering roflumilast with a more selective CYP1A2 inhibitor (von Richter *et al.*, 2007).

Furthermore, although roflumilast and theophylline should not be used concomitantly, a drug interaction study in healthy volunteers has reported that the pharmacokinetics of theophylline were not altered by repeated oral administration of roflumilast. The AUC of roflumilast increased by 28% following repeated theophylline co-administration, but the AUC of roflumilast N-oxide was unaffected and there was no change in the C_{max} of roflumilast or roflumilast N-oxide. In addition, no safety concerns were raised when theophylline and roflumilast were administered concomitantly for a short period of up to 5 days. However, as there are no clinical data available to support the co-administration of both drugs, concomitant treatment is not recommended for maintenance therapy (Böhmer *et al.*, unpublished data).

The effects of co-medications frequently used in COPD on the pharmacokinetics of roflumilast and roflumilast N-oxide have also been studied in healthy subjects. Co-administration of roflumilast with salbutamol, budesonide or formoterol had no significant effect on the mean tPDE4i activity of roflumilast (Bethke *et al.*, 2006; Hermann *et al.*, 2007b; Lahu *et al.*, 2010a). No dose adjustment of roflumilast is required with co-administration of montelukast (Böhmer *et al.*, 2009). The effects of concomitant therapy with warfarin, enoxacin and cimetidine were also evaluated. Co-administration of warfarin and roflumilast had no significant effect on the mean tPDE4i activity of roflumilast, and no clinically relevant adverse events were reported during the study (Lahu *et al.*, 2010a). Co-administration of enoxacin and roflumilast resulted in a mean increase in tPDE4i activity of 25%, although this is unlikely to be clinically relevant (Lahu *et al.*, 2010b). Co-administration of cimetidine and roflumilast resulted in a mean increase of 47% in tPDE4i activity, but dose adjustment of roflumilast is not required (Böhmer *et al.*, 2010).

Efficacy

Early studies

Early studies with roflumilast used lung function [primary endpoint being post-bronchodilator forced expiratory volume in 1 s (FEV_1)] and quality of life as efficacy endpoints (Table 2). The beneficial effect of roflumilast on lung function was initially demonstrated in a 6-month study in subjects with moderate-to-severe COPD (M2-107) (Rabe *et al.*, 2005), followed by a 12-month study in severe COPD (M2-112) (Calverley *et al.*, 2007).

Study M2-107 was a double-blind, multicentre, placebo-controlled study that involved 1411 patients with moderate-to-severe COPD (FEV_1 30–80% predicted), treated with roflumilast, 250 μg or 500 μg, or placebo once daily for 24 weeks (Rabe *et al.*, 2005). There were significant improvements in post-bronchodilator FEV_1 in both roflumilast groups compared with placebo (74 mL for roflumilast 250 μg and 97 mL for roflumilast 500 μg; $P < 0.0001$). Improvements were also seen in quality of life, as assessed by St. George's Respiratory Questionnaire (SGRQ) total score (–1.6 for roflumilast 250 μg and –1.7 for roflumilast 500 μg compared with placebo; $P = 0.077$ and $P = 0.053$ respectively).

M2-112 was a randomized, double-blind, placebo-controlled, parallel-group study of 1513 patients with severe COPD ($FEV_1 \leq 50\%$ predicted) treated with roflumilast 500 μg or placebo once daily for 1 year (Calverley *et al.*, 2007). The primary efficacy variables were the change from baseline to endpoint in post-bronchodilator FEV_1, and the number of moderate or severe exacerbations per patient per year.

Concomitant inhaled corticosteroids (ICS) were permitted and were used by about 60% of patients. As in study M2-107, post-bronchodilator lung function improved significantly with roflumilast treatment (39 mL compared with placebo, $P = 0.001$). This improvement was achieved in a patient population with poor baseline reversibility. In addition, fewer moderate-to-severe exacerbations were observed among patients receiving roflumilast than in the placebo group, but this reduction failed to reach significance.

The heterogeneous nature of COPD needs to be considered in the development of novel therapies as different drugs are likely to benefit different patient subpopulations. Consequently, it was suggested that certain subgroups of patients with COPD would be more likely to benefit from the anti-inflammatory action of roflumilast than others. In order to improve understanding of the effects of roflumilast on COPD exacerbations and to examine which patient populations might gain the most benefit from roflumilast, a *post-hoc*, pooled analysis of two replicate 12-month studies (M2-111 and M2-112) was performed (Rennard *et al.*, 2011). This analysis showed a 14.3% reduction in the rate of moderate-to-severe exacerbations with roflumilast vs. placebo (0.52 vs. 0.61 exacerbations per year; $P = 0.026$). It was also able to identify responsive patient subgroups that showed greatest benefit with roflumilast: patients with chronic bronchitis or with high cough or sputum scores in the week prior to randomization, and patients receiving concomitant ICS or SAMAs (Figure 3) (Rennard *et al.*, 2011). The preferential effect of roflumilast in certain patient subgroups suggested that a tailored approach was required to optimize treatment for COPD. This analysis facilitated the design of subsequent clinical trials, which consistently demonstrated the efficacy of roflumilast, focussing on the identified patient groups (Calverley *et al.*, 2009; Fabbri *et al.*, 2009).

Recent studies

The two pivotal, 12-month studies that followed (M2-124 and M2-125) used the information gained from the pooled analysis to investigate the effects of roflumilast in a patient population with a background of chronic bronchitis who are at higher risk of exacerbations (Calverley *et al.*, 2009). These two trials were randomized, double-blind studies comparing roflumilast 500 μg once daily ($n = 1537$) with placebo ($n = 1554$), and were designed to examine the effects of roflumilast on lung function and exacerbation rate. Patients had severe-to-very-severe COPD ($FEV_1 \leq 50\%$ predicted) and were required to have bronchitic symptoms and a history of exacerbations. ICS were not allowed during the study but LABAs or SAMAs could be used. As well as significantly improving pre-bronchodilator FEV_1, treatment with roflumilast was associated with a significant reduction in the annual rate of exacerbations. In a pooled analysis, the mean rate of

Table 2

Phase III studies with roflumilast

Study	Patients	Study design	Therapy	Key findings
M2-107 (Rabe *et al.*, 2005)	$N = 1411$ Post-bronchodilator FEV_1 30–80% predicted; post-bronchodilator FEV_1:FVC ratio ≤ 70%	Multicentre, double-blind, parallel-group study	Roflumilast 250 μg ($n = 576$) or 500 μg ($n = 555$) or placebo ($n = 280$) once daily for 24 weeks	Roflumilast 500 μg significantly improved post-bronchodilator FEV_1 compared with placebo (difference 97 mL, $P < 0.0001$) and health-related quality of life
M2-111 (Data on file Nycomed GmbH) (Nycomed GmbH, 2010a)	$N = 1176$ Post-bronchodilator FEV_1:FVC ratio ≤ 70% Post-bronchodilator ≤ 50% predicted	Multicentre, double-blind, parallel-group study	Roflumilast 500 μg ($n = 568$) or placebo ($n = 608$) once daily for 52 weeks	Roflumilast 500 μg significantly improved pre-bronchodilator FEV_1 compared with placebo (difference 36 mL, $P < 0.0001$) Roflumilast 500 μg significantly improved post-bronchodilator FEV_1 compared with placebo (difference 38 mL, $P < 0.0001$)
M2-112 (Calverley *et al.*, 2007)	$N = 1513$ Post-bronchodilator FEV_1 ≤ 50% predicted, post-bronchodilator FEV_1:FVC ratio ≤ 0.70	Multicentre, randomized, placebo-controlled, double-blind, parallel-group trial (identical to study M2-111)	Roflumilast, 500 μg once daily or placebo for 1 year Note: unlike M2-124/125, patients in this study were not required to have symptoms of chronic bronchitis or a history of exacerbations	Post-bronchodilator FEV_1 increased by 39 mL with roflumilast compared with placebo by 52 weeks ($P = 0.001$) The mean exacerbation rate per patient per year was low and comparable (0.86 vs 0.92 for roflumilast and placebo respectively). In a retrospective analysis, the exacerbation rate per patient per year in patients in GOLD stage IV disease was 36% lower in patients treated with roflumilast than in those treated with placebo (1.01 vs. 1.59, respectively; $P = 0.024$)
M2-124 (Calverley *et al.*, 2009)	$N = 1523$ Post-bronchodilator FEV_1 ≤ 50% predicted, bronchitic symptoms, and a history of exacerbations	Multicentre, double-blind, randomized, parallel-group study	Roflumilast 500 μg ($n = 765$) once daily or placebo ($n = 758$) for 1 year	Pre-bronchodilator FEV_1 increased in the roflumilast group by 46 mL, but was almost unchanged (8 mL increase) in the placebo group ($P = 0.0003$) There was also 14.9% reduction in the exacerbation rate in the roflumilast group vs placebo ($P = 0.0278$)
M2-125 (Calverley *et al.*, 2009)	$N = 1568$ Post-bronchodilator FEV_1 ≤ 50% predicted, bronchitic symptoms, and a history of exacerbations	Multicentre, double-blind, randomized, parallel-group study	Roflumilast 500 μg once daily ($n = 772$) or placebo ($n = 796$) for 1 year	Roflumilast increased pre-bronchodilator FEV_1 by 33 mL compared with a 25 mL decrease in the placebo group ($P < 0.0001$) Roflumilast also reduced the rate of moderate or severe COPD exacerbations compared with placebo by 18.5%; $P = 0.0035$
M2-127 (Fabbri *et al.*, 2009)	$N = 933$ Post-bronchodilator FEV_1 40–70% predicted	Double-blind, randomized, parallel-group, multicentre study	Roflumilast 500 μg ($n = 466$) or placebo ($n = 467$), once daily for 24 weeks, in addition to salmeterol 50 μg twice daily	Compared with placebo, roflumilast consistently improved mean pre-bronchodilator FEV_1 by 49 mL ($P < 0.0001$) in patients treated with salmeterol. Similar improvement in post-bronchodilator FEV_1 was noted. Furthermore, roflumilast had beneficial effects on other lung function measurements and on selected patient-reported outcomes
M2-128 (Fabbri *et al.*, 2009)	$N = 743$ Post-bronchodilator FEV_1 40–70% predicted	Double-blind, randomized, parallel-group, multicentre study	Roflumilast 500 μg ($n = 371$) or placebo ($n = 372$) once daily for 24 weeks, in addition to tiotropium 18 μg once daily	Compared with placebo, roflumilast consistently improved mean pre-bronchodilator FEV_1 by 80 mL ($P < 0.0001$) in those treated with tiotropium. Similar improvement in post-bronchodilator FEV_1 was noted. Furthermore, roflumilast had beneficial effects on other lung function measurements and on selected patient-reported outcomes

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

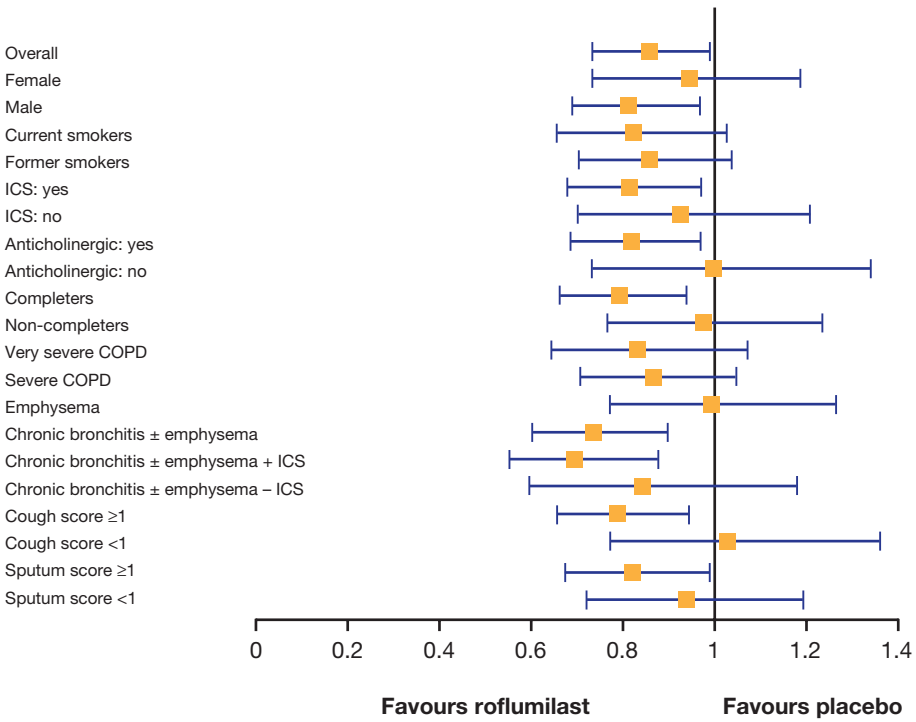


Figure 3

Effect of roflumilast treatment by disease severity according to rate ratios for reduction in moderate-to-severe COPD exacerbations (Rennard *et al.*, 2011). Error bars represent 95% confidence intervals. (Reproduced by courtesy of BioMed Central).

moderate or severe exacerbations per patient per year was 1.14 with roflumilast and 1.37 with placebo [17% reduction, rate ratio 0.83 (95% CI 0.75–0.92); $P = 0.0003$].

The most effective pharmacological treatment for patients with moderate-to-severe COPD is the regular use of inhaled long-acting bronchodilators, combined with ICS in patients with severe disease who are at risk of exacerbations (Global Initiative for Chronic Obstructive Lung Disease, 2009). As roflumilast is an anti-inflammatory agent rather than a bronchodilator, it should be used concomitantly with other treatments, most notably long-acting bronchodilators. Consequently, two recent 6-month studies examined the effects of roflumilast on pre-bronchodilator FEV_1 when used concomitantly with salmeterol (study M2-127) or tiotropium (study M2-128) (Fabbri *et al.*, 2009). These trials were multicentre, double-blind, randomized, parallel-group studies evaluating patients with moderate-to-severe COPD (FEV_1 40–70% predicted). M2-128 recruited patients who were more symptomatic as they were required to have a history of chronic cough and sputum production and frequent use of short-acting $beta_2$ agonists. Patients were randomly assigned to receive roflumilast 500 μg or placebo once daily for 24 weeks, in addition to concomitant treatment with salmeterol 50 μg twice daily ($n = 933$ treated) or tiotropium 18 μg once daily ($n = 743$ treated).

In the salmeterol study, mean pre-bronchodilator FEV_1 improved by 49 mL in the roflumilast 500 μg group compared with placebo ($P < 0.0001$), while in the tiotropium study, the improvement was 80 mL ($P < 0.0001$). Furthermore, similar improvements were seen in post-bronchodilator FEV_1, in the roflumilast 500 μg group compared with placebo, with improvements of 60 mL and 81 mL (both $P < 0.0001$) in the salmeterol and tiotropium studies respectively. In view of the poor baseline reversibility of these patients (partial reversibility to albuterol ≤ 12%), these improvements in FEV_1 show that roflumilast can provide additional benefit to patients already receiving long-acting bronchodilator therapy. Although these studies were powered to detect an improvement in lung function, M2-127 noted a reduction in the mean annual exacerbation rate (moderate or severe) by 36.8% ($P = 0.0315$; *post-hoc*). This reduction was not significant in M2-128: concomitant treatment reduced the mean annual exacerbation rate (moderate or severe) by 23.2% (rate ratio = 0.768; $P = 0.196$; Figure 4) (Chapman and Rabe, 2010). The low levels of exacerbations in the 6-month versus 12-month trials are illustrated in Figure 4. However, these 6-month studies in moderate-to-severe COPD may have been of an insufficient duration to permit reliable detection of an effect on exacerbations. Furthermore, patients were included in these studies who were not at risk from exacerbations or who had no prior history of exacerbations.

In order to further examine the effects of roflumilast in patients receiving concomitant treatments, a pooled analysis of studies M2-124 and M2-125 was performed. This analysis focused on the impact of roflumilast on exacerbations, not only when used concomitantly with long-acting bronchodilators but also in patients previously treated with an ICS (Bateman *et al.*, unpublished data). The mean rate of moderate and severe exacerbations per patient per year in patients

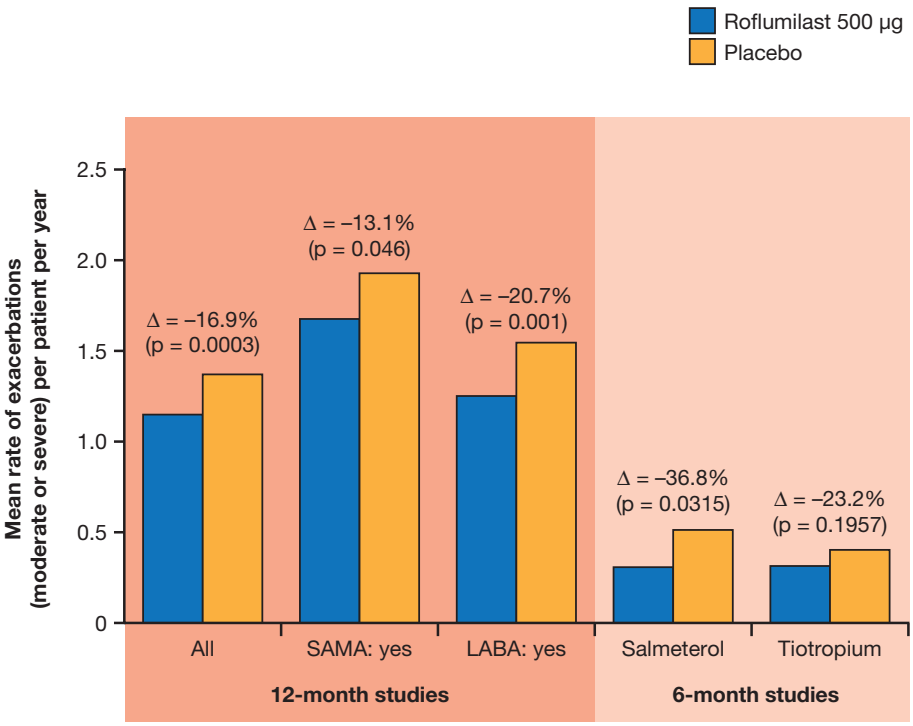


Figure 4

Effects on moderate or severe exacerbations after treatment with roflumilast 500 µg or placebo in patients receiving concomitant short-acting muscarinic antagonists (SAMAs) or long-acting beta$_2$-adrenergic receptor agonists (LABAs) in studies M2-124 and M2-125 (12-month studies) and M2-127 (concomitant administration with salmeterol) and M2-128 (concomitant administration with tiotropium) (Calverley *et al.*, 2009; Fabbri *et al.*, 2009; Bateman *et al.*, unpublished data).

receiving roflumilast was significantly lower than in those receiving placebo, regardless of concomitant use of LABA (20.7%; $P = 0.0110$), SAMA (13.1%; $P = 0.0458$) or previous ICS treatment (19.3%; $P = 0.0038$ all pre-specified analyses). Both pre-bronchodilator (improvement of 48 mL) and post-bronchodilator FEV_1 (improvement of 55 mL) were also significantly improved in patients treated with roflumilast compared with placebo, irrespective of concomitant LABA or SAMA use or previous ICS treatment ($P < 0.0001$). Furthermore, patients receiving concomitant ICS responded well to roflumilast, with an 18.8% reduction in exacerbations compared with placebo ($P = 0.014$) in a pooled analysis of two other 12-month studies (M2-111 and M2-112) (Rennard *et al.*, 2011). These findings, together with the results of M2-127 and M2-128 (Figures 4 and 5) (Calverley *et al.*, 2009; Fabbri *et al.*, 2009; Bateman *et al.*, unpublished data) support the addition of roflumilast in the treatment of patients whose symptoms are not adequately controlled with other therapies.

Safety

Roflumilast has been generally well tolerated in clinical studies to date. The most common adverse events observed are those that would be expected with PDE4 inhibitors, namely gastrointestinal effects and weight loss. In a pooled analysis of over 6000 patients receiving roflumilast in clinical trials, the overall adverse event rate was similar to that among patients receiving placebo (Calverley *et al.*, 2010a). Higher rates of diarrhoea, weight decrease, nausea, headache, back pain, insomnia, decreased appetite and dizziness were reported with roflumilast 500 µg than with placebo. By contrast, the incidence of COPD exacerbations, dyspnoea, upper respiratory tract infections, bronchitis, pneumonia and hypertension were lower with roflumilast 500 µg than with placebo (Calverley *et al.*, 2010b) (Table 3). In a pooled analysis of M2-124 and M2-125 (pivotal COPD studies pool), a range of adverse events occurred with roflumilast that were centrally mediated, namely insomnia, nausea, headache and gastrointestinal (predominantly diarrhoea) disturbance. Vomiting was not observed, in contrast to studies of cilomilast (Calverley *et al.*, 2009). These side effects were most evident in the first 4–12 weeks of therapy and were mostly mild or moderate in intensity. In this analysis, there were no cases of mesenteric vasculitis, as demonstrated by the absence of its most common clinical manifestation, ischaemic colitis (Nycomed GmbH, 2009), and no neurological or cardiac toxicity was noted. The incidence of adverse events was 67% with roflumilast and 62% with placebo; serious adverse events were reported in 19 and 22% of patients respectively. Discontinuations due to adverse events, however, were more common with roflumilast (14%) than with placebo (11%) in the 12-month M2-124 and M2-125 studies.

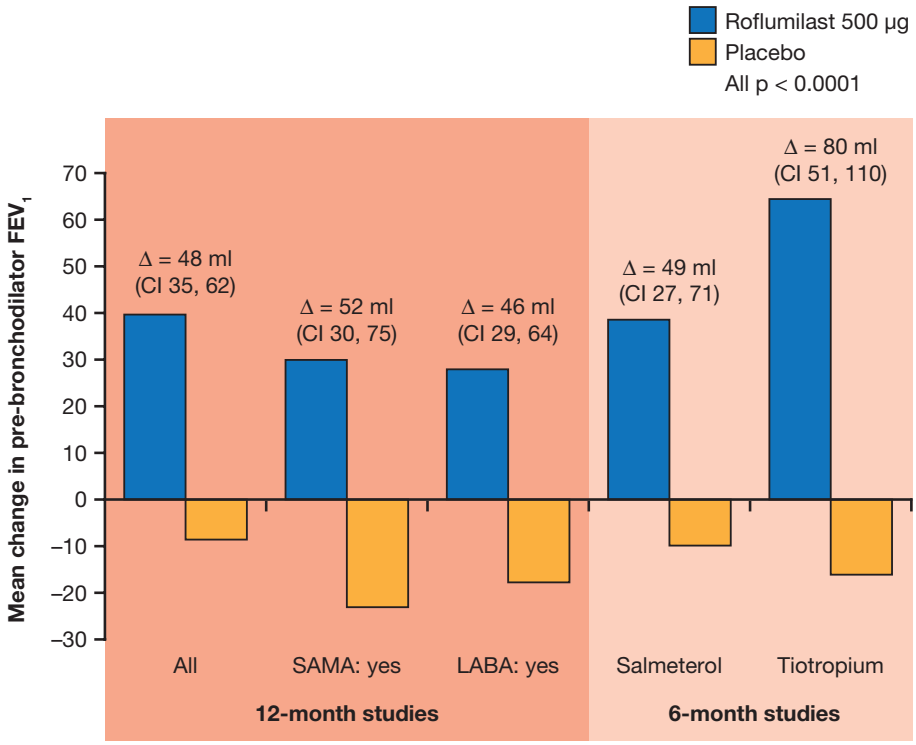


Figure 5

Effects on pre-bronchodilator FEV_1 after treatment with roflumilast 500 µg or placebo in patients receiving concomitant short-acting muscarinic antagonists (SAMAs) or long-acting $beta_2$-adrenergic receptor agonists (LABAs) in studies M2-124 and M2-125 (12-month studies) and in patients randomized to concomitant administration of roflumilast or placebo with salmeterol (M2-127) or concomitant administration of roflumilast or placebo with tiotropium (M2-128) (Calverley *et al.*, 2009; Fabbri *et al.*, 2009; Bateman *et al.*, unpublished data).

Class-specific adverse events

Gastrointestinal disturbances are class-related adverse events for PDE4 inhibitors (Spina, 2003). Investigations into the possible causes of these effects have focused on the tissue distribution of the PDE4 isoforms. For example, PDE4B is the predominant PDE4 subtype in monocytes and neutrophils and is thought to have a role in the inflammatory processes (Wang *et al.*, 1999), whereas PDE4D is highly expressed in the lung, cortex, cerebellum and in T-cells (Erdogan and Houslay, 1997; Jin *et al.*, 1998), and plays an important role in airway smooth muscle contraction (Mehats *et al.*, 2003). Studies in knockout mice have suggested that PDE4D is the main isoform associated with emesis (Robichaud *et al.*, 2002), while PDE4B appears to be the main isoform responsible for mediating release of tumour necrosis factor alpha (Jin and Conti, 2002). Further, binding of inhibitors to PDE4 is influenced by the N-terminal domain structure. There appears to be two binding sites: a high-affinity site with a Ki approximately 50–1000 times greater than binding to the low-affinity site. High-affinity binding predominates in the central nervous system, while low-affinity binding predominates in inflammatory cells, leading to important clinical differences in the pharmacological properties of inhibitors (Halpin, 2008). Strategies to improve the therapeutic ratio of PDE4 inhibitors have been suggested, such as targeting isoforms that appear to be expressed only as part of the inflammatory process in COPD, such as PDE4A4, or to develop dual-specificity inhibitors that inhibit PDE4 and either PDE1, PDE3 or PDE7 (Giembycz, 2005). However, as research progresses, the picture continues to become more complex. The complex arrangement of transcriptional units and multiple promoters have led to the identification of over 20 PDE4 isoforms (splice variants), each with unique N-terminal properties, enabling complex regulation mechanisms and intracellular compartmentalization (Peter *et al.*, 2007). Although roflumilast shows a similar specificity for PDE4D4 as for other subtypes, the gastrointestinal adverse events are less severe than with other PDE4 inhibitors. For example, cilomilast is 10 times more selective for PDE4D than other isozymes, and this selectivity for PDE4D-type nausea-inducing neurons could explain the lower tolerability seen with this compound (Lipworth, 2005).

Weight loss and glucose metabolism

Weight loss has been reported in subjects treated with roflumilast (Stanescu *et al.*, 1996; Calverley *et al.*, 2009), and is also seen with the non-selective PDE inhibitor theophylline (Boswell-Smith *et al.*, 2006a). Investigation of the mechanisms of lipolysis in human adipocytes found that PDE3B and PDE4 regulate cAMP pools that affect the activation/phosphorylation state of AMP-activated protein kinase, thereby influencing lipolysis (Omar *et al.*, 2009). Rolipram, a selective PDE4 inhibitor has been shown to increase plasma glucagon-like peptide-1 (GLP-1) concentrations in rats, suggesting PDE4D may play an important role in regulating

Table 3

Adverse event (AE) frequency with roflumilast (COPD safety pool) (Calverley *et al.*, 2010b)

	Roflumilast 500 μg·day^{-1} (*n* = 5766) n (%)	Placebo (*n* = 5491) n (%)
Patients with AEs	3873 (67.2)	3447 (62.8)
Patients with SAEs	781 (13.5)	782 (14.2)
Deaths	84 (1.5)	86 (1.6)
AEs with suggested causality (investigator)	1003 (17.4)	294 (5.4)
Study discontinued due to AEs	824 (14.3)	503 (9.2)
Most common adverse events (frequency ≥2% of patients in any treatment group)		
Infections and infestations	1492 (25.9)	1508 (27.5)
Nasopharyngitis	364 (6.3)	346 (6.3)
Upper respiratory tract infection	219 (3.8)	234 (4.3)
Bronchitis	177 (3.1)	192 (3.5)
Influenza	145 (2.5)	132 (2.4)
Pneumonia	104 (1.8)	110 (2.0)
Respiratory, thoracic and mediastinal disorders	1476 (25.6)	1607 (29.3)
COPD (exacerbation)	1142 (19.8)	1271 (23.1)
Dyspnoea	84 (1.5)	120 (2.2)
Gastrointestinal disorders	1271 (22)	587 (10.7)
Diarrhoea	585 (10.1)	143 (2.6)
Nausea	297 (5.2)	79 (1.4)
Investigations	811 (14.1)	584 (10.6)
Weight decreased	394 (6.8)	101 (1.8)
Nervous system disorders	615 (10.7)	304 (5.5)
Headache	266 (4.6)	110 (2.0)
Dizziness	139 (2.4)	65 (1.2)
Musculoskeletal and connective tissue disorders	590 (10.2)	445 (8.1)
Back pain	176 (3.1)	117 (2.1)
General disorders	369 (6.4)	321 (5.8)
Psychiatric disorders	344 (6.0)	164 (3.0)
Insomnia	148 (2.6)	50 (0.9)
Cardiac disorders	326 (5.7)	326 (5.9)
Metabolism and nutrition disorders	311 (5.4)	186 (3.4)
Decreased appetite	125 (2.2)	22 (0.4)
Injury, poisoning and procedural complications	209 (3.6)	220 (4.0)
Skin and subcutaneous tissue disorders	206 (3.6)	154 (2.8)
Vascular disorders	196 (3.4)	229 (4.2)
Hypertension	95 (1.6)	136 (2.5)
Neoplasms (benign, malignant and unspecified)	118 (2.0)	92 (1.7)

MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

intracellular cAMP, linked to the regulation of GLP-1 release (Ong *et al.*, 2009). Furthermore, GLP-1 analogues used for the treatment of diabetes mellitus type 2 (DM2) have demonstrated weight loss in obese patients without DM2 (Astrup *et al.*, 2009).

The pivotal COPD studies pool (M2-124 and M2-125) showed that the incidence of patients with measured weight loss was higher with roflumilast than with placebo (Calverley *et al.*, 2009). However, the weight loss observed with roflumilast was generally small (<3% of baseline weight). Body weight in the placebo groups remained almost unchanged. Most weight loss occurred in the first 6 months of treatment and was partially reversible within 12 weeks of stopping treatment (Martinez *et al.*, 2010). When stratified by body mass

index (BMI) category, all patient subsets showed a greater weight loss in the roflumilast arm than with placebo. The most pronounced weight change was observed in obese patients; this subgroup also had the highest proportion of patients with weight loss and with weight loss classified as clinically relevant (16.5% of patients vs. 9.1% in the overweight subgroup, 12.3% in the normal weight subgroup and 12.6% in the underweight subgroup). Underweight patients did not show a more notable weight loss than patients in the other BMI categories (Calverley *et al.*, 2010b). As might be expected from the involvement of PDE in lipolysis, the weight loss with roflumilast is primarily due to loss of fat mass. Bioimpedance measurements in study M2-128, which included an investigation into the effects of roflumilast on weight change as part of the safety assessment, showed that with roflumilast, the decline in fat-free mass index was most pronounced during the first 4 weeks and then reached a plateau until the end of treatment (Wouters *et al.*, 2010b). In contrast, the corresponding BMI values declined progressively during the 6-month duration of the study; these decreases levelled out after 3–4 months, and thereafter reached a plateau, the differential between fat-free mass and BMI constituting a reduction in fat mass. At the end of 6 months, almost two-thirds of the total weight decrease of –2.1 kg could be attributed to a loss of fat mass. These changes were reversible after withdrawal of study drug (Wouters *et al.*, 2010b). These findings are in accordance with those of Losco *et al.* (2004), who also found an association between weight loss and loss of fat mass with the PDE4 inhibitor, SCH351591, in monkeys (Losco *et al.*, 2004). In this study, weight loss was dose-dependent and reached a plateau after 2–3 weeks, with some animals (males) gradually regaining the weight lost.

As COPD is associated with insulin resistance and an increased risk of DM2 (Bolton *et al.*, 2007), which may be the result of elevated levels of systemically active pro-inflammatory molecules contributing to an altered metabolic state and insulin resistance, it is of interest to examine the effect of roflumilast on glucose metabolism, body composition and weight loss in patients with diabetes. In pooled analyses of roflumilast studies, roflumilast-treated patients with concomitant diabetes showed either no change in fasting or non-fasting blood glucose levels [pivotal COPD studies pool (M2-124 and M2-125)] or even decreased glucose levels (COPD safety pool; pooled data from the safety populations of 14 COPD studies). Placebo-treated patients with diabetes showed an increase in glucose levels from baseline to last visit (Wouters *et al.*, 2010a). In patients without concomitant diabetes, there were slight increases in glucose levels from baseline to last visit in both treatment groups. The difference in blood glucose level between the roflumilast and placebo groups was statistically significant only for patients with concomitant diabetes in the COPD safety pool (P = 0.0135) (Wouters *et al.*, 2010a).

In a 12-week, placebo-controlled study of roflumilast 500 μg once daily in 205 newly diagnosed, treatment-naïve patients with DM2 (study M2-401), plasma glucose levels decreased significantly more in the roflumilast group than in the placebo group [least square (LS) mean (standard error, SE) difference –1.04 (0.30), P = 0.0006] (Wouters *et al.*, 2010a). Marked attenuation of the glucagon response after the fixed meal test was observed in the roflumilast treatment group, and the rise in glucose levels following a fixed meal was also reduced in this group (EFM Wouters, unpublished data). Patients in both groups lost weight over the course of the study; LS means (SE) –1.9 kg (0.3) versus –1.2 kg (0.3) for roflumilast versus placebo, respectively [LS means (SE) difference –0.7 kg (0.4), P = 0.0584] (EFM Wouters, unpublished data). Type II diabetes is characterized by a severely reduced or absent incretin effect (Nauck *et al.*, 1986), and these effects of roflumilast on glucose and glucagon levels, and effects on weight, may involve incretins – gastrointestinal hormones released from endocrine cells in the distal ileum and the colon in response to food intake with subsequent amplification of insulin secretion (Holst, 2007).

Other adverse events

Cardiac adverse events have been seen with some PDE4 inhibitors, namely rolipram (Larson *et al.*, 1996) and SCH351591 (Losco *et al.*, 2004). In the pooled safety results for roflumilast, however, the incidence of cardiac adverse events was similar in the roflumilast 500 μg and placebo groups (5.7% vs. 5.9%) (Calverley *et al.*, 2010a).

Of the other adverse events that have been suggested as potential problems with PDE4 inhibitors, the safety analyses from the roflumilast trials have not been able to show any reason for concern with respect to proconvulsant effects, infections or tumours (Calverley *et al.*, 2010a). Moreover, no proconvulsant effect would be expected with roflumilast due to PDE4 selectivity. In clinical COPD studies, there was no difference between roflumilast and placebo in the frequency of adverse events associated with potential proconvulsant effects of roflumilast (i.e. convulsions, epilepsy, partial seizure, *petit mal* seizure) (Calverley *et al.*, 2010a). The incidence of infections was similar across all groups: 27.5% in the placebo group, 23.6% with roflumilast 250 μg and 25.9% with roflumilast 500 μg. As COPD patients are known to be prone to pneumonia, these events were analysed separately and showed no appreciable differences between roflumilast and placebo (1.8% vs. 2.0%) (Calverley *et al.*, 2010a). The rate of tumours in the COPD safety pool was slightly higher with roflumilast than placebo (1.5% vs. 1.3%). None of these tumour events was assessed as related to the study medication (Calverley *et al.*, 2010b). Comparison of these results with tumour incidence in the COPD general population using data from an epidemiological study based on 35 772 COPD patients revealed a higher incidence in the time-adjusted incidence of tumours in this COPD population than in the COPD safety pool (27.8 vs. 27.3 respectively) (Schneider *et al.*, 2010). The majority of cancers observed in the COPD safety pool were solid tumours (175/185; (Calverley *et al.*, 2010b); these are known to require several years to develop before diagnosis. The risk of a tumour adverse event did not increase over time but remained constant over the treatment period of up to 1 year, suggesting that the tumours were not causally related to roflumilast treatment. Furthermore, the events were detected during the first 6 months of treatment with no difference in incidence between placebo and roflumilast detected after 6 months of treatment, suggesting against a causal relationship to treatment.

In the COPD safety pool, psychiatric disorders occurred in 6.0% of patients receiving roflumilast 500 μg compared with

3.0% of placebo patients. Although there were more cases of depression (1.21% vs. 0.82%) and suicidal ideation/attempt (0.03% vs. 0.02%) with roflumilast 500 μg compared with placebo, overall this affected very few patients (Food and Drug Administration, 2010). The incidence of completed suicide in patients receiving roflumilast in the COPD safety pool (two in the 500-μg group and one in the 250-μg group vs. none receiving placebo) has recently been identified as a subject of significant concern by the US Food and Drug Administration (Food and Drug Administration, 2010); however, none was identified as being related to study medication.

Conclusions

Current management of COPD requires an incremental approach in which patients are first treated with bronchodilators (beta-adrenergic receptor agonists or anticholinergic agents), which can be followed by anti-inflammatory treatment (inhaled or oral corticosteroids) if needed. However, this approach has limited overall efficacy in this disease that presents with a wide variety of clinical phenotypes.

PDE4 inhibitors are the first novel class of drug to emerge for the treatment of COPD in the last decade. Roflumilast is the first member of this class to be licensed, and is indicated in the European Union for the maintenance treatment of severe COPD associated with chronic bronchitis and a history of frequent exacerbations as an add-on to bronchodilator treatment. Clinical trials have demonstrated that roflumilast improves lung function and, more importantly, reduces exacerbation frequency in COPD. Furthermore, its mode of action may provide a unique approach to targeting the inflammatory process underlying COPD compared with other currently available medication. Roflumilast is effective when used concomitantly with all forms of bronchodilator and even in patients treated with ICS. Roflumilast thus represents an important addition to current therapeutic options for COPD patients with chronic bronchitis, including those who remain symptomatic despite treatment.

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Conflict of interest

KFR has served as a consultant, participated in advisory board meetings, has received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Pfizer, Novartis, Nycomed, Merck Sharp and Dohme, and GlaxoSmithKline, and has received research funding from Altana Pharma, Novartis, AstraZeneca, Boehringer Ingelheim, Roche and GlaxoSmithKline.

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