



Australian Government

Department of Health and Ageing  
Therapeutic Goods Administration

# Australian Public Assessment Report for Roflumilast

Proprietary Product Name: Daxas, Xevex,  
Dalveza

Sponsor: Nycomed Pty Ltd

**December 2011**

**TGA** Health Safety  
Regulation

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# I. Introduction to Product Submission

## Submission Details

<i>Type of Submission:</i>	New Chemical Entity
<i>Decision:</i>	Withdrawn
<i>Date of Decision:</i>	16 November 2011
<i>Active ingredient(s):</i>	Roflumilast
<i>Product Name(s):</i>	Daxas/Xevex/Dalveza
<i>Sponsor's Name and Address:</i>	Nycomed Pty Ltd 2 Lyon Park Road Macquarie Park North Ryde NSW 2113
<i>Dose form(s):</i>	Film coated tablet
<i>Strength(s):</i>	500 µg
<i>Container(s):</i>	Blister pack
<i>Pack size(s):</i>	10, 30 or 90 tablets
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	500 µg daily

## Product Background

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in Europe, and is a major public health problem.<sup>1</sup> COPD is generally but not exclusively associated with tobacco smoking. Tobacco smoke is considered the most important risk factor for COPD worldwide.

COPD comprises pathological changes in four different compartments of the lungs (central airways, peripheral airways, lung parenchyma, and pulmonary vasculature), which, in turn, give rise to the physiological abnormalities in COPD: mucous hypersecretion and ciliary dysfunction, airflow limitation and hyperinflation, gas exchange abnormalities, pulmonary hypertension, and systemic effects.<sup>1</sup>

Prevalence and morbidity data greatly underestimate the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent and moderately advanced.<sup>1</sup>

The most widely accepted classification of the severity of COPD is according to The Global Initiative for Chronic Obstructive Lung Disease (GOLD). The GOLD classification is based on the degree of impairment of lung function. Four categories are recognised: mild, moderate, severe, very severe (Stages I-IV).<sup>1</sup>

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<sup>1</sup> EMA. CHMP Assessment Report for Daxas (EPAR). Available at:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Public\\_assessment\\_report/human/001179/WC500095213.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001179/WC500095213.pdf)

The most important aspect of management of the condition is educational and social: the avoidance and cessation of tobacco smoking. The medications for COPD currently available can reduce or abolish symptoms, increase exercise capacity, reduce the number and severity of exacerbations and improve health status. At present no treatment is shown to modify the rate of decline in lung function. Combining different agents produces a greater change in spirometry and symptoms than single agents alone.<sup>1</sup>

This AusPAR describes the evaluation of an application by Nycomed Pty Ltd (the sponsor) to register the new chemical entity, roflumilast (Daxas).<sup>2</sup> It was initially proposed for:

*Maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations.*

After the receipt of the clinical evaluation report, the proposed indication was changed to:

*Maintenance treatment of severe chronic obstructive pulmonary disease (COPD) in adult patients with chronic bronchitis and recent history of exacerbations as add on to bronchodilator treatment.*

Roflumilast is a selective phosphodiesterase type 4 (PDE4) inhibitor. PDE4 is an important regulator of cyclic adenosine monophosphate (cAMP) in most cell types involved in inflammatory processes. Inhibition of PDE4 reduces the breakdown of cAMP, which in turn downregulates the inflammatory process.<sup>1</sup>

### **Regulatory Status**

A similar application has been submitted in the European Union (EU) where approval was granted on 5 July 2010 for the indication:

*Daxas is indicated for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV<sub>1</sub> postbronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.*

It was also approved in Canada on 23 November 2010 for the indication:

*Daxas (roflumilast) administered once daily (500 mcg tablet per day) is indicated, as add-on therapy to bronchodilator treatment, for the maintenance treatment of severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis (i.e. patients with a history of chronic cough and sputum) in adult patients with a history of frequent exacerbations.*

*Daxas should not be used as a rescue medication.*

It was also approved in the US on 28 February 2011 for the indication:

*Daliresp is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Limitations of Use: Daliresp is not a bronchodilator and is not indicated for the relief of acute bronchospasm.*

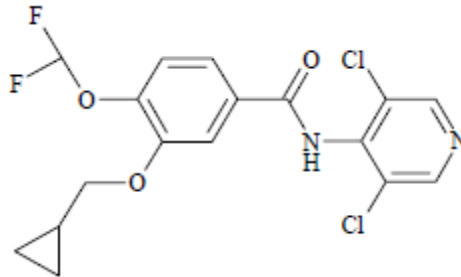
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<sup>2</sup> Three tradenames are proposed: Daxas, Xevex and Dalveza. It will be referred to as Daxas for the remainder of this AusPAR.

## II. Quality Findings

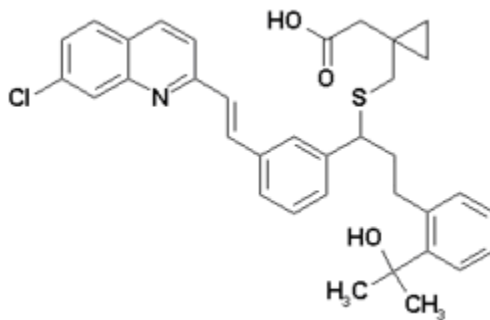
### Drug Substance (active ingredient)

Roflumilast is a synthetic pyridine derivative; it is weakly basic. Particle size is controlled and solubility is low. Control of the drug substance was considered acceptable.

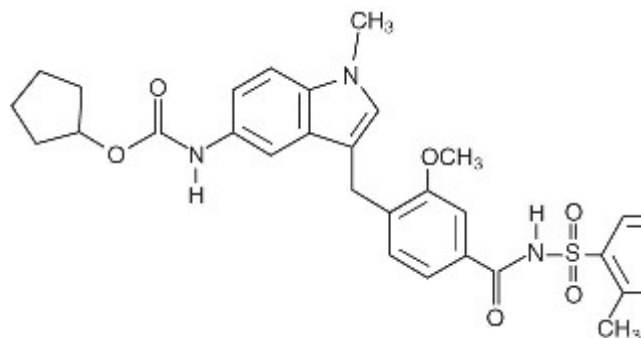


**roflumilast**

Roflumilast is not closely related to structures of theophylline (a non-selective PDE inhibitor) or to the asthma drugs montelukast or zafirlukast (leukotriene receptor antagonists):



**montelukast**



**zafirlukast**

### Drug Product

Roflumilast is presented as 500 µg film coated, immediate release tablets under three trade names. Formulation details are conventional. The tablets are to be packed in PVC/PVDC/Al blister packs. There were no significant changes detected on storage.

### Biopharmaceutics

Roflumilast is rapidly metabolised to roflumilast N-oxide, an active metabolite.

The absolute bioavailability of roflumilast from Formulation B tablets was investigated in an old study (Study 242E/98) which used insufficient sampling to properly characterise elimination of the dominant, active N-oxide. Absorption is extensive but not precisely quantified; it was concluded: "Interpretation of absolute bioavailability when the active

metabolite is present in substantial quantities is problematic. While comparison of roflumilast parameters suggests an absolute bioavailability of 79%, N-oxide also reflects the availability of pharmacologically active species associated with the absorption of roflumilast and suggests 100% absorption. Because of the weaknesses in the data, the results for the N oxide are considered unreliable however, it would be misleading to quote absolute bioavailability of 79% based on roflumilast without indicating that the N oxide suggests complete absorption.”

Various tablet formulations were investigated. Almost all clinical studies used uncoated 250 and 500 µg tablets. The pertinent tablet formulations are:

Formulation B: uncoated tablets used in almost all clinical studies. Dose strengths were shown to be bioequivalent to each other.

Formulation C: a bigger 500 µg tablet intended for development but not bioequivalent to formulation B (with respect to the maximum plasma concentration [ $C_{max}$ ]). Formulation C was not used in clinical studies. It is clearly distinguished from B by a dissolution test.

Formulation E: formulation proposed for registration.

The effect of food on the bioavailability of Formulation B tablets was investigated in Study 11/98K. Food reduced and delayed  $C_{max}$ . Comparisons of the area under the plasma concentration time curve (AUC) were somewhat confounded by the blood sampling used and the observed effects were different for roflumilast and for the N-oxide. While fed and fasting dosing is not strictly bioequivalent, the food effect is not dramatic.

### **Formulation Bioequivalence Study**

The relative bioavailability of pivotal clinical trial Formulation B and the proposed (Formulation E) tablets was investigated in Study EM-056 [= 473/2007]. The study concluded bioequivalence (both in terms of roflumilast and its N oxide).

### **Advisory Committee Considerations**

This application was considered at the 133rd meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). The subcommittee wished to review the application again before it was considered by the ACPM.

The PSC recommended:

1. The PSC has reviewed data and comments provided by the sponsor and the TGA on the biopharmaceutical aspects of the evaluations.
2. The PSC agreed that the issues of concern in relation to the biopharmaceutical data raised at a previous meeting have now been resolved to the satisfaction of the TGA.
3. The PSC therefore concluded that there should be no objection on pharmaceutical and biopharmaceutical grounds to the approval of this application.
4. There is no requirement for this application to be reviewed again by the PSC before it is presented for consideration by the Advisory Committee on Prescription Medicines.

The chemistry and quality control questions were resolved.

### **Quality Summary and Conclusions**

Registration was recommended with respect to chemistry, quality control and bioavailability aspects.

## III. Nonclinical Findings

### Introduction

The overall quality of the submitted dossier was mostly high, with all pivotal toxicity studies conducted under Good Laboratory Practice (GLP) conditions using the proposed clinical route (oral [PO]).

### Pharmacology

#### Primary pharmacodynamics

##### *Rationale and mechanism of action*

Phosphodiesterase 4 (PDE4), a cAMP-specific phosphodiesterase, is the major class of PDE expressed in inflammatory cells, in particular in macrophages, eosinophils and neutrophils, the main cell types present in the lungs of COPD patients. PDE4 is also expressed in airway smooth muscle, pulmonary epithelial, pulmonary vascular endothelial and sensory nerve cells. cAMP is a secondary messenger that regulates various physiological functions including the suppression of cytokine release from inflammatory cells, thereby reducing their proliferation and further infiltration by inflammatory cells. It is anticipated that inhibition of PDE4 will increase intracellular cAMP levels with a resultant antiinflammatory effect and a reduction in the intensity of COPD symptoms.

##### *Efficacy*

The inhibitory potency for roflumilast on the PDE4 isozyme was >1000 fold its potency at other PDE isozymes, with a median inhibitory concentration (IC<sub>50</sub>) of 0.2–4.3 nM (1 to 22 times the peak free concentration of roflumilast expected in patients or 4 to 90 times less than the total concentration at the clinical C<sub>max</sub>. The sponsor noted that in human plasma, roflumilast N-oxide represents the major carrier of pharmacological activity; the IC<sub>50</sub> values for PDE4 inhibition by roflumilast N-oxide (0.3 to 0.8 µg/L) are in the range of the plasma C<sub>max</sub> of unbound roflumilast N-oxide in humans (C<sub>maxfree</sub> 0.7 µg/L). Roflumilast had approximately equal inhibitory potency at the PDE4A, PDE4B and PDE4D subtypes (IC<sub>50</sub>, around 0.5 nM) and approximately 7 fold lower potency for the PDE4C subtype (IC<sub>50</sub>, 3.6 nM). The PDE4 A, B and D subtypes are variously expressed (and co-expressed) by human immune cells (Spina, 2008).<sup>3</sup>

Roflumilast inhibited superoxide formation and leukotriene synthesis in stimulated human polymorphonuclear leukocytes and eosinophils, tumour necrosis factor (TNFα) release from stimulated human monocytes and macrophages, and inhibited proliferation of and cytokine release (IL-2, IL-4, IL-5 and IFNγ) from human T cells. All of these effects are consistent with the drug acting to elevate cAMP levels in the target cells (Torphy, 1998).<sup>4</sup> IC<sub>50</sub> values ranged from 1.2 to around 8 µg/L (3–20 nM). When tested in whole blood, the potency for inhibition of TNFα release from inflammatory cells was much lower (IC<sub>30</sub> values, 20–25 µg/L or 50–62 nM). The reduced activity in whole blood was attributed to a high degree of protein binding by roflumilast in human plasma (99%). Roflumilast increased ciliary beating frequency *in vitro* in the rat airway.

Mice and rats were challenged with lipopolysaccharide (LPS) from *E. coli* to simulate the pulmonary inflammation and exaggerated constrictor responses seen in COPD (Toward

<sup>3</sup> Spina, D. PDE4 inhibitors: current status. *Br J Pharmacol* 2008; 155: 308–315.

<sup>4</sup> Torphy TJ. Phosphodiesterase isozymes: Molecular targets for novel antiasthma agents. *Am J Respir Crit Care Med* 1998; 157: 351–370.



and Broadley, 2001).<sup>5</sup> When given 1 or 6–7 hours (h) prior to LPS challenge, roflumilast inhibited TNF $\alpha$  release in mice (ED<sub>50</sub>, 2.0 mg/kg PO and 2.8 mg/kg PO, respectively) and in rats (ED<sub>50</sub>, 0.13 mg/kg PO and 0.6 mg/kg PO, respectively). These doses are estimated to have yielded about 0.2 to 2 times the clinical exposure based on AUC.<sup>6</sup> When given 1 or 16 h prior to LPS challenge, roflumilast inhibited neutrophil and leukocyte accumulation (ID<sub>50</sub>, 0.45 mg/kg PO) and suppressed MCP-1 and MIP-1 $\alpha$  release (ID<sub>50</sub>, 0.15–0.78 mg/kg PO) in the airway of rats. Inhibition of cytokine release, inflammatory cell accumulation, matrix degradation and parenchymal destruction by roflumilast was demonstrated in smoke induced lung injury models in the mouse and guinea pig.

Roflumilast N-oxide, the major metabolite of roflumilast also inhibited PDE4, but with about a 2 to 3 times lower potency than roflumilast. This metabolite also inhibited superoxide formation and leukotriene synthesis in human polymorphonuclear leukocytes and eosinophils, TNF $\alpha$  release from monocytes and macrophages, cytokine release from T cells. *In vivo*, roflumilast N-oxide, administered orally prior to LPS challenge, inhibited neutrophil and leukocyte accumulation in the bronchoalveolar lavage fluid of rats with similar efficacy to roflumilast. Dealkylated roflumilast (M5), a metabolite in animals, had 300 fold lower potency for PDE4 than roflumilast, while the rodent metabolites, ADCP (4-amino-3,5-dichloropyridine) and ADCP N-oxide, showed no significant inhibition of PDE4. Therefore, at exposures similar to that expected clinically, roflumilast inhibited cytokine release, as well as other indicators of a bronchial inflammatory response, in rodent models of COPD. Based on potency and pharmacokinetic data, roflumilast N-oxide is expected to be the major contributor to PDE4 inhibition in patients.

### Pharmacodynamic drug interactions

Additive or synergistic interactions were observed with roflumilast (or roflumilast N-oxide) and  $\beta$  and  $\beta_2$  adrenoceptor agonists, the glucocorticosteroid dexamethasone, antagonists of leukotriene, histamine H<sub>1</sub> and muscarinic receptors and the PDE5 inhibitor sildenafil in various assay systems (*in vitro* and *in vivo*, including models of bronchoconstriction). Potentiation of cellular/tissue responses is to be expected in situations where both agents act to increase intracellular cAMP.

### Secondary pharmacodynamics

In isolated tissue preparations, roflumilast and roflumilast N-oxide did not interact directly with muscarinic, histaminergic, purinergic or adrenergic receptors. Weak, non-specific relaxation was observed in some of the tissue preparations at very high concentrations.

### Safety pharmacology

cAMP is a component of a large number of signalling pathways throughout the body and PDE4 isozymes are widely expressed. Thus, the potential for pharmacological activity in other tissues, including the central nervous system (CNS), the cardiovascular system, the reproductive organs and the gastrointestinal tract, exists. Specialised safety pharmacology studies investigated the central and autonomic nervous systems, the cardiovascular,

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<sup>5</sup> Toward TJ, Broadley KJ. Chronic lipopolysaccharide exposure on airway function, cell infiltration, and nitric oxide generation in conscious guinea pigs: effect of rolipram and dexamethasone. *J Pharmacol Exp Ther* 2001; 298: 298–306.

<sup>6</sup> Data for mice were estimated from Study 99/2002, where an oral dose of 12 mg/kg roflumilast resulted in an AUC<sub>0-∞</sub> ~8  $\mu\text{M}\cdot\text{h}$  (combined roflumilast and roflumilast N-oxide), while data for rats were estimated from Study 199/96, where a dose of 0.5 mg/kg PO resulted in an AUC<sub>0-∞</sub> 0.65  $\mu\text{M}\cdot\text{h}$  (roflumilast and roflumilast N-oxide). Clinically, a 500  $\mu\text{g}$  dose resulted in an AUC<sub>0-∞</sub> ~1.1  $\mu\text{M}\cdot\text{h}$  (roflumilast and roflumilast N-oxide).

respiratory, renal and gastrointestinal systems. The majority of the studies were not GLP compliant but the design, conduct and reporting of the studies were mostly adequate to reveal any treatment related effects.

Neurological effects observed in mice and rats given roflumilast or roflumilast N-oxide included hypoactivity, hyperpnoea, increased maintenance activity, tremor, isolation and ptosis. Dose and time dependent reductions in body temperature and spontaneous locomotor activity with impaired coordination were also seen in treated mice. These effects occurred at doses resulting in peak plasma concentrations of roflumilast and roflumilast N-oxide estimated to be  $\geq 4.5$  times higher than that expected clinically.<sup>7</sup> Such effects have been reported for other PDE4 inhibitors (Wachtel, 1982; Matsuhita et al., 1977) and they are likely associated with the primary pharmacological activity and increased cerebral cAMP levels.<sup>8,9</sup> PDE4 isozymes are expressed in the brain cortex, hippocampus and striatum, and mice deficient in PDE4B and PDE4D isozymes have displayed anxiogenic like behaviour and behavioural deficits in associative learning, respectively (Zhang et al., 2008; Rutten et al., 2008).<sup>10,11</sup> The sponsor noted that PDE4 inhibition has been also reported/discussed to be related to antidepressive effects (Zhang et al. 2009) and to cognition enhancement (Reneerkens et al. 2009).<sup>12,13</sup> Given the relatively small safety margin, the crudeness of behavioural tests, and the effects noted in knockout mice, some effects on CNS associated behaviour may occur in the clinical setting.

Roflumilast had pro-convulsant effects in mice. At  $\geq 3$  mg/kg PO (estimated relative exposure based on  $C_{max}$  [ $ER_{C_{max}}$ ], 22), the latency time to occurrence of tonic convulsions was reduced, while higher oral doses (30 mg/kg) reduced the threshold for seizures and increased lethality after both electrically induced and pentetrazole induced seizures. There was no effect at 1 mg/kg PO. Increased cAMP levels are associated with seizure onset (Boulton et al., 1993) and anticonvulsants have been reported to prevent cAMP accumulation (Chang et al., 2009), suggesting the effects are likely to be pharmacologically mediated.<sup>14,15</sup> Aggravation of seizures in patients is not expected at therapeutic doses.

No significant inhibition of hERG  $K^+$  channels was observed with roflumilast at concentrations up to 24  $\mu\text{g/L}$  (60 nM) nor roflumilast N-oxide up to 84  $\mu\text{g/L}$  (200 nM), while higher roflumilast N-oxide concentrations (600 nM) resulted in only 11% inhibition. Though the tested concentrations are only marginally higher than the maximum clinical plasma concentrations of roflumilast and roflumilast N-oxide (18 and 57 nM, respectively), based on free fraction concentrations (0.20 and 1.9 nM for roflumilast and roflumilast N-oxide, respectively) there is a sufficient safety margin for there to be no apparent clinical

<sup>7</sup> Based on data in Studies 99/2002, 199/96 and 226/98.

<sup>8</sup> Wachtel H. Characteristic behavioural alterations in rats induced by rolipram and other selective adenosine cyclic 3',5'-monophosphate phosphodiesterase inhibitors. *Psychopharm* 1982; 77: 309-316.

<sup>9</sup> Matsuhita N, Shibazaki Y, Kawamata S, Ohnishi M, Nakayoshi T. General pharmacological properties of rolipram. *Kiso to Rinsho* 1977; 31: 1009-1033.

<sup>10</sup> Zhang J, Snyder RD, Herman EH *et al*. Histopathology of vascular injury in Sprague-Dawley rats treated with phosphodiesterase IV inhibitor SCH 351591 or SCH 534385. *Toxicol Path* 2008; 36: 827-839.

<sup>11</sup> Rutten K, Misner DL, Works M *et al*. Enhanced long-term potentiation and impaired learning in phosphodiesterase 4D-knockout (*PDE4D*<sup>-/-</sup>) mice. *Eur J Neurosci* 2008; 28: 625-632.

<sup>12</sup> Zhang H. Cyclic AMP-Specific Phosphodiesterase-4 as a Target for the Development of Antidepressant Drugs, *Current Pharmaceutical Design* 2009; 15: 1688-1698.

<sup>13</sup> Reneerkens O, Rutten K, Steinbusch H, Blokland A, Prickaerts J. Selective phosphodiesterase inhibitors: a promising target for cognition enhancement, *Psychopharmacology* 2009; 202:419-443.

<sup>14</sup> Boulton, CL, McCrohan CR, O'Shaughnessy CT. Cyclic AMP analogues increase excitability and enhance epileptiform activity in rat neocortex *in vitro*. *Eur J Pharmacol* 1993; 236: 131-136.

<sup>15</sup> Chang P, Chandler KE, Williams RSB, Walker MC. Inhibition of long-term potentiation by valproic acid through modulation of cyclic AMP. *Epilepsia* 2009; doi: 10.1111/j.1528-1167.2009.02412.x.

concerns ( $\geq 30$  fold; Redfern et al., 2003).<sup>16</sup> No electrocardiogram (ECG) effects were seen in safety pharmacology studies (cats treated with 7 mg/kg IV roflumilast and minipigs treated with 70  $\mu$ g/kg intravenous [IV] roflumilast;  $ER_{C_{max}}$ , 870 and 12, respectively) or in pivotal repeat dose toxicity studies in dogs (up to 2 mg/kg/day PO;  $ER_{C_{max}}$ ,  $>10$ ) or monkeys (up to 0.5 mg/kg/day PO;  $ER_{C_{max}}$ , 10). Increased QRS, Q $\alpha$ T and QT times were only seen in rats treated with a high lethal dose (8 mg/kg/day PO; estimated  $ER_{C_{max}}$ , 38), while no effect was seen at the lower dose (4 mg/kg/day). Based on these findings, there is unlikely to be an effect on ECG parameters with roflumilast at clinical exposure levels.

Haemodynamic effects in dogs ( $\geq 1$   $\mu$ g/kg IV) and cats ( $\geq 100$   $\mu$ g/kg IV) included increased heart rate, blood pressure, left ventricular pressure and cardiac contractility. These doses in dogs are estimated to result in maximum plasma concentrations significantly below the clinical  $C_{max}$ . No effects on blood pressure, left ventricular pressure or cardiac contractility were seen in pithed rats treated with 8 mg/kg IV roflumilast (estimated  $ER_{C_{max}}$ ,  $\sim 270$ ) or in minipigs treated with 70  $\mu$ g/kg IV roflumilast ( $ER_{C_{max}}$ ,  $\sim 12$ ). The haemodynamic effects seen in cats and dogs can be attributed to a vasodilatory effect. Dogs treated with rolipram, another PDE4 inhibitor, displayed similar effects on cardiac function and blood pressure (Matsuhita et al., 1987).<sup>9</sup>

The sponsor provided an expert report to explain cardiovascular findings. PDE4D is closely associated with  $\beta_2$ -adrenoceptor signalling in cardiomyocytes (Xiang et al., 2005) and the effects on heart rate and cardiac contractility by PDE4 inhibitors could be prevented by  $\beta$ -adrenoceptor blockade.<sup>17</sup> Taken together it suggests the observed effects of PDE4 inhibitors in dogs are likely mediated by downstream signalling alterations rather than a direct inotropic effect as seen with PDE3 inhibitors (Weishaar et al., 1987).<sup>18</sup> In dogs, clear spatial distribution differences exist for cAMP-hydrolysing PDE isoforms (Weishaar et al., 1987); this may explain the particular sensitivity of the species to cardiovascular effects with PDE4 inhibitors.<sup>18</sup> Less compartmentalisation has been suggested in human cardiomyocytes, and it is possible that the presence of another co-expressed PDE isoform in both rat and human cardiomyocytes compensates for the absence of PDE4 activity.

No depressant effects on the respiratory system were observed in rats, guinea pigs or cats. A modest increase in respiratory rate and tidal volume was seen with roflumilast and roflumilast N-oxide, respectively, in cats following IV infusion at doses  $\leq 7$  mg/kg, and, as indicated above, hyperpnoea was observed in the CNS safety pharmacology studies in rodents.

No significant effects on contraction or intestinal motility were observed in specialised gastrointestinal safety studies in rodents. However, roflumilast increased basal gastric acid secretion in rats (at  $\geq 40$   $\mu$ g/kg IV) and increased stomach weight in mice (consistent with increased acid secretion or inhibition of stomach emptying) at doses  $\geq 1$  mg/kg IV or PO. Stimulation of gastric acid secretion in rats was pronounced and prolonged at doses  $\geq 0.4$  mg/kg IV (estimated  $ER_{C_{max}}$ ,  $>13$ ) but minor and transient at lower doses. This is likely to be a pharmacological effect, with PDE4 inhibition leading to elevated parietal cell

<sup>16</sup> Redfern WS, Carlsson L, Davis AS et al. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. *Cardiovascular Res* 2003; 58: 32–45.

<sup>17</sup> Xiang Y, Naro F, Zoudilova M, Jin S-LC, Conti M, Kobilka B. Phosphodiesterase 4D is required for  $\beta_2$  adrenoceptor subtype-specific signalling in cardiac myocytes. *Proc Natl Acad Sci USA* 2005; 102: 909–914.

<sup>18</sup> Wieshaar, RE, Kobylarz-Singer DC, Steffen RP, Kaplan HR. Subclasses of cyclic AMP-specific phosphodiesterase in left ventricular muscle and their involvement in regulating myocardial contractility. *Circ Res* 1987; 61: 539–547.

cAMP levels, stimulating acid secretion (Barnette et al., 1995).<sup>19</sup> While stomach erosions and gastrointestinal inflammation were observed in rat toxicity studies, these were only observed at high doses (8 mg/kg PO; estimated relative exposure based on AUC [ER<sub>AUC</sub>], 16). Emesis was observed in dogs ( $\geq 0.2$  mg/kg/day PO; ER<sub>AUC</sub>, 0.5) and monkeys ( $\geq 0.5$  mg/kg/day PO; ER<sub>AUC</sub>, 10); the other tested species are non-vomiting. Emetic activity has been reported for other PDE4 inhibitors. PDE4 is present in parietal cells and in emetic centres (area postrema, nucleus tractus solitaries). It is unclear if the mechanism for the emetic effect is related to alterations in gastric secretion and gastric emptying or solely has an origin in the CNS (Giembycz, 2002).<sup>20</sup> The involvement of inhibition of the PDE4D subtype in particular has been suggested (Boswell-Smith and Spina, 2007).<sup>21</sup>

In rats, roflumilast ( $\geq 1$  mg/kg PO; estimated ER<sub>Cmax</sub>, 4) induced a reduction in urinary volume with a concomitant increase in osmolality. These effects have been reported for other PDE4 inhibitors (Matsuhita et al., 1977) and given their nature, have no toxicological relevance.<sup>9</sup> There was no evidence of renal toxicity at reasonably high exposures in the submitted toxicity studies.

### Pharmacokinetics

Roflumilast was rapidly absorbed in all species. There were no apparent gender differences. The plasma half-life was relatively short in mice, rats, hamsters, guinea pigs, rabbits, dogs and monkeys (~1–4 h) but longer in minipigs and cats (12.5 h) and in humans (18 h). The volume of distribution was greater than total body water in all tested species. Clearance was roughly similar in dogs, monkeys, cats and humans, and higher in the rodent species and rabbits. Bioavailability was low ( $\leq 25\%$ ) in mice, rats, hamsters, rabbits and dogs after oral gavage with 4% methocel as the vehicle. Higher oral bioavailabilities were seen in monkeys using a polyethylene glycol (PEG) vehicle (34–48%) and in dogs with tablet formulations (50–60%). The oral bioavailability was 79% in clinical studies with roflumilast tablets.

Roflumilast N-oxide was a significant metabolite in rats, hamsters, guinea pigs, rabbits, monkeys and in humans, but not dogs. Greater exposure to roflumilast N-oxide relative to roflumilast was evident after oral compared with IV administration, suggesting some first pass metabolism. With the exception of dogs, exposure to roflumilast N-oxide was greater than to the parent in all species (PO administration); molar AUC ratios (roflumilast N-oxide to roflumilast) were 2–4 (in mice), ~20 (rats), 21–46 (hamsters), <0.15 (dogs), 3 (monkeys) and 10 (humans). Based on these and other data, it can be seen that roflumilast N-oxide significantly contributes to the pharmacological action of roflumilast in most species.

Plasma protein binding by roflumilast and roflumilast N-oxide was high in animal and human serum. There was no indication of concentration dependent binding. Considerable interspecies differences in protein binding were seen; levels of free roflumilast and roflumilast N-oxide were 2 to 3 times higher in rodent compared with human plasma. In all species, the free fraction was several fold higher for the metabolite compared with the parent (3 times in humans; 3.4% vs 1.1%). Given that roflumilast N-oxide has ~3 fold less

<sup>19</sup> Barnette MS, Grous M, Cieslinski LB, Burman M, Christensen SB, Torphy TJ. Inhibitors of phosphodiesterase IV (PDE IV) increase acid secretion in rabbit isolated gastric glands: correlation between function and interaction with a high-affinity rolipram binding site. *J Pharmacol Exp Ther* 1995; 273: 1396–1402.

<sup>20</sup> Giembycz MA. 4D or not 4D — the emetogenic basis of PDE4 inhibitors uncovered? *Trends Pharmacol Sci* 2002; 23: 548.

<sup>21</sup> Boswell-Smith V, Spina D. PDE4 inhibitors as potential therapeutic agents in the treatment of COPD—focus on roflumilast. *Int J Chron Obstruct Pulmon Dis* 2007; 2: 121–129.

inhibitory potency on PDE4, the equivalent *in vivo* activities of roflumilast and roflumilast N-oxide can be explained by this difference in protein binding.

Tissue distribution studies were performed in mice, rats and hamsters following IV or PO administration. Two forms of <sup>14</sup>C-radiolabelled roflumilast were used, with the label either in the phenyl ring/amide linkage (carbonyl) or in the pyridinyl (ADCP) region. In rats, exposure to radioactivity was very high in the nose following [ADCP-<sup>14</sup>C]-roflumilast administration (tissue:plasma AUC, ~5–8), even surpassing that of the organs of excretion (liver and kidneys). This was not seen following [carbonyl-<sup>14</sup>C]-roflumilast administration, consistent with the high level of radioactivity identified in the nose following [ADCP-<sup>14</sup>C]-roflumilast administration being due to a <sup>14</sup>C-ADCP-containing metabolite rather than roflumilast (or roflumilast N-oxide) itself. Specific <sup>14</sup>C-ADCP distribution studies confirmed uptake in the nasal mucosa of rats. Preferential nasal mucosal localisation of radioactivity was in the submucous (Bowman's) glands, which are known to be highly metabolically-active (Thorton-Manning and Dahl, 1997).<sup>22</sup> In the other rodent species, distribution of [ADCP-<sup>14</sup>C]-roflumilast derived radioactivity to the nose was observed, but at lower levels compared with the rat. The hamster, but not the mouse, also showed preferential uptake of radioactivity into the Bowman's gland following administration of <sup>14</sup>C-ADCP. Low penetration across the blood brain barrier was indicated.

Roflumilast was extensively metabolised in all species with >16 drug related entities detected. All metabolites in humans were found in at least one other species. Roflumilast N-oxide was the major circulating metabolite in all species. Little absorbed roflumilast was excreted intact. Besides N-oxidation, metabolism involved dealkylation, oxidation at another site, hydrolysis of the amide linkage to ADCP (which underwent further modification; for example, to ADCP N-oxide), dechlorination and glucuronide or sulfate conjugation. *In vitro* studies with recombinant human cytochrome P450 enzymes (CYPs) indicated major roles for CYP3A4 and CYP1A2 in the formation of roflumilast N-oxide; CYP3A4, and to a lesser extent, CYP2C19, were responsible for the dealkylation of roflumilast. Hydrolysis of roflumilast to ADCP is unlikely to be a P450-mediated reaction. The pyridinyl metabolites (ADCP and its derivatives) were significant metabolites in the plasma of rats and hamsters (20–30%), less significant in mouse, rabbit and dog plasma/serum (<10%), minor in monkey plasma, and not detected in human plasma. However, ADCP N-oxide was identified as a metabolite in the urine of humans, suggesting some hydrolysis occurs. Based on metabolite profiles, monkeys were the laboratory animal species most closely resembling humans. Dogs had low plasma levels of the major human metabolite (roflumilast N-oxide) in some, but not all studies. Studies involving direct administration of the metabolite were conducted to compensate for this. Rodents displayed some unique nasal metabolism.

Metabolism of roflumilast and/or ADCP was high in olfactory epithelial microsomes from mice, rats, hamsters and dogs, with ADCP N-oxide the main metabolite formed from ADCP. Minimal to low metabolism of roflumilast and ADCP was observed in olfactory microsomes from monkeys and humans. Metabolism of ADCP N-oxide to hydroxyl-ADCP N-oxide was evident in rat and hamster olfactory microsomal incubations. The nasal cavity toxicity seen in rodent toxicity studies has been attributed to an intermediate in the formation of the hydroxyl-ADCP N-oxide metabolite, with severity of lesions correlating with the relative rate of formation (see *Toxicity*). Due to negligible levels of ADCP/ADCP N-oxide and differences in olfactory metabolism in humans, the hydroxyl-ADCP N-oxide metabolite would not be expected to occur clinically.

<sup>22</sup> Thorton-Manning JR, Dahl AR. Metabolic capacity of nasal tissue interspecies comparisons of xenobiotic-metabolising enzymes. *Mutat Res* 1997; 380: 43–59.

Mass balance studies using  $^{14}\text{C}$ -roflumilast were conducted in mice, rats, hamsters, rabbits, dogs, monkeys, minipigs and humans. Drug related material was excreted in both the urine and the faeces with urine typically the greater route. Biliary excretion was demonstrated in rats. Mass balance studies using roflumilast metabolites indicated both urinary and faecal excretion after  $^{14}\text{C}$ -roflumilast N-oxide administration but predominantly urinary excretion following  $^{14}\text{C}$ -ADCP administration.

### Pharmacokinetic drug interactions

Roflumilast N-oxide, the predominant metabolite in human plasma, is predominantly formed by CYP3A4 (78%) and to a lesser extent CYP1A2. While inhibition of either of these enzymes would likely increase roflumilast exposure, it is not expected to affect the exposure of pharmacologically active material. While *in vitro* studies indicated that both roflumilast and roflumilast N-oxide were able to act as inhibitors of various human CYPs (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5 and/or 4A9/11), the  $K_i$  values were >40 times the anticipated clinical  $C_{\text{max}}$  of roflumilast or roflumilast N-oxide and are therefore considered not to be clinically relevant at the proposed dose level. Aside from a weak induction of CYP2B6 (~1.3 fold), no significant induction of CYP1A2, 2A6, 2C9, 2C19 or 3A4/5 was seen with roflumilast at concentrations up to 0.1  $\mu\text{M}$  in cultures of human hepatocytes (~6 times the clinical  $C_{\text{max}}$  for roflumilast). No significant inhibition of P-glycoprotein was seen with roflumilast at 100  $\mu\text{M}$  (>5000 times the clinical  $C_{\text{max}}$ ). While there was no specific investigation to determine whether roflumilast is a substrate for P-glycoprotein, this seems unlikely as inhibition of P-glycoprotein-mediated substrate transport would be expected to have been seen if there was competition for uptake. Taken together, there are unlikely to be any clinically significant P450- or P-glycoprotein mediated pharmacokinetic interactions with roflumilast at the proposed dose level.

### Toxicology

#### Acute toxicity

The acute toxicity of roflumilast and roflumilast N-oxide was investigated in mice, rats and dogs, with studies using animals of both sexes using the clinical (PO) and, in rodents, the IV route, and an observation period of 14 days, in accordance with the TGA-adopted EU guideline for single dose toxicity. All doses tested would be expected to generate maximum plasma concentrations in excess of that attained clinically. All animals were subjected to gross examination; in some cases, microscopic examination was also performed. The maximum non-lethal dose of roflumilast by the oral route was 600 mg/kg and 100 mg/kg in mice and rats, respectively, and the highest tested dose in dogs, 18 mg/kg. These doses in rodents would be expected to result in exposures >100 times that anticipated clinically, indicating a low order of acute oral toxicity for the drug. Similar findings were seen with roflumilast and roflumilast N-oxide. The gastrointestinal (GI) tract was identified as a target organ for toxicity in rodents following oral dosing, and the nasal passage a target in rats only. Clinical signs were observed in all species, and these included piloerection, tremor, hypoactivity, hunched posture, dyspnoea and/or ptosis, with vomiting also seen in dogs (see *Safety pharmacology* above). Histopathological findings in the GI tract of rodents following oral dosing included gastric ulcers and mucosal bleedings, submucosal inflammation and thickening of the intestinal wall. Nasal lesions were characterised by slight disorganisation and necrotic inflammation of the olfactory epithelium. No gross pathological findings were seen in dogs.

#### Repeat dose toxicity

Studies by the oral route of up to 6 months were conducted in mice and rats, 3 months in hamsters, 12 months in dogs and 9.5 months in cynomolgus monkeys. A number of toxicity studies using the inhalational and IV routes were also submitted but these were of

short duration (2–4 weeks); only studies using the clinical (oral) route are evaluated in detail in this report. Additional studies were conducted with roflumilast N-oxide (administered PO) in mice (6 months), rats (1 month) and dogs (up to 12 months). As roflumilast N-oxide is not a major metabolite following administration of roflumilast to dogs, the long term study with roflumilast N-oxide in dogs was considered prudent. No marked differences were noted in the toxicity profiles of roflumilast and roflumilast N-oxide. Given their similar pharmacological activity and their *in vivo* interconversion, this is not surprising. Toxicities discussed below primarily refer to findings in roflumilast studies. The duration of the pivotal studies, the species used, group sizes and the use of both sexes were consistent with TGA-adopted EU guidelines. Dose selection in the pivotal studies was appropriate (limited by nasal toxicity in rodents, cardiovascular toxicity and emesis in dogs and reduced bodyweight gain in monkeys).

### ***Relative exposure***

Relative exposure levels achieved in the repeat dose studies have been calculated as the ratio of the combined AUC for roflumilast and roflumilast N-oxide in animals to that of humans at the recommended dose (500 µg/day). As roflumilast N-oxide is the dominant circulating compound in humans and laboratory animals (except dogs), possessing similar *in vivo* pharmacological activity to roflumilast, the summed exposures of roflumilast and roflumilast N-oxide were considered a more accurate reflection of safety margins than roflumilast exposure ratios alone. As roflumilast N-oxide was the major drug related material in the plasma of rats, in situations where plasma kinetic data for this metabolite were not available, exposure ratios were determined based on data from other rat studies. Roflumilast N-oxide was only a minor fraction of drug related material in dog plasma (<10%), and in cases where roflumilast N-oxide kinetic data were not available, the derivation of exposure levels using only roflumilast data was considered acceptable for this species. The sponsor used the free fraction to determine exposure ratios in order to account for interspecies differences (see *Pharmacokinetics*). While this is generally acceptable for highly protein bound compounds (ICH3A<sup>23</sup>), total plasma concentrations have been used for the calculations here as this better accounts for the equivalent *in vivo* activity of roflumilast and its N-oxide metabolite; (that is, while there is a higher percentage of free roflumilast N-oxide compared with its parent, this compound is not as pharmacologically active). Animal AUC values for roflumilast and roflumilast N-oxide were averaged across all time points.

High relative exposures ( $\geq 25$ ) were obtained at the highest doses in the mouse and hamster studies, with lower relative exposures (<10) obtained in the rat, dog and monkey studies (Table 1).

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<sup>23</sup> ICH3A: Toxicokinetics: guidance on the assessment of systemic exposure in toxicity studies.

**Table 1: Relative exposure to roflumilast and the N-oxide in repeat dose toxicity studies**

Species (strain)	Study	Treatment duration	Dose (mg/kg/day); PO	AUC <sub>0-24h</sub> (µM·h)		Exposure ratio <sup>a</sup>
				Roflumilast	Roflumilast N-oxide	
Mouse (B6C3F1)	33/2002	6 months	4	0.5	1.4	1.7
			12	2	4.8	6
			36	19	51	62
	54/2002	6 months	4#	0.09	3.9	4
			10#	0.28	10.7	10
			25#	1.0	75	67
	97/2001 [carcinogenicity]	104 weeks	0.5	0.06	0.17	0.2
			2	0.18	0.56	0.7
			6	0.57	1.9	2
			12 (♀)	1.5	4.4	5
			18 (♂)	2.3	7.1	8
Rat (Wistar)	31/2001 [81/95]	4 weeks	0.5	0.031	0.62	0.6
			1.5	0.143	3.2	3
	62/99 [juveniles]	4 weeks	0.8 (3 weeks old)	0.23	0.90	1
			(7 weeks old)	0.045	1.0	1
	14/96	6 months	0.5	0.033	-	0.8*
			1.5	0.087	-	3*
			2.5	0.153	-	5*
191/2000	6 months	0.8	0.08	1.8	1.7	
Hamster (Golden)	252/98	3 months <sup>b</sup>	4	0.062	1.4	1.3
			8	0.10	3.6	3
			16	0.26	6.7	6
	7/2002; 233/2003 [carcinogenicity]	104 weeks	0.25	nd	0.21	0.2
			1	nd	0.63	0.6
			4	0.093	3.1	3
			8	0.22	8.4	8
			16	1.3	27	25
Dog (Beagle)	68/95	4 weeks	2	2.3	-	2
			6	6.7	-	6
			18	9.6	nd	9
	94/96	6 months	0.2	0.48	-	0.4
			1	1.3	-	1
			4	4.4	-	4
	132/2000	12 months	0.2	0.48	0.031	0.5
			0.6	1.3	0.16	1.3
			2	2.6	0.19	2.5
	162/2001	12 months	0.1#	-	0.03	0.03
0.4#			0.004	0.14	0.1	
0.8#			0.023	0.38	0.4	
1.2#			0.07	1.0	0.9	
Monkey (Cynomolgus)	95/2001	4 weeks	0.5	3.1	8.3	10
			0.1	0.24	0.87	1
	232/2001	42 weeks	0.25	0.65	2.3	3
			0.5	2.0	5.9	7
Human		repeat dose	[500 µg]	0.089	1.04	-

<sup>a</sup> = calculated as animal:human sum of AUC<sub>0-24h</sub> values for roflumilast and N-oxide; <sup>b</sup> derived for the interval 0-8h (AUC<sub>0-8h</sub>) in animal data; # N-oxide; \* estimate based on extrapolation of data; - data not obtained/not applicable; nd = not detected



Target organs/systems varied across species. The nasal mucosa and GI tract were the major targets of toxicity in rodents, the male reproductive system was a target in mice and rats and the heart a target in dogs; emesis and body weight loss were observed in both non-rodent species (dogs and cynomolgus monkeys).

### ***Gastrointestinal toxicity***

Gastric ulcers, mucosal bleedings, serositis of the stomach and intestine, as well as thickening of the intestine wall were reported following administration of high single oral doses of roflumilast to mice and rats ( $\geq 600$  mg/kg and  $\geq 100$  mg/kg, respectively). Stomach erosions, peritonitis of the abdominal cavity and inflammation of the jejunum were seen in rats that had received 8 mg/kg/day PO roflumilast (estimated  $ER_{AUC}$ , 16) for 4 weeks. Male mice treated at  $\geq 6$  mg/kg/day in the 2 year carcinogenicity study displayed erosions/ulcerations of the glandular stomach ( $ER_{AUC}$ , 2–5) and transient inflammation in the pyloric region of the stomach was observed in the pivotal monkey study (at 4 weeks).

No treatment related GI tract lesions were seen, though, after administration of roflumilast to mice at  $\leq 36$  mg/kg/day for 6 months ( $ER_{AUC} \leq 60$ ), in hamsters ( $\leq 16$  mg/kg/day for 2 years;  $ER_{AUC} \leq 25$ ), dogs ( $\leq 18$  mg/kg/day for 4 weeks [ $ER_{AUC} \leq 9$ ] or  $\leq 2$  mg/kg/day for 12 months [ $ER_{AUC} \leq 2.5$ ]) or in monkeys after 9.5 months of treatment (at  $\leq 0.5$  mg/kg/day;  $ER_{AUC} \leq 7$ ). As there were no gastric effects following IV administration (based on single dose toxicity studies), these findings are more likely to be a result of local irritation from roflumilast rather than due to a direct pharmacological effect of the drug to increase secretion of gastric acid (see *Safety pharmacology*). As obvious gastric irritation only occurred at relatively high relative exposures based on AUC, and very much higher relative local doses in the stomach, the effects are unlikely to be of particular concern for clinical use at the proposed dose level.

Roflumilast had an emetic effect at all doses tested in dogs ( $\geq 0.2$  mg/kg/day PO) and at  $\geq 0.5$  mg/kg/day PO in a 4 week study in monkeys ( $ER_{AUC}$ , 0.5 and 10 in the respective species). This was associated with reduced food intake and bodyweight loss in monkeys and (at the upper doses) in dogs. Suppression of bodyweight gain and decreased food intake were seen in the absence of vomiting at doses  $\geq 0.25$  mg/kg/day PO in monkeys in the 9.5-month study ( $ER_{AUC} \geq 3$ ); significant body weight loss ( $\geq 5\%$ ) was seen at 5 mg/kg/day ( $ER_{AUC}$ , 7). The three rodent species used in the repeat dose toxicity program (mice, rats and hamsters) are non-vomiting species and therefore are not appropriate to assess emetic effects. Emesis appears to be a class effect of PDE4 inhibitors (Losco et al., 2004; Larson et al., 1996; Robichaud et al., 2002a) and has been attributed largely to a CNS effect involving PDE4D inhibition in the brainstem, mimicking the effect of an  $\alpha_2$ -adrenoceptor antagonist (Giembycz, 2002; Robichaud et al., 2002b), although the peripheral effects of increased stomach acidity and increased digestive secretions may also contribute (Barnette et al., 1995).<sup>19,20,24,25,26,27</sup> Given the low exposure margins, with vomiting in dogs at subclinical exposure levels and effects on body weight in monkeys at a low multiple of the clinical exposure, emesis, nausea and body weight losses may be expected clinically.

<sup>24</sup> Losco PE, Evans EW, Barat SA et al. The toxicity of SCH 351591, a novel phosphodiesterase-4 inhibitor, in cynomolgus monkeys. *Toxicol Pathol* 2004; 32: 295–308.

<sup>25</sup> Larson JL, Pino MV, Geiger LE, Simeone, CR. The toxicity of repeated exposures to rolipram, a type IV phosphodiesterase inhibitor in rats. *Pharmacol Toxicol* 1996; 78: 44–49.

<sup>26</sup> Robichaud A, Savoie C, Stamatiou PB et al (2002a). Assessing the emetic potential of PDE4 inhibitors in rats. *Br J Pharmacol* 2002; 135: 113–118.

<sup>27</sup> Robichaud A, Stamatiou PB, Jin S-LC et al (2002b). Deletion of phosphodiesterase 4D in mice shortens  $\alpha_2$ -adrenoceptor-mediated anaesthesia, a behavioural correlate of emesis. *J Clin Investigat* 2002; 7: 1045–1052.

### **Cardiovascular toxicity**

In repeat dose toxicity studies, dogs treated with  $\geq 0.6$  mg/kg/day PO roflumilast had lesions in the right atrium/auricle (haemorrhages, haemosiderin deposits, myocarditis and/or inflammatory cell infiltration). The No Observable Effect Level (NOEL) was 0.2 mg/kg/day PO ( $ER_{AUC}$ , 0.5). No haemorrhagic effects were seen in other species (mice, rats, hamsters and monkeys). In safety pharmacology studies, dogs appeared to be particularly sensitive to the inotropic effects of roflumilast, probably as a result of species differences in  $\beta$ -adrenoceptor signalling and PDE compartmentalisation (see *Safety pharmacology*). The observed heart lesions in dogs are consistent with chronic administration of a vasodilator affecting cardiac output (Dogterom et al., 1992) and as minimal inotropic effects were observed in other species, the dog is not considered a relevant model with regard to these findings.<sup>28</sup> Vasculitis in the heart, mesentery and liver of animals has been reported for other PDE4 inhibitors and has been suggested to be an irreversible PDE4 inhibitor class effect (Giembycz, 2006; Losco et al., 2004; Zhang et al., 2008).<sup>10,24,29</sup> A low incidence of peri/arteritis was observed in the heart of mice treated with  $\geq 12$  mg/kg/day PO roflumilast ( $ER_{AUC}$ , 6–60, and at the NOEL,  $\sim 2$ ) and a single male monkey treated with 0.5 mg/kg/day PO roflumilast for 9.5 months had myocarditis ( $ER_{AUC}$ , 7, and at the NOEL, 3). There was no indication of vasculitis/cardiac lesions in hamsters treated with  $\leq 16$  mg/kg/day PO for 2 years ( $ER_{AUC}$ , 25). Given the data and the historical occurrences of vasculitis with PDE4 inhibitors, a relationship with treatment in affected animals cannot be excluded. The absence of overt findings, though, especially in mice and hamsters where very substantial multiples of the clinical exposure were obtained, gives some reassurance of likely limited clinical significance.

Relative to the wild type, PDE4D deficient mice have been reported to have a progressive cardiomyopathy characterised by increased bodyweight relative heart weight, accelerated progression of heart failure following myocardial infarction and exercise induced cardiac arrhythmias (Lehnart et al., 2005).<sup>30</sup> The latter was also observed with the PDE4 inhibitor, rolipram, though there was no effect on baseline sympathetic activity. The authors suggested chronic administration of PDE4 inhibitors could lead to cardiac dysfunction and arrhythmias. Aside from an increase in heart weights in male mice treated with roflumilast for 6 months with  $\geq 4$  mg/kg/day PO roflumilast ( $ER_{AUC}$ ,  $\geq 1.7$ ; a NOEL could not be established), and an increased incidence of hearts with distended chambers in male mice after 2 years at 18 mg/kg/day ( $ER_{AUC}$ , 8, and at the NOEL, 2) there was no observed effect on heart weights in female mice, dogs (although detection in this species would be confounded by other myocardial lesions) or monkeys. In cardiovascular safety studies, no arrhythmias were detected in treated cats or dogs. Therefore, the findings of progressive cardiomyopathy presented by PDE4D deficient mice reported in Lehnart et al. (2005) are not evident in roflumilast nonclinical studies.<sup>30</sup> However, this does not exclude the possibility of adverse cardiac events in individuals with pre-existing cardiomyopathy.

### **Nasal cavity toxicity**

Nasal cavity and olfactory epithelial changes were observed in rodents treated with roflumilast. Findings included the presence of secreted fibre like material, respiratory metaplasia, squamous metaplasia and inflammation of the nasal cavity, olfactory epithelial degeneration/necrosis/disorganisation and Bowman's gland hyperplasia. NOELs for nasal

<sup>28</sup> Dogterom P, Zbinden G, Reznik, GK. Cardiotoxicity of vasodilators and positive inotropic/vasodilating drugs in dogs: an overview. *Crit Rev Toxicol* 1992; 22: 203–241.

<sup>29</sup> Giembycz MA. An update and appraisal of the cilomilast Phase III clinical development programme for chronic obstructive pulmonary disease. *Br J Clin Pharmacol* 2006; 62: 138–152.

<sup>30</sup> Lehnart SE, Wehrens XHT, Reiken S et al. Phosphodiesterase 4D deficiency in the ryanodine-receptor complex promotes heart failure and arrhythmias. *Cell* 2005; 123: 25–35.

toxicity were 6 mg/kg/day in mice (ER<sub>AUC</sub>, 2), 0.8 mg/kg/day in rats (ER<sub>AUC</sub>, 1.7) and 4 mg/kg/day in hamsters (ER<sub>AUC</sub>, 1.3). An increased incidence of nasal cavity tumours were observed in hamsters treated with  $\geq 8$  mg/kg/day PO roflumilast for 2 years (ER<sub>AUC</sub> at the NOEL, 3) (see *Carcinogenicity*). No nasal toxicity was observed in dogs or monkeys ( $\leq 18$  mg/kg/day and  $\leq 0.5$  mg/kg/day in the respective species; ER<sub>AUC</sub>, 7–9). The sponsor conducted a number of studies in an attempt to elucidate the mechanism of olfactory toxicity in rodents. In rat distribution studies with various labelled forms and derivatives of the drug, it was the ADCP moiety (and not roflumilast *per se*) that localised excessively to the nasal cavity. Degeneration of the olfactory epithelium was seen in rats following roflumilast, ADCP and ADCP N-oxide administration, suggesting that the ADCP moiety is involved in the toxicity findings. Olfactory epithelial degeneration in rats could be prevented by CYP450 inhibition and was potentiated by glutathione depletion. *In vitro*, the metabolism of ADCP N-oxide by rat nasal olfactory epithelial microsomes (forming hydroxyl-ADCP N-oxide) was fully inhibited by an anti-CYP2G1 antibody and greatly reduced by the addition of glutathione. Mouse CYP2G1 (but not human CYP1A1, 1A2, 1B1, 2B6, 2C8, 2C18, 2D6, 2E1, 2J2, 3A4 OR 3A5) was also shown to catalyse this reaction. The CYP2G1 isozyme is uniquely expressed in the olfactory mucosa of rodents and rabbits. The sponsor proposed that a labile epoxy derivative is formed from ADCP (or ADCP N-oxide) by an olfactory specific CYP450 mediated reaction (that is, by CYP2G1), which can react with glutathione or proteins (thereby leading to the observed effects) or undergo spontaneous rearrangement to the stable hydroxy-ADCP N-oxide. While the proposed identity of the labile intermediate cannot be verified by submitted data, the correlation of toxicity with ADCP/ADCP N-oxide levels, the involvement of CYP2G1 and the detectable formation of hydroxyl-ADCP N-oxide, all lends support to the proposed mechanism. Another ADCP containing PDE4 inhibitor, RP 73401 (piclamilast), has also been shown to cause nasal cavity toxicity in rats that was suggested to result from metabolic activation rather than be due to PDE4 inhibition (Pino et al., 1999).<sup>31</sup> Plasma kinetic data indicate that the metabolite precursors of the reactive intermediate implicated in nasal toxicity, ADCP and ADCP N-oxide, were significantly less readily formed in dogs and monkeys compared with rodents (indeed, ADCP N-oxide was not detected in the non-rodent species). Neither ADCP nor ADCP N-oxide were detectable in human plasma, and humans (as well as dogs and monkeys) do not have a functional CYP2G1 (Ding and Kaminsky, 2003).<sup>32</sup> Therefore the nasal cavity findings observed in rodents are considered not to be of relevance to humans.

### ***Testicular toxicity***

Treatment with roflumilast or roflumilast N-oxide produced consistent, dose related effects on male reproductive tissues in rats; sperm granuloma in the epididymides and testicular tubular dilation, degeneration and atrophy (at  $\geq 1.5$  mg/kg/day [ER<sub>AUC</sub>, 3]; NOEL, 0.8 mg/kg/day [ER<sub>AUC</sub>, 1.7]) with associated oligo/aspermia. Increased testicular weights were observed in mice at doses  $\geq 4$  mg/kg/day (ER<sub>AUC</sub>, 1.7) in the 6 month study, and epididymal oligospermia/atrophy was observed in the mouse carcinogenicity study at 18 mg/kg/day (ER<sub>AUC</sub>, 8). No testicular or epididymal findings were seen in other species (hamsters, dogs and monkeys) at doses resulting in exposures up to 25, 9 and 7 times the clinical AUC, respectively. Mechanistic studies indicated the testicular findings in rats were not attributable to ADCP or ADCP N-oxide and were unaffected by P450 inhibition,

<sup>31</sup> Pino MV, Valerio MG, Miller GK et al. Toxicologic and carcinogenic effects of the type IV phosphodiesterase inhibitor RP 73401 on the nasal olfactory tissue in rats. *Toxicol Pathol* 1999; 27: 383–394.

<sup>32</sup> Ding X, Kaminsky LS. Human extrahepatic cytochromes P450: function in xenobiotic metabolism and tissue-selective chemical toxicity in the respiratory and gastrointestinal tracts. *Ann Rev Pharmacol Toxicol* 2003; 43: 149–173.

indicating the toxicity findings resulted from a distinct mechanism from those seen in the nasal cavity; decreases in testosterone levels were observed in the absence of testicular lesions in these studies. Testicular degeneration in rats, rabbits and monkeys has been reported for another PDE4 inhibitor (cilomilast; Giembycz, 2006) and rolipram, the prototypical PDE4 inhibitor, has been shown to affect the cytoplasmic localisation of junctional proteins, which are essential for development and maintenance of spermatogenesis, in Sertoli cells (Fiorini et al., 2004).<sup>29,33</sup> Hence, an association of testicular degeneration with pharmacological activity (PDE4 inhibition) cannot be dismissed. It has been suggested that rats have a higher level of PDE4 activity and thus are more sensitive to PDE4 inhibitors (Bian et al., 2004).<sup>34</sup> Therefore a lack of histopathological findings in dogs and monkeys may be as a result of this difference in sensitivity. Consistent with this hypothesis, testicular degeneration occurred in rats exposed to lower levels of cilomilast than monkeys (~20 fold; Giembycz, 2006).<sup>29</sup> The absence of testicular toxicity in hamsters, dogs and monkeys is probably adequate to allay clinical concerns for effects on male reproductive tissues.

### ***Olfactory and taste perception***

cAMP is an essential signalling component in the mammalian olfactory system. PDE4A is present in the dendrites, soma and axons of olfactory neurons (Lau and Cherry, 2000) and treatment of mice with the PDE4 inhibitor, rolipram, altered the odour perception profile of mice (Pho et al., 2005).<sup>35,36</sup> Although not tested in submitted studies, roflumilast may also be expected to have a similar effect. Therefore patients receiving roflumilast may experience alterations in olfactory perception, which may have follow on taste effects. These effects are not likely to be adverse and would be expected to be reversible.

### **Genotoxicity**

The potential genotoxicity of roflumilast was investigated in the standard battery of tests and in assays for mammalian gene mutation and DNA adduct formation. The conduct of the studies was in accordance with TGA-adopted EU guidelines. Concentrations/doses were appropriate. A suitable set of *S. typhimurium* and *E. coli* strains were used in the bacterial mutagenicity studies and animals of both sexes were used in the *in vivo* clastogenicity studies. Roflumilast N-oxide was tested directly for mutagenicity and indirectly (via metabolic formation) in clastogenicity studies. ADCP was also tested in the mouse micronucleus assay. Neither roflumilast nor roflumilast N-oxide were mutagenic in bacterial or mammalian mutation assays or clastogenic in *in vitro* assays. Roflumilast did not cause DNA adduct formation in the nasal mucosa, liver or testes of rats, or the nasal mucosa or liver of hamsters. Roflumilast was weakly positive in the mouse micronucleus test at oral doses  $\geq 300$  mg/kg (producing mortalities; estimated ER<sub>AUC</sub>, 160). This minor increase in micronuclei was attributed to an erythropoietic effect as a result of the drug decreasing body temperature. The balance of evidence would indicate that neither roflumilast nor roflumilast N-oxide are genotoxic. ADCP was not genotoxic in the mouse micronucleus assay, and did not cause DNA adduct formation in rat nasal mucosa, liver or testes. However, in light of nasal cavity tumours in carcinogenicity studies (see below) and

<sup>33</sup> Fiorini C, Tilloy-Ellul A, Chevalier S, Charuel C, Pointis G. Sertoli cell junctional proteins as early targets for different classes of reproductive toxicants. *Reprod Toxicol* 2004; 18: 413–421.

<sup>34</sup> Bian H, Zhang J, Wu P et al. Differential type 4 cAMP-specific phosphodiesterase (PDE4) expression and functional sensitivity to PDE4 inhibitors among rats, monkeys and humans. *Biochem Pharmacol* 2004; 68: 2229–2236.

<sup>35</sup> Lau YE, Cherry JA. Distribution of PDE4A and G $\alpha$  immunoreactivity in the accessory olfactory system of the mouse. *Neuroreport* 2000; 11: 27–32.

<sup>36</sup> Pho V, Butman ML, Cherry JA. Type 4 phosphodiesterase inhibition impairs detection of low odour concentrations in mice. *Behav Brain Res* 2005; 161: 245–253.

to support the proposed mechanism involving an ADCP (N-oxide) derivative and its reactivity, studies to assess the mutagenicity/clastogenicity of ADCP (N-oxide) following metabolic activation by rodent olfactory microsomes or CYP2G1 would have been desirable.

### **Carcinogenicity**

The carcinogenic potential of roflumilast by the oral route was investigated in 2 year studies in mice and hamsters (GLP compliant). Group sizes were appropriate and dual control groups were used, as recommended in the TGA-adopted EU guideline on carcinogenic potential. The highest dose in the mouse study (18 mg/kg/day to males) produced excessive mortality, with only nine males (18%) surviving at the scheduled necropsy. As the majority of the unscheduled deaths (37 of 41) occurred after Week 81, this is not considered to have adversely affected the adequacy of the mouse study to reveal potential carcinogenic effects. Two hamster carcinogenicity studies were performed, the second using a higher maximum dose than the original one. The mortality was high in females in the hamster studies, with none of the treatment groups (nor the vehicle control group) having the desired number of surviving animals ( $\geq 25$ ) at the termination of the study. The observed mortality rate is not uncommon for long term hamster studies (Sher, 1982) and, based on there being an adequate number of animals that survived to 18 months treatment, the study is considered acceptable.<sup>37</sup> Although relative exposures at the highest doses in the mouse study were modest (only 5 and 8 times the clinical AUC in females and males, respectively), the maximum tolerated dose, at least in males, was clearly used. The exposure at the highest dose in the hamster study, resulting in 25 times the clinical AUC, is considered adequate.

No treatment related increase in tumour incidence was observed in the mouse study. An increased incidence of myeloid hyperplasia was seen in male mice at the highest dose level, but in the absence of similar findings in other studies, this is likely to represent an adaptive response to generalised inflammation and congestion and not a pre-neoplastic concern. In hamsters, a statistically significant higher incidence of undifferentiated carcinoma of the olfactory epithelium was seen at doses  $\geq 8$  mg/kg/day PO ( $ER_{AUC}$ , 8), while adenomas and adenocarcinomas of Bowman's gland were seen at 16 mg/kg/day ( $ER_{AUC}$ , 25). These nasal cavity tumours are consistent with the basal cell hyperplasia seen in the Bowman's gland of treated mice, rats and hamsters (see *Repeat dose toxicity*). Mechanistic studies indicated that the olfactory findings in the general toxicity studies are likely related to further metabolism of ADCP and/or ADCP N-oxide, metabolites not found in human serum. Tumours of the nasal olfactory region have been reported in rats treated with another ADCP-containing PDE4 inhibitor (RP 73401, piclamilast) (Pino et al., 1999).<sup>31</sup> Although minimal details were provided, these tumours were also attributed to the metabolic conversion of piclamilast by olfactory epithelial cells rather than an association with PDE inhibition. The tumour forming metabolite was not identified in the manuscript. Due to the rodent specificity of the nasal cavity toxicity, these nasal tumours are not considered to indicate that roflumilast poses a carcinogenic hazard to patients.

A statistically significant increase in the incidence of uterine leiomyoma was seen in hamsters at doses  $\geq 8$  mg/kg/day PO ( $ER_{AUC}$ , 8). Incidences in these dose groups (15% at 8 mg/kg/day and 17% at 16 mg/kg/day) were higher than concurrent controls (3–7%) and at the upper range or just outside the reported spontaneous tumour incidence for this strain of hamster (5–15%; Kamino et al., 2001).<sup>38</sup> The dose relationship was not strong

<sup>37</sup> Sher SP. Tumors in control hamsters, rats and mice: literature tabulation. *Crit Rev Toxicol* 1982; 49–79.

<sup>38</sup> Kamino K, Tillmann T, Mohr U. Spectrum and age-related incidence of spontaneous tumours in a colony of Han:AURA hamsters. *Exp Toxic Pathol* 2001; 52: 539–544.

however (that is, a >3-fold increase in exposure was associated with a minimally higher incidence) and uterine leiomyosarcoma was not increased. Combined incidences of uterine leiomyoma (benign) and leiomyosarcoma (malignant) showed no significant increase with treatment, and were less than the level seen in controls in the second study. Thus, the apparent increase in uterine leiomyoma is consistent with natural variation in the continuum from benign to malignant for these spontaneous smooth muscle tumours and is considered unlikely to be treatment related.

### **Reproductive toxicity**

A standard set of GLP compliant reproductive toxicity studies were submitted and examined male and female fertility (in rats), embryofetal toxicity (rats and rabbits) and pre/postnatal development (mice). Adequate animal numbers were used and treatment periods were appropriate. Unfortunately, supportive toxicokinetic data submitted for the reproductive toxicity studies were very limited. Where necessary, exposure values have been estimated by extrapolation (except mouse AUC<sub>0-4h</sub> data), including based on data obtained in other appropriate studies (Table 2). Exposures achieved in the reproductive studies were low (<4 times the clinical AUC) and were for the most part subclinical, limiting the usefulness of negative findings in these studies.

Decreased fertility was observed in rats at 1.8 mg/kg/day (ER<sub>AUC</sub>, 3.5) in a study in which both male and female animals were treated and mated. This coincided with testicular/epididymal changes (increased testicular weight, tubular atrophy, degeneration and dilatation and epididymal spermiogenic granuloma) and a slight decrease in sperm count. No adverse effects on fertility were observed at 1.5 mg/kg/day (ER<sub>AUC</sub>, 3.0) in a subsequent study in rats in which only females were treated. Increases in post-implantation loss and abortion were also observed at 1.8 mg/kg/day in the first study. This occurred in the absence of other signs of maternal toxicity and post-implantation loss was not increased in other studies in rats at the same or similar dose levels; the findings may therefore reflect paternal effects on sperm quality and integrity. The 6 month repeat dose toxicity study with roflumilast in mice included an assessment of male fertility, with no effect found ( $\leq 36$  mg/kg/day PO; ER<sub>AUC</sub>, 60). Given that the male reproductive system of rats appears to be particularly sensitive to the pharmacological effects of roflumilast compared with other species, and that there was no impairment of fertility in male mice at a very high exposure multiple, and no adverse spermatology findings were recorded for treated dogs and monkeys, these effects may not be of clinical relevance.

**Table 2: Relative exposure in reproductive toxicity studies**

Study	Species & strain	Dose (mg/kg/day); PO	AUC <sub>0-24h</sub> (µM·h)		Exposure ratio based on AUC
			Roflumilast	Roflumilast N-oxide	
Pre- & postnatal development; 127/2002 <sup>a</sup>	<b>Mouse</b> (NMRI) [pregnant females]	1.5	0.21	0.29	0.4
		3	0.43	0.58	1
		6	0.85	1.2	2
		12	1.7	2.3	3.5
Fertility; 19/97; 114/2002 <sup>b</sup>	<b>Rat</b> (Wistar) [non-pregnant females & males]	0.2	0.012	0.25	0.2
		0.5	0.031	0.62	0.6
		0.6	0.037	0.74	0.7
		0.8	0.076	1.7	1.6
		1.5	0.143	3.2	3.0
		1.8	0.172	3.8	3.5
Embryofetal development; 8/96 <sup>c</sup>	<b>Rat</b> (Wistar) [pregnant females]	0.2	0.016	0.52	0.5
		0.6	0.048	1.6	1.5
		1.8	0.099	4.1	3.7
Embryofetal development; 191/95 <sup>d</sup>	<b>Rabbit</b> (Himalayan) [pregnant females]	0.2	0.022	0.180	0.2
		0.4	0.044	0.359	0.4
		0.8	0.087	0.718	0.7
[Module 2.7]	<b>Human</b>	[500 µg]	0.089	1.04	–

<sup>a</sup>estimated from AUC<sub>0-4h</sub> data in Study 126/2002; <sup>b</sup>estimated from data in Study 31/2001; <sup>c</sup>estimated from data in Study 372/2004; <sup>d</sup>Estimated from non-pregnant female single-dose data in Study 66/2002

An increase in the number of corpora lutea per dam was observed in female rats that had received roflumilast ( $\geq 0.5$  mg/kg/day; ER<sub>AUC</sub>, 0.6). The number of implantations was unaffected, so this resulted in an apparent increase in pre-implantation loss. The finding is consistent with published reports where inhibition of PDE4 after FSH-induced follicular maturation mimics an LH surge (elevated cAMP levels in granulosa cells) and enhances ovulation (McKenna et al., 2005; Tsafirri et al., 1996).<sup>39,40</sup> As a consequence, PDE4 inhibitors, including roflumilast, are being considered for assisted reproduction (Palmer et al., 2008).<sup>41</sup> While acute administration of roflumilast appeared to increase corpora lutea number, chronic administration increased the incidence of uteri displaying atrophy in mice ( $\geq 12$  mg/kg/day; ER<sub>AUC</sub>, 6, and at the NOEL, 2), reduced oestrus events with prolonged diestrus in rats ( $\geq 1.5$  mg/kg/day; ER<sub>AUC</sub>, 3, and at the NOEL, 1.7) and prolonged the menstrual cycle in monkeys (0.5 mg/kg/day; ER<sub>AUC</sub>, 7 and at the NOEL, 3), suggesting a perturbation of the oestrous/menstrual cycles, possibly as a result of alterations in follicle stimulating hormone (FSH) and luteinising hormone (LH) levels. While the sponsor suggested these oestrous/menstrual cycle changes could be attributed to stress, there was no apparent reduction in serum LH levels or rise in adrenocorticotrophic hormone (ACTH)

<sup>39</sup> McKenna SD, Pietropaolo M, Tos EG et al. Pharmacological inhibition of phosphodiesterase 4 triggers ovulation in follicle-stimulating hormone-primed rats. *Endocrinol* 2005; 146: 208–214.

<sup>40</sup> Tsafirri A, Chun S-Y, Zhang R, Hsueh AJW, Conti M. Oocyte maturation involves compartmentalisation and opposing changes of cAMP levels in follicular somatic and germ cells: studies using selective phosphodiesterase inhibitors. *Develop Biol* 1996; 178: 393–402.

<sup>41</sup> Palmer S, McKenna S, Tepper M, Eshkol A, Macnamee MC. Methods of inducing ovulation. US Patent Application 2008, No. 20080293622.

levels, which are generally indicative of stress (Collu et al., 1979; Rivier and Rivest, 1991).<sup>42,43</sup> Furthermore, alterations in oestrous cycling has also been reported for another PDE4 inhibitor (rolipram; Nishiyama et al., 2006), suggesting a possible pharmacologically mediated effect.<sup>44</sup> If these changes in menstrual cycling are clinically relevant, then it is likely that this would be evident from the clinical data.

Roflumilast and/or its metabolites readily crossed the placenta in rats, with fetal exposure similar to that in maternal plasma. In the rat embryofetal development study, there was an increase in the incidence of incomplete ossification of the parietal bone at doses  $\geq 0.6$  mg/kg/day ( $ER_{AUC}$ , 1.5, and at the NOEL, 0.5) and of the interparietal and supraoccipital bones at 1.8 mg/kg/day ( $ER_{AUC}$ , 3.7); there was no treatment related increase in malformations. These variations first occurred at non-maternotoxic doses, suggesting a direct drug effect on growth retardation. At 1.8 mg/kg/day, though, they occurred in conjunction with maternal toxicity (decreased body weight gain and food consumption). In a second study, in which females were treated prior to mating through to Gestation Day 15, no treatment related increase in skeletal variations was observed. No maternotoxicity was seen at the highest tested dose (1.8 mg/kg/day;  $ER_{AUC}$ , 3.5). No fetal variations or malformations were observed in the rabbit embryofetal study but exposures achieved in this study were subclinical and thus no great weight can be placed on the negative finding. As there were no apparent adverse effects on maternal body weight in the treated rabbits, higher doses may have been feasible. Given the evidence of fetal damage at low exposure multiples in the rat and the inadequacy of the rabbit study, roflumilast should not be used in pregnancy unless the benefits to the mother clearly outweigh the potential risk to the fetus. Placement in Pregnancy Category B3 is appropriate.

In pilot pre/postnatal development studies in mice, roflumilast had a pronounced tocolytic effect ( $\geq 2$  mg/kg/day; a NOEL could not be established). This is consistent with the expression of PDE4 in the myometrium and its role in cAMP degradation in near term pregnancy. Several published reports indicate that PDE4 inhibitors potentiate the relaxant effects of  $\beta$ -adrenergic agonists and inhibit myometrial contractions at the end of pregnancy (Méhats et al., 2007).<sup>45</sup> Due to the effect on near term pregnancies, the definitive pre/postnatal study involved the temporary suspension of treatment for the final three days of gestation. Treatment in this manner resulted in a decrease in the number of pups/litter and increased stillbirths and total litters lost at  $\geq 3$  mg/kg/day ( $ER_{AUC}$ , 1). Similar findings and a decrease in pup birth weight and survival to Day 4 post partum were seen in the pilot studies. Reduced litter sizes and decreased viability have been reported for mice deficient in PDE4D (Jin et al., 1999), suggesting the observed effects are associated with roflumilast's primary pharmacology.<sup>46</sup> Pup survival was not seen to be affected in the definitive study, and there were no effects on postnatal development other than reduced locomotor activity in the female offspring of dams treated at 6 mg/kg/day ( $ER_{AUC}$ , 2). Reduced locomotor activity has also been reported for

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<sup>42</sup> Collu R, Tache Y, Ducharme JR. Hormonal modifications induced by chronic stress in rats. *J Steroid Biochem* 1979; 11: 989-1000.

<sup>43</sup> Rivier C, Rivest S. Effect of stress on the activity of the hypothalamic-pituitary-gonadal axis: peripheral and central mechanisms. *Biol Reprod* 1991; 45: 523-532.

<sup>44</sup> Nishiyama S, Okudaira M, Saito N. Mechanisms of rolipram-induced increase in the incidence of mammary adenocarcinoma: histopathological study of a 104-week oral carcinogenicity study in female Sprague-Dawley rats. *Arch Toxicol* 2006; 80: 88-97.

<sup>45</sup> Méhats C, Schmitz T, Oger S, Hervé R, Cabrol D, Leroy M-J. PDE4 as a target in preterm labour. *BMC Preg Childbirth* 2007; 7: S12.

<sup>46</sup> Jin S-LC, Richard FJ, Kuo W-P, D'Ercole AJ, Conti M. Impaired growth and fertility of AMP-specific phosphodiesterase PDE4D-deficient mice. *Proc Natl Acad Sci USA* 1999; 96: 11998-12003.



PDE4B deficient mice (Siuciak et al., 2008), suggesting this may be a pharmacological effect.<sup>47</sup>

Roflumilast and/or its metabolites were found to be readily excreted in milk in rats and could be detected in feeding pups. Given its excretion in milk and the apparent pharmacological activity in breast fed pups, roflumilast should not be used women who are breastfeeding.

### Use in children

Roflumilast is not indicated for use in children and adolescents below 18 years of age. No adverse effects were observed in a study conducted in juvenile rats (3 weeks old at commencement), involving treatment at  $\leq 0.8$  mg/kg/day PO for 3 months. However, relative exposure at the highest dose in the study was low ( $ER_{AUC}$ , 1).

### Local tolerance

Local tolerance studies in rats and rabbits indicated that roflumilast was not significantly irritating following intramuscular (IM), IV, intra-arterial or paravenous injections. Neither roflumilast nor roflumilast N-oxide were skin sensitisers in the guinea pig maximisation test.

### Immunotoxicity

No dedicated immunotoxicity studies were submitted. Large reductions in lymphocyte counts (~40–65%), accompanied by decreased bodyweight relative thymus weight (and sometimes also spleen weight), were seen in the 6 month studies in mice (in males at  $\geq 4$  mg/kg/day roflumilast [ $ER_{AUC}$ , 1.7] and in both sexes at  $\geq 4$  mg/kg/day roflumilast N-oxide [ $ER_{AUC}$ , 4]), and in rats treated with roflumilast at 8 mg/kg/day in a 4-week study ( $ER_{AUC}$ , 16). Lymphocyte counts were also reduced (by 33–42%) in the pivotal monkey study at 0.5 mg/kg/day ( $ER_{AUC}$ , 7). However, there were no such effects in female rats in the pivotal study with roflumilast ( $ER_{AUC}$ , 60), nor in the studies in dogs ( $ER_{AUC}$ ,  $\leq 9$ ) or hamsters ( $ER_{AUC}$ ,  $\leq 25$ ). Histopathological examinations revealed treatment related lymphoid depletion only in the mouse carcinogenicity study, with a significant increase in incidence observed in males treated with roflumilast at 18 mg/kg/day ( $ER_{AUC}$ , 8), which exceeded the maximum tolerated dose. There was no indication of an increase in the number of infections or skin sores/wounds in the repeat dose studies and no immunosuppressive effects of roflumilast (1 mg/kg/day) were found in a rat kidney transplant model of acute rejection. Based on these findings, there appears to be no apparent consistent or overt immunosuppression. However, concerns over the immunotoxic potential of the drug remain unresolved.

Roflumilast is a PDE4 inhibitor intended as an antiinflammatory agent. In submitted pharmacology studies, roflumilast inhibited T-cell proliferation and suppressed TNF $\alpha$  release following bacterial LPS challenge, suggesting some effects on immune competence may be expected. Pharmacological inhibition of PDE4 or genetic ablation of PDE4B have been shown to affect the ability of animals to mount an adequate immune response (in particular T cell proliferation), leading to an increased incidence of infections even though baseline lymphocyte/leukocyte levels appeared unaffected (Losco et al., 2004; Jin and Conti, 2002; Soares et al., 2003).<sup>24,48,49</sup> A lack of increased infection incidence in the

<sup>47</sup> Siuciak JA, McCarthy SA, Chapin DS, Martin AN. Behavioural and neurochemical characterisation of mice deficient in the phosphodiesterase-4B (PDE4B) enzyme. *Psychopharmacol* 2008; 197: 115–126.

<sup>48</sup> Jin S-LC, Conti M. Induction of the cyclic nucleotide phosphodiesterase PDE4B is essential for LPS-activated TNF $\alpha$  responses. *Proc Natl Acad Sci USA* 2002; 99: 7628–7633.

<sup>49</sup> Soares AC, Souza DG, Pinho V et al. Impaired host defense to *Klebsiella pneumoniae* infection in mice treated with the PDE4 inhibitor rolipram. *Br J Pharmacol* 2003; 140: 855–862.

submitted studies could be misleading given that the laboratory animals under investigation would have been housed in a relatively protected environment and an increase in infections may only be obvious in cases of extreme immunosuppression. Based on a weight of evidence review in accordance with the relevant guideline, the drug's pharmacology and the suggestion of potential immune effects in the existing studies support the need for specialised immunotoxicity studies. A study to assess T-cell dependent antibody responses, in particular, should have been conducted to further investigate whether roflumilast poses an immunotoxic risk. Without this evidence, based on its intended mode of action, effects on T-cell dependent immune responses may be expected. These effects would be expected to be reversible upon cessation of treatment.

### **Impurities and residual solvents**

The specifications proposed for all identified impurities/degradants are within thresholds outlined in International Council on Harmonisation (ICH) guidelines. Specifications for the residual solvents are acceptable according to limits given in ICH Guideline Q3C or have been adequately justified based on toxicological data.

### **Nonclinical Summary and Conclusions**

*In vitro*, roflumilast inhibited phosphodiesterase 4 (PDE4) with nanomolar potency and >1000 fold specificity compared with other PDE enzymes. PDE4 degrades cAMP in various immune, airway and other cells. Inhibition of inflammatory responses from stimulated human polymorphonuclear leukocytes and eosinophils, monocytes and macrophages and human T-cell proliferation and cytokine release were demonstrated. *In vivo*, at exposures similar to that expected clinically, roflumilast inhibited cytokine release, as well as other indicators of a bronchial inflammatory response such as inflammatory cell accumulation, in rodent models of COPD. The major human metabolite, roflumilast N-oxide, was equipotent *in vivo*, and is expected to be the main contributor to PDE4 inhibition in patients.

Roflumilast did not interact directly with muscarinic, histaminergic, purinergic or adrenergic receptors in isolated tissue preparations. Roflumilast's inhibition of cAMP degradation potentiated the effects of various drugs, most notably those of  $\beta_2$ -adrenoceptor agonists.

Primary pharmacology studies, showing inhibition of cytokine release and T-cell proliferation, and antiinflammatory activity in rodent models of COPD, support the drug's use for the proposed indication.

Roflumilast exhibited very high specificity for PDE4, and no relevant secondary pharmacological targets were identified. Pharmacodynamic studies show that potentiation of cellular/tissue responses to various drugs can be expected to occur where both agents act to increase intracellular cAMP; this is most relevant to  $\beta_2$ -adrenoceptor agonists.

Safety pharmacology studies covered the central and autonomic nervous systems, cardiovascular, respiratory, gastrointestinal and renal systems. Nervous system effects in mice and rats included hypoactivity, hypothermia and impaired coordination (at  $\geq 4.5$  times the clinical  $C_{max}$ ). Roflumilast had pro-convulsant effects in mice ( $\geq 22$  times the clinical  $C_{max}$ ). No significant inhibition of hERG  $K^+$  channels was seen (up to 30-fold the clinical unbound  $C_{max}$ ). Abnormalities in ECG parameters (QRS and QT prolongation) were only observed in rats treated with a high lethal dose, and not in other species at high to very high multiples of the clinical  $C_{max}$ . Alterations in heart rate, blood pressure and cardiac contractility suggestive of a vasodilatory effect were restricted to dogs and cats. These occurred at subclinical plasma concentrations. No such effects were seen in other species (at least 9 times the clinical  $C_{max}$ ). No effects on contraction or gastrointestinal

motility were observed in specialised safety studies but an increase in basal gastric acid secretion was seen in rats (~2-fold the clinical  $C_{max}$ ). An increase in urinary volume with a concomitant increase in osmolality was seen in the rat but is not considered toxicologically significant. Roflumilast was not a respiratory depressant. No clinically relevant cardiovascular effects were seen; dogs are highly sensitive to cardiovascular effects due to PDE4 inhibition and are not an appropriate model for this drug. Central and autonomic nervous system effects occurred at modest relative exposures, are possibly directly related to PDE4 inhibition, and may be of clinical concern. Increased gastric acid secretion (also pharmacologically mediated) may alter the absorption of co-administered oral drugs, but otherwise is of minimal toxicological concern.

Pharmacokinetic studies indicated rapid absorption of roflumilast in all species. The plasma half-life was shorter in laboratory animal species (~1–4 h in most) than humans (18 h). Plasma protein binding by roflumilast and roflumilast N-oxide was high in animal and human serum and tissue distribution of roflumilast and/or its metabolites in rodents was wide; penetration across the blood-brain barrier was observed. Roflumilast was extensively metabolised in all species with the CYP3A4 derived metabolite roflumilast N-oxide the main circulating drug-related compound in all species, except dogs. ADCP and its derivatives were significant circulating metabolites in rodents, less significant in non-rodent species, and not detectable in the plasma of humans. Drug related material was excreted in both the urine and the faeces, with biliary excretion demonstrated in rats.

There was no clinically significant inhibition and/or induction of the human CYP450 isozymes, CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5 or 4A9/11. Although roflumilast is chiefly metabolised by CYP3A4, inhibitors or inducers of this isozyme are not expected to affect the overall exposure to pharmacologically-active material. No significant inhibition of P-glycoprotein was seen with roflumilast at 100  $\mu$ M (>5000 times the clinical roflumilast  $C_{max}$ ).

Roflumilast had a low order of acute oral toxicity in tested animal species.

Repeat dose toxicity studies were performed in mice (up to 6 months), rats (6 months), hamsters (3 months), dogs (12 months) and cynomolgus monkeys (9.5 months) using the clinical route (oral; PO). High relative exposures ( $\geq 25$  based on AUC) were obtained at the highest doses in mouse and hamster studies, while more modest relative exposures ( $\leq 10$ ) were obtained in rat, dog and monkey studies.

Changes consistent with irritation of the gastrointestinal tract (gastric ulcers, stomach erosions, mucosal bleedings, serositis and thickening of the intestine wall) were seen at high oral doses in rodents ( $\geq 17$  times the clinical AUC). Roflumilast was emetic in dogs and monkeys (at 0.5 and 10 times the clinical AUC, respectively). Reduced body weight gain was seen in the absence of vomiting in monkeys at 3 times the clinical AUC (exposure at the NOEL was equivalent to that expected in patients).

The nasal cavity was a target for toxicity in rodents. Olfactory epithelial degeneration/necrosis/disorganisation, respiratory metaplasia, squamous metaplasia, inflammation and Bowman's gland hyperplasia were seen in roflumilast treated rodents (exposure at the NOEL was 1–2 times the clinical AUC). Nasal cavity tumours developed in hamsters. Mechanistic studies indicated the nasal toxicity was associated with the formation of a reactive metabolite by a rodent specific CYP450 (2G1) expressed in the olfactory mucosa. Cardiac lesions (haemorrhages and myocarditis) were restricted to roflumilast treated dogs (equivalent to the clinical AUC). These were secondary to the inotropic effects of roflumilast in this species. No hamsters and only a small number of mice and monkeys had indications of potentially treatment related cardiac lesions (arteritis or myocarditis; at 25, 6 and 7 times the clinical AUC in the respective species). Testicular toxicity (epididymal

sperm granuloma, testicular tubular dilation, degeneration and atrophy, and/or oligo/aspermia) was seen in treated rats and mice (at exposures  $\geq 3$  and 8 times the clinical AUC). No testicular or epididymal findings were observed in other tested species.

Gastrointestinal irritation and nasal cavity findings in rodents, testicular/epididymal findings in mice and rats and cardiac lesions in dogs occurred at sufficiently high exposures or in uniquely sensitive species and are not considered to indicate likely hazards in humans.

Emesis, occurring in dogs at subclinical exposures and possibly directly related to PDE4 inhibition, and adverse effects on body weight, seen in monkeys at low multiples of the clinical exposure, are identified as the main toxicological concerns.

Neither roflumilast nor roflumilast N-oxide were mutagenic in bacterial or mammalian mutation assays or clastogenic in *in vitro* assays. Roflumilast was weakly positive in the mouse micronucleus tests but only at high oral doses (producing mortality and 160 times the clinical AUC). The weight of evidence supports that roflumilast is not genotoxic. In 2 year oral carcinogenicity studies, no treatment related increase in tumour incidence was observed in mice, while an increase in the incidence of nasal cavity tumours was observed in hamsters (from 8 times the clinical AUC); the finding, however, is not considered to be relevant to humans on mechanistic grounds.

Decreased fertility was evident in male rats, associated with testicular lesions and a slight decrease in sperm count. No adverse effects on fertility were evident in female rats, although an increase in corpora lutea was indicated (at 0.6 times the clinical AUC), and altered oestrous/menstrual cycling was seen after chronic administration to female mice, rats and monkeys. Placental transfer of roflumilast (and/or its metabolites) was demonstrated (in rats) and increased incidences of fetal skeletal variations (impaired ossification of skull bones) were observed in rats in one study (from 1.5 times the clinical AUC) but not in a second study (3.5 times the clinical AUC). While no fetal variations or malformations were seen in the rabbit embryofetal development study, estimated exposures in this study were subclinical and thus no great weight can be placed on the negative findings.

Altered oestrous/menstrual cycling, at low relative exposures in females from three species, is potentially of clinical significance. Decreased male fertility in rats, occurring in the context of testicular toxicity, is unlikely to be clinically relevant.

Roflumilast had a pronounced tocolytic effect in the mouse when given near term. Increased still births and decreased survival of offspring were evident in postnatal studies. Roflumilast and/or its metabolites were readily excreted in milk in rats and could be detected in feeding pups. Reduced locomotor activity was seen in female pups of mice treated with roflumilast during gestation and lactation (at 2 times the clinical AUC).

Exposure levels achieved in the reproductive toxicity studies were low (<4 times the clinical AUC in mice and rats, and subclinical in rabbits), limiting their predictive value. Increases in gestation duration, difficulties in delivering, increased fetal skeletal abnormalities, increased stillbirths and decreased neonatal survival, justify significant caution with use in pregnancy. As roflumilast is excreted in milk and appears to be pharmacologically active in breast fed animals, the drug should not be used during lactation.

Following on from *in vitro* findings of inhibition of T-cell proliferation, large reductions in lymphocyte counts were seen in a number of the repeat dose toxicity studies (in mice, rats and monkeys). No dedicated immunotoxicity studies were submitted. The absence of specialised immunotoxicity studies to investigate T-cell dependent antibody responses is

considered a deficiency of the application. Impairment of T-cell responses to foreign challenge may be expected given the drug's pharmacology.

Many of the adverse effects are attributed to PDE4 inhibition at non-target sites. PDE4 is expressed in numerous cells/tissues, including in the CNS. The low relative exposure for these effects is a particular concern given the intended chronic administration.

There were no nonclinical objections to the registration of Daxas provided that concerns regarding potential immunosuppression were adequately addressed by clinical data and that a favourable benefit:risk profile is demonstrated.

## IV. Clinical Findings

### Introduction

The Phase I program comprised a total of 65 studies evaluating the pharmacokinetics and pharmacodynamics of roflumilast in healthy volunteers and patients. There were 18 Phase II and III studies investigating the efficacy and safety of roflumilast in patients with moderate to very severe COPD classified according to the American Thoracic Society/European Respiratory Society (ATS/ERS) COPD guidelines or the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.<sup>50,51</sup> All the efficacy studies were placebo controlled and complied with the TGA-adopted EU guideline for investigation of medicinal products in the chronic treatment of patients with COPD.<sup>52</sup>

Two pivotal, 52 week studies compared the efficacy of roflumilast 500 µg once daily (od) vs placebo on exacerbation rate and lung function in 3096 patients with severe to very severe COPD associated with chronic bronchitis and a history of exacerbations (Studies M2-124 and M2-125). Two 6 month studies investigated the effects of roflumilast 500 µg od treatment in patients with moderate to severe COPD receiving long acting bronchodilator maintenance treatment (salmeterol in Study M2-127 or tiotropium in Study M2-128).

Seven other studies were considered supportive by the sponsors. Two 1 year studies (Studies M2-111 and M2-112) assessed the effect of roflumilast 500 µg od vs placebo on exacerbation rate and lung function in 2686 patients with severe to very severe COPD and five 6 month placebo controlled studies focussed on the effects of roflumilast on lung function in patients with moderate to severe COPD. Study FK1 101 was a dose range and proof of concept study with administration of placebo and two doses of roflumilast (250 µg and 500 µg od) in 516 patients with moderate to severe COPD. The dose finding was further explored in study M2-107 involving 1411 patients applying the same doses as in Study FK1 101. Study M2-110 evaluated efficacy related to lung function with the 500 µg roflumilast dose, while Study M2-121 investigated the effects of roflumilast on hyperinflation. Study FK1 103 investigated the effect of roflumilast withdrawal after 12 weeks of treatment, in addition to comparing a 24 week treatment of roflumilast with placebo. Seven additional studies were classified as "other studies" as they were of shorter duration (IN-108, M2-119, M2-118), had a different study design (FK1 102 and FHP 030,

<sup>50</sup> American Thoracic Society/European Respiratory Society Task Force. Standards for the diagnosis and management of patients with COPD [Internet]. Version 1.2. New York; 2004 [updated 2005 September 8]. Available from: <http://www.thoracic.org/sections/copd>.

<sup>51</sup> Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2008, from the *Global Strategy for the Diagnosis, Management and Prevention of COPD*. Available from: <http://www.goldcopd.org>.

<sup>52</sup> EMEA, Committee for Proprietary Medicinal Products (CPMP), 19 May 1999. Points to consider on clinical investigation of medicinal products in the chronic treatment of patients with chronic obstructive pulmonary disease (COPD). CPMP/EWP/562/98; available at <http://www.tga.gov.au/pdf/euguide/ewp056298en.pdf>

open label or crossover) or were conducted under supervision of a different sponsor in Japan (JP-706 and JP-708). These provided limited information and were not evaluated in detail.

## Pharmacokinetics

### Introduction

The section examining the pharmacokinetics (PK) of roflumilast describes 58 studies. Five of these studies represented assay method validations, 9 were *in vitro* studies and 3 were population PK reports. The total PK study cohort of 707 subjects was comprised of 663 healthy subjects, aged 18 to 78 years, 24 children (aged 6 to 17 years) with mild to moderate asthma, 12 patients with severe renal impairment (aged 34 to 65 years) and 8 patients (aged 43 to 67 years) with impaired hepatic function (note these numbers do not include subjects included in population PK reports).

### Methods

#### *Pharmacokinetic data analysis*

Studies examining roflumilast were heterogeneous in design due to the variety of objectives addressed. They were in general conducted as mono-centre studies and randomised. Studies were open label, when the assessment of objective variables was the primary purpose (for example, PK) or were blinded when the assessment of safety and tolerability was the primary objective. Double blind, placebo controlled designs were in particular applied for the evaluation of special safety parameters or in the assessment of special pharmacodynamic (PD) parameters (for example, forced expiratory volume in one second [FEV<sub>1</sub>], a measure of lung function).

### Absorption

#### *Bioavailability*

In study FHP006, the absolute bioavailability following administration of single oral dose of 500µg roflumilast (compared with IV infusion of 150 µg) was 79%; the volume of distribution was 2.92 L/kg and clearance was 0.137 L/h/kg. Following oral administration of roflumilast, the AUC of roflumilast N-oxide was about 12.5 fold higher than the AUC of roflumilast, whereas following IV administration the AUC of roflumilast N-oxide was about 7.5 fold higher.

#### *Bioequivalence*

In study FHP015, the area under the plasma concentration time curve from time zero to infinity (AUC<sub>∞</sub>) and C<sub>max</sub> of roflumilast following administration of the 3 tablet strengths (100 µg, 250 µg and 500 µg) were similar and ranged from 33.5 - 33.9 ng.h/L and 7.75 - 8.18 ng/L, respectively. For roflumilast N-oxide, the AUC<sub>∞</sub> ranged from 368 - 383 ng.h/L and C<sub>max</sub> ranged from 9.70 - 9.84 ng/L, respectively. The point estimates and the 90% confidence intervals (CIs) for the roflumilast/roflumilast N-oxide ratios fell well within the levels of bioequivalence indicating that the three tablet strengths were bioequivalent. In study FHP016, the AUC<sub>∞</sub> of the three tablet formulations (250 µg each) were similar and ranged from 33.0 - 35.3 ng.h/L and C<sub>max</sub> ranged from 5.53 to 7.59 ng/L. Applying bioequivalence ranges of 80 to 125% for AUC and 70 to 143% for C<sub>max</sub>, as predefined in the study protocol, Formula B was bioequivalent to Formula B, whereas Formula B and Formula C<sup>53</sup> were not bioequivalent. In study EM056 evaluating bioequivalence of 2

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53 Formula A: used in 4 early phase I/II studies, galenical formula B-FG1

Formula B: present study formulation, galenical formula B-OPW

Formula C: planned market formulation, galenical formula C-OPW

formulations of Rof500, Formula B (used in pivotal Phase III studies) and Formula E (proposed marketing formulation), roflumilast  $AUC_{\infty}$  was 51.1 and 51.3  $\text{ng}\cdot\text{h}/\text{L}$  following Formula E and B, respectively, and  $C_{\text{max}}$  was 9.59 and 8.21  $\text{ng}/\text{L}$ , respectively. The  $AUC_{\infty}$  (568 and 574  $\text{ng}\cdot\text{h}/\text{L}$ ) and  $C_{\text{max}}$  (9.78 and 9.53  $\text{ng}/\text{L}$ ) for roflumilast N-oxide was also similar for both the clinical trial and proposed marketing formulations and the two formulations were bioequivalent.

### ***Influence of Food***

In study FHP010, the AUC of roflumilast under fed and fasted conditions was 34.8 and 31.2  $\text{ng}\cdot\text{h}/\text{L}$ , respectively;  $C_{\text{max}}$  was 3.84 and 6.51  $\text{ng}/\text{L}$ , respectively. For roflumilast N-oxide, AUC was 304 and 350  $\text{ng}\cdot\text{h}/\text{L}$  under fed and fasted conditions, respectively, and  $C_{\text{max}}$  was 8.40 and 8.81  $\text{ng}/\text{L}$ , respectively. By contrast, the ADCP metabolite (4-amino-3,5-dichloropyridine) was difficult to detect and an AUC could not be calculated suggesting low formation of this metabolite, however, the  $C_{\text{max}}$  for ADCP was 0.065 and 0.075  $\text{ng}/\text{L}$  in the fed and fasted subjects, respectively. Under fed conditions, roflumilast AUC increased by 12% while  $C_{\text{max}}$  decreased by 41% compared to the fasted condition. For the N-oxide metabolite, AUC decreased by 9% while  $C_{\text{max}}$  decreased by 5% under fed conditions. Food affected both the AUC (12% increase under fed conditions) and  $C_{\text{max}}$  (41% decrease under fed conditions) of roflumilast. For N-oxide metabolite, a food effect was seen with respect to AUC (9% decrease under fed conditions) but not  $C_{\text{max}}$  (90% CIs: 90 - 101). Under fed and fasted conditions, the formation of roflumilast N-oxide was similar (about 9-fold higher under fed and 11-fold higher under fasted conditions when compared with roflumilast).

### ***Evaluator's Comments***

Formula B was used in the clinical development program. However, it was not clear from study report FHP016 why the wider bioequivalence range was used for  $C_{\text{max}}$  and if the more typical 80 to 125% bioequivalence range was used, then none of the 3 formulations (Formula A, Formula B and Formula C/) can be considered bioequivalent.

The clinical trial and proposed marketing formulations of roflumilast were bioequivalent as the 90% CIs for AUC and  $C_{\text{max}}$  for both roflumilast and roflumilast N-oxide fell within the accepted interval of 0.80 - 1.25.

Based on the 90% CI criteria of 80 - 125%, food led to a significant decrease in the  $C_{\text{max}}$  of roflumilast but did not appear to significantly affect the AUC of roflumilast or AUC and  $C_{\text{max}}$  of roflumilast N-oxide.

## **Distribution**

### ***Plasma Protein Binding***

#### ***In vitro studies***

*In vitro* study [96/2002] showed that there is a high degree of concentration independent binding of roflumilast and roflumilast N-oxide to human plasma proteins (99% and 97%, respectively). Roflumilast and roflumilast N-oxide principally bind to human albumin and to a smaller extent to  $\alpha$ 1-acid glycoprotein.

#### ***In vivo studies***

In study [FHP036], which evaluated the distribution, metabolism, excretion (mass balance) and PK of [ $^{14}\text{C}$ ]-roflumilast after oral and IV administration, the  $C_{\text{max}}$  of roflumilast and roflumilast N-oxide were similar (8.83 and 8.49  $\text{ng}/\text{L}$ , respectively), however the  $AUC_{\infty}$  of the metabolite was approximately ten times higher (28.1 and 314  $\text{ng}\cdot\text{h}/\text{L}$ , respectively) and the half-life ( $t_{1/2}$ ) of the metabolite was longer (13.4 and 17.7 h,

respectively). The time to maximum plasma concentration ( $t_{\max}$ ) of roflumilast following both oral and IV administrations occurred at 0.5 h, whereas the  $t_{\max}$  of roflumilast N-oxide was longer following the oral dose (3.67 and 6.00 h, respectively). Oral absorption of [ $^{14}\text{C}$ ]-roflumilast 500  $\mu\text{g}$  (Rof500) was 84%, based on dose normalised plasma [ $^{14}\text{C}$ ]-radioactivity, and 99%, based on dose normalised amounts excreted in urine. Bioavailability based on the dose corrected AUC ratio for unchanged roflumilast in plasma after oral and IV administration was 64%. The total amount of [ $^{14}\text{C}$ ]-radioactivity recovered was 91% 10 days after IV administration and 90% 15 days after oral administration. Approximately 70% of both dose forms were excreted in urine over these time periods. Based on plasma AUC, the sum of roflumilast and roflumilast N-oxide accounted for 57% and 5% of the total radioactivity after IV and oral administration, respectively, suggesting the formation of metabolites other than roflumilast N-oxide.

A positron emission tomography (PET) study investigated the PK and distribution of [ $^{18}\text{F}$ ]-roflumilast into the lung, nose, stomach and brain after a single 500  $\text{mg}$  oral administration [FHP011] in 6 healthy subjects. There was a rapid uptake of the tracer from the gastrointestinal tract with significant non-vascular localisation in lung, muscle and brain tissue. In the brain, the non-vascular concentration was about 8% of that of plasma, in muscle 15% and in lung 45% (corrected under the assumption that drug was not distributed into the alveolar air). No selective accumulation was found in the nasal mucosa. The tissue to blood ratio was close to 1.0 (tissue to plasma ratio: 0.6), with no signs of increase from 2 h after the administration of study medication. Following drug administration, the  $\text{AUC}_{\infty}$ ,  $C_{\max}$  and  $t_{\max}$  of roflumilast were 39.9  $\text{ng}\cdot\text{h}/\text{L}$ , 5.36  $\text{ng}/\text{L}$  and 12.5 hours, respectively. As the  $t_{\max}$  of roflumilast N-oxide ranged between 2 and 10 h, there were insufficient sampling points in the terminal phase of elimination to determine the AUC and  $t_{1/2}$ , whereas, the  $C_{\max}$  equalled 10.6  $\text{ng}/\text{L}$ . Concentrations of ADCP were below the lower limit of quantification (LLOQ) and therefore the PK characteristics of this metabolite could not be determined.

#### *Evaluator's Comments:*

As the  $t_{1/2}$  and the  $t_{\max}$  of the N-oxide metabolite are 25.7 and 8.53 hours, respectively, it is unlikely the sampling times described in the PET study FHP011, 24 and 8 h, that investigated the PK and distribution of [ $^{18}\text{F}$ ]-roflumilast into the lung, nose, stomach and brain after a single 500  $\text{mg}$  oral administration were adequate.

### **Elimination**

#### ***Excretion***

Study FHP036 in the previous section provided information regarding the excretion and major elimination routes of roflumilast. In summary, the total amount of radioactivity recovered following a 300  $\text{mg}$  and 500  $\text{mg}$  dose of IV and oral [ $^{14}\text{C}$ ]-roflumilast, respectively, was 91%, 10 days after the IV administration, and 90%, 15 days after the oral administration. Approximately 70% of both dose forms were excreted in the urine over these time periods and a further 20 % was excreted in the faeces.

#### ***Metabolism***

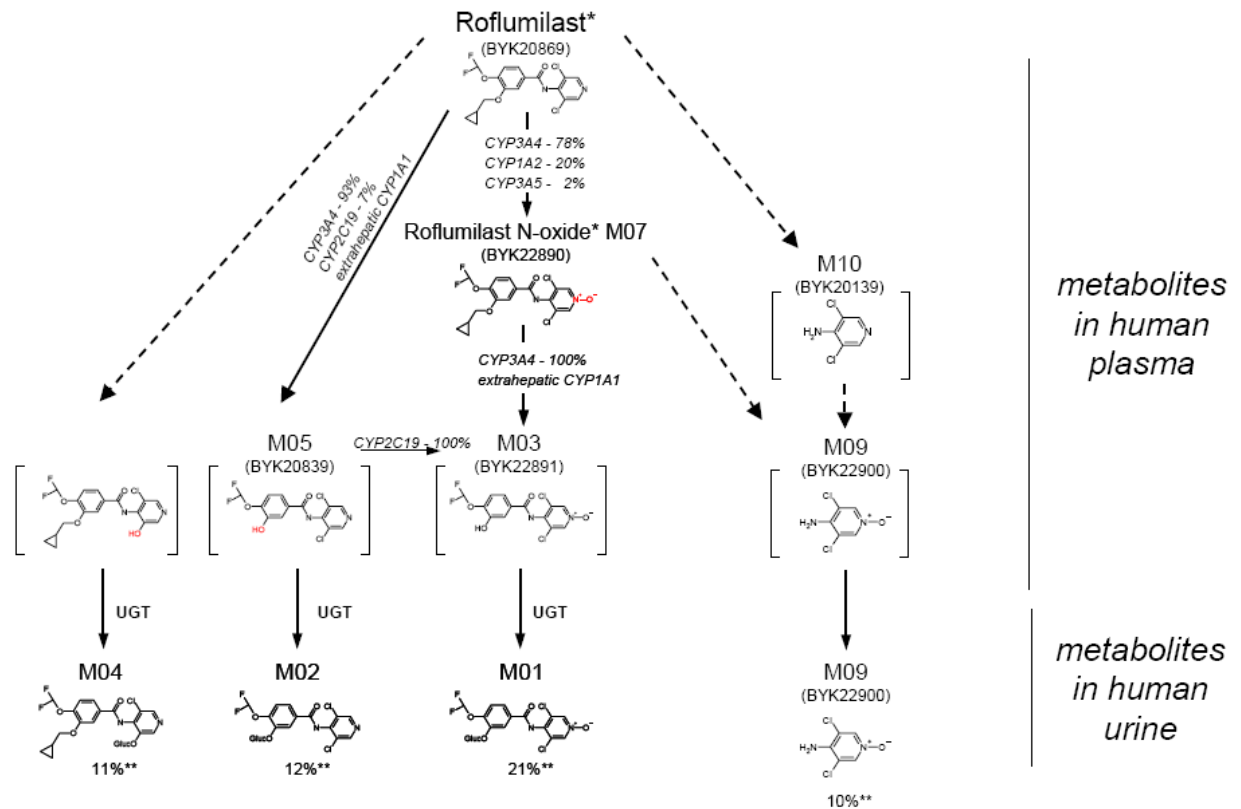
##### *In vitro Studies*

Five major metabolites were identified in study 212/2002. The distribution patterns of the radioactivity were similar following both oral and IV doses. Roflumilast was not detected in urine, whereas roflumilast N-oxide was a trace metabolite (less than 1%). The major metabolic routes in man included the loss of the cyclopropylmethyl group resulting in a phenol, N-oxidation to form a quaternary N-oxide, and oxidative dechlorination to generate a phenol moiety, followed by glucuronidation. Another route of roflumilast



metabolism in humans occurred via cleavage of the amide bond resulting in an ADCP-related metabolite. The proposed metabolic pathway of roflumilast is shown in Figure 1.

**Figure 1: Roflumilast metabolites**



#### Pharmacokinetics of metabolites

All information regarding the PK of roflumilast N-oxide, the major and active metabolite of roflumilast, is reported alongside the PKs of roflumilast in the relevant studies. The comparative pharmacokinetics from a total of 15 single dose studies (212 subjects) and 10 repeated dose studies (231 subjects) were summarised. In all of these studies the oral dose used (500 µg roflumilast) od was administered in fasted state in the morning.

After a single oral dose of 500 mg roflumilast, the median AUC of roflumilast across studies was 40.5 µg.h/L, ranging from 26.6 to 61.0 µg.h/L; the median C<sub>max</sub> was 7.04 µg/L, (ranging from 3.1 to 9.60 µg/L); t<sub>1/2</sub> was 18.4 h, (ranging from 9.7 to 33.1 h); and t<sub>max</sub> was 1 h (ranging from 0.5 to 2 h). By contrast, the median AUC of roflumilast N-oxide across studies was 415 µg.h/L, ranging from 154 to 780 µg.h/L, therefore exceeding the exposure to roflumilast by approximately tenfold. The median C<sub>max</sub> of roflumilast N-oxide was 9.49 µg/L (ranging from 6.6 to 13.1 µg/L); t<sub>1/2</sub> was 25.7 h (ranging from 19.6 to 44.0 h); and the t<sub>max</sub> was 8.53 h (ranging from 4 to 13 h). The across study variability of roflumilast N-oxide was generally consistent with findings seen for the parent drug roflumilast, that is, higher or lower PK results of roflumilast were mirrored by roflumilast N-oxide.

Following repeated oral doses of Rof500 od the median AUC across studies was 35.9 µg.h/L (ranging from 30.8 to 67.2 µg.h/L); C<sub>max</sub> 7.29 µg/L (ranging from 5.19 to 10.1 µg/L); minimum plasma concentration (C<sub>trough</sub>) 0.72 µg/L (ranging from 0.47 to 1.86 µg/L); t<sub>1/2</sub> 16.6 h (ranging from 8.2 to 30.9 h); and t<sub>max</sub> 1 h (ranging from 0.5 to 2.6 h). By contrast,

the median AUC of roflumilast N-oxide across studies was 436  $\mu\text{g}\cdot\text{h}/\text{L}$  (ranging from 351 to 717  $\mu\text{g}\cdot\text{h}/\text{L}$ );  $C_{\text{max}}$  24.4  $\mu\text{g}/\text{L}$  (ranging from 21.5 to 42.7  $\mu\text{g}/\text{L}$ );  $C_{\text{trough}}$  14.5  $\mu\text{g}/\text{L}$  (ranging from 11.6 to 29.3  $\mu\text{g}/\text{L}$ );  $t_{1/2}$  was 29.7 h (ranging from 10.6 to 46.5 h); and  $t_{\text{max}}$  3 h (ranging from 2 to 5.9 h). Compared with single dose results, a similar order of magnitude in the across study variability was found for plasma  $t_{1/2}$  and  $C_{\text{max}}$  and the across study variability of roflumilast N-oxide was generally consistent with findings seen for the parent drug.

#### *Consequences of possible genetic polymorphism*

As CYP1A2 and CYP3A4 were key enzymes involved in the metabolism of roflumilast, two studies determined the *in vivo* enzymatic activity (phenotyping) of 1A2 [CP-053] and 3A4 [CP-054] in a single female subject, aged 41 years, who exhibited unexpectedly high plasma concentrations of roflumilast and roflumilast N-oxide during study FHP027 and compared it to the enzymatic activity in 6 healthy female control subjects aged 24 to 45 years. Caffeine phenotyping suggested a 1A2 activity of less than 50% in this subject compared with the control group. This finding was thought likely to contribute to the unexpectedly high exposure of roflumilast in this subject. Comparison with the historical control group of 57 healthy subjects taken from published data showed that the subject's weight normalized clearance was in the lower percentile (range: 2.61 to 3.88  $\text{mL}/(\text{min}\cdot\text{kg})$ ) of the reference, suggesting that this subject had a reduced 3A4 activity, which possibly contributed to her unexpectedly high plasma concentrations of roflumilast and roflumilast N-oxide.

Report [269/2003] represented a summary/expert report on the PK and pharmacogenetic analysis of the increased systemic exposure to roflumilast shown by this subject. The low 3A4 activity was likely related to the presence of a newly identified CYP 3A4\*20 allele that lacked enzymatic activity. The genetic basis for the low 1A2 activity could not be established. The calculated frequency for the potential occurrence of another such individual (with co-existent low 1A2 and 3A4 activity) was less than 0.0006%. For the single 3A4 mutation, the maximum CYP3A4\*20 allele frequencies to be potentially expected in Caucasians, African Americans and Chinese populations were determined to be smaller than 0.12%, 0.26% and 0.22%, respectively. Despite the high exposure of this subject to roflumilast and roflumilast N-oxide, the subject did not exhibit more adverse events than control subjects who displayed lower exposure.

#### *Evaluator's Comments:*

In human plasma, one major metabolite, roflumilast N-oxide, was identified in addition to the parent compound. Although strong, the inhibition observed following co-administration of roflumilast with 3A4 inhibitors ketoconazole and azamulin was not complete, suggesting that 3A4, although a major contributor is not the only enzyme responsible for the formation of despropyl roflumilast N-oxide in human liver microsomes.

Of the CYP enzymes evaluated, 3A4 appears to be a major contributor to the formation of despropyl roflumilast N-oxide. Several other CYP enzymes may also play a minor role in the formation of despropyl roflumilast N-oxide (for example, 2B6 and 2C8). In addition, 1A1 may contribute to the O-dealkylation of roflumilast N-oxide to despropyl roflumilast N-oxide in extra-hepatic tissue. By contrast, FMO enzymes do not appear to play a role in metabolism of roflumilast.

Roflumilast (1 pM - 100 pM) resulted in a weak induction of 2B6 (ranging from a 1.24- to 1.34-fold increase), whereas, no induction of 1A2, 2C9 and 2C19 was seen. By contrast, roflumilast induced small increases in 2A6 and 3A4/5, particularly at the highest dose of 0.1 nM. The rank order of roflumilast N-oxide for inhibiting the various CYP enzymes

studied (based on  $K_i$  values) was: CYP 3A4/5  $\approx$  CYP 2C8 < CYP 2C9 < CYP 1A2 < CYP 2C19 < CYP 2B6 < CYP 2A6 < CYP 2D6  $\approx$  CYP 2E1.

Mutations in the 1A2 and 3A4 genes that induce low CYP activity can cause large changes in the PK of roflumilast and its N-oxide metabolite. This finding was based on the study of a single patient as the calculated frequency for the potential occurrence of another such individual was less than 0.0006%. However, a detailed evaluation of the PK of roflumilast in patients with different 3A4 genotypes was not conducted.

## **Dose proportionality and time dependency**

### ***Dose proportionality***

In Study FHP001 at the dose of 2500  $\mu\text{g}$ , drug related adverse effects (AEs) such as nausea, dizziness and headache were considered dose limiting. Hence, the single oral administration of roflumilast 1000  $\mu\text{g}$  was the preliminary maximum tolerated dose (MTD) for further clinical studies. -Consistent with the initial tolerability [FHP001] study a single oral dose of roflumilast 1000  $\mu\text{g}$  was tolerated in a small cohort of healthy male subjects [FHP002], while a dose of roflumilast 2500  $\mu\text{g}$  was considered hardly tolerable due to the AE profile. The PK and tolerability results of study [FHP005] suggested that a 150  $\mu\text{g}$  dose would be at least required for a study investigating absolute bioavailability in humans.

In study FHP040, the AUC of roflumilast ranged from 6.6 to 40.4  $\text{ng}\cdot\text{h}/\text{L}$  following administration of single oral doses of 125, 250 and Rof500, whereas the  $C_{\text{max}}$  ranged from 2.27 to 7.34  $\text{ng}/\text{L}$ . The  $t_{\text{max}}$  of roflumilast, as in previous studies was similar for all doses, however the  $t_{1/2}$  increased from 8.43 to 18.2 h between the 125 and 500  $\text{ng}$  doses. The AUC of roflumilast N-oxide ranged from 96.6 to 434  $\text{ng}\cdot\text{h}/\text{L}$  for the three doses, whereas the  $C_{\text{max}}$  ranged from 2.37 to 9.4  $\text{ng}/\text{L}$ . The  $t_{\text{max}}$  of roflumilast N-oxide, as in previous studies was similar for all doses, as was the  $t_{1/2}$  which ranged from 23.5 to 25.3 h.

In order to verify dose proportionality, the AUC and  $C_{\text{max}}$  values were does normalised to the 250  $\text{ng}$  dose and analysis of variance was performed. The  $\text{AUC}_{\infty}$  and  $C_{\text{max}}$  (for both roflumilast and roflumilast N-oxide) for the 500  $\text{ng}$  dose were bioequivalent to the 250  $\text{ng}$  dose. By contrast, the AUC and  $C_{\text{max}}$  of roflumilast for the 125  $\text{ng}$  dose were lower and higher, respectively, whereas, the AUC and  $C_{\text{max}}$  for roflumilast N-oxide were bioequivalent to the 250  $\text{ng}$  dose. The AUC and  $C_{\text{max}}$  of roflumilast and ADCP increased proportionally with dose, approximately doubling following repeated dosing with Rof500 and 1000  $\mu\text{g}$  over 7 days in study FHP004 128E/97. The  $C_{\text{max}}$  of roflumilast increased by about 35% following administration of 500  $\text{ng}$  twice daily (bd) roflumilast, compared with 500  $\text{ng}$  od roflumilast. The systemic exposure of ADCP was 6 to 8 times lower than that of roflumilast. In addition, the PK parameters of roflumilast N-oxide were retrospectively determined and the AUC (351  $\text{ng}\cdot\text{h}/\text{L}$ ) after repeated dosing of 500  $\text{ng}$  roflumilast od was approximately 11 fold higher than that of roflumilast. ADCP N-oxide could not be detected in any of the samples. Study FHP009 following 3 weeks administration of Rof500 showed similar results.

Following administration of increasing repeated oral doses (500, 750 and 1000  $\mu\text{g}$ ) of roflumilast in study FHP023, the AUC of roflumilast for the three doses ranged from 32.6 to 65.9  $\text{ng}\cdot\text{h}/\text{L}$  and for roflumilast N-oxide ranged from 347 to 799  $\text{ng}\cdot\text{h}/\text{L}$ . The  $C_{\text{max}}$  of roflumilast ranged from 4.74 to 11.1  $\text{ng}/\text{L}$  and for its metabolite from 20.6 to 50.6  $\text{ng}/\text{L}$ . Overall, the AUC and  $C_{\text{max}}$  of roflumilast N-oxide were roughly 11 fold and fourfold higher, respectively, than the parent compound. By contrast, the  $t_{1/2}$  and  $t_{\text{max}}$  were independent of dose and following the final dose, the  $t_{1/2}$  was 14.6 h for roflumilast and 19.6 h for roflumilast N-oxide. The AUC increased dose proportionally for both roflumilast and

roflumilast N-oxide.  $C_{max}$  increased dose proportionally between the 750 and 1000 mg doses for both roflumilast and roflumilast N-oxide, however, between 500 and 750 mg a dose proportional increase was only seen for the  $C_{max}$  of roflumilast N-oxide and not for roflumilast.

Following single and repeat oral doses of 250 or 500 µg roflumilast [FHP039], the AUC and  $C_{max}$  of roflumilast and roflumilast N-oxide, on the whole, increased dose proportionally. By contrast, the  $t_{1/2}$  and  $t_{max}$  values of roflumilast and roflumilast N-oxide were independent of dose, whereas ADCP and ADCP N-oxide concentrations were low or below the LLOQ.

### ***Time dependency***

In study [CP-043], the AUC of roflumilast was 40.6 and 38.9 mg.h/L following morning and evening administration, respectively, whereas the  $C_{max}$  was 3.79 and 3.06 mg/L. The AUC of roflumilast N-oxide was 377 and 386 mg.h/L following morning and evening administration, respectively whereas the  $C_{max}$  was 6.61 and 6.79 mg/L. The  $AUC_{\infty}$  of roflumilast was not affected by the timing of administration, whereas the  $C_{max}$  of roflumilast was lower after evening relative to morning administration. By contrast, the AUC and  $C_{max}$  of roflumilast N-oxide following both morning and evening administrations of roflumilast were similar.

### **Intra- and inter-individual variability**

Within subject (*intra*-individual) and between subject variability was assessed in study EM-056 using a replicated design. The within subject variability for AUC and  $C_{max}$  of roflumilast ranged from 13.4 to 15.0% for Formula E (proposed marketing formulation) and from 11.1 to 16.2% for Formula B (used during clinical development), and that of roflumilast N-oxide from 13.0 to 13.5% for Formula E and 6.25 to 6.49% for Formula B. The between subject variability for AUC and  $C_{max}$  of roflumilast ranged from 21.0 to 41.5% for Formula E and 19.0 to 44.3% for Formula B, and that of roflumilast N-oxide from 23.3 to 37.4% for Formula E and 24.1 to 40.6% for Formula B.

#### *Evaluator's Comments:*

Intra-subject variability was below the 30% threshold, therefore, the number of subjects that were used in the study to determine variability (n=24) appears to be adequate. It must be noted that the bioequivalence study FHP015 only examined 18 subjects.

### **Pharmacokinetics in the target population**

#### ***Population Pharmacokinetics***

The population PK of roflumilast and roflumilast N-oxide in COPD patients was examined in study [343/2008]. The population PK model of roflumilast and roflumilast N-oxide for COPD patients was an extension of the existing Phase I model. Two Phase II/III studies with PK sampling data were used, namely BY217/IN-108 and BY217/M2-110. A sparse sampling schema was used in both studies.<sup>54</sup> Using the derived model the influential covariates on population mean parameters of roflumilast were:

1. COPD on clearance: clearance was 39.4% lower in COPD patients, therefore, the typical clearance for COPD patients would be 6.36 L/h compared with 10.5 L/h in healthy subjects;

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<sup>54</sup> "Sparse" refers to a technique employed in population pharmacokinetic studies where a small number of samples are obtained from a large number of subjects.

2. COPD on central volume of distribution: central volume of distribution was 184% larger in COPD patients, therefore, the typical central volume of distribution for COPD patients would be 40.6 L compared with 14.3 L in healthy subjects.

For roflumilast N-oxide, the influential covariates on population mean parameters were:

1. COPD on clearance: the clearance was 7.85% lower in COPD patients when compared to healthy subjects, therefore, the typical clearance for COPD patients would be 0.81 L/h, compared with 0.883 L/h in healthy subjects;
2. COPD on volume of distribution: the volume of distribution was 21.4% smaller in COPD patients, therefore the typical volume of distribution in COPD patients would be 51.7 L compared with 65.8 L in healthy subjects.

### **Special populations**

The PK of roflumilast was not evaluated in the target population of patients with COPD.

#### ***Children***

A 250 µg dose of roflumilast in children <40 kg with mild to moderate asthma resulted in similar (but not bioequivalent) exposure (based on AUC and C<sub>max</sub>) to 500 µg in healthy adults (≥ 60 kg). A 375 µg dose in children ≥40 kg to <60 kg and adolescents ≥40 kg to <60 kg resulted in a slight underexposure. In addition, adolescents ≥60 kg receiving a 500 µg dose were also underexposed by approximately 30% compared to adults ≥60 kg.

#### ***Elderly***

The steady state PK of 500 µg roflumilast in healthy elderly (≥ 65 years) subjects were compared with healthy young (18 to 45 years) and healthy middle aged (46 to 64 years) subjects in study [CP-050]. The AUCs of roflumilast and roflumilast N-oxide were 26% and 18% higher, respectively, in elderly vs young subjects whereas the AUC and C<sub>max</sub> were similar in middle aged and young subjects. Similarly, the C<sub>max</sub> of roflumilast and roflumilast N-oxide were 16% and 13% higher, respectively, in the elderly vs young subjects, whereas in middle aged subjects the C<sub>max</sub> of roflumilast N-oxide was 8% lower than in young subjects. No comparison was made between the middle aged and elderly subjects. In all age groups higher systemic exposures and peak concentrations were noted in females, compared with male subjects for roflumilast and the N-oxide.

#### ***Impaired renal function***

The PK of roflumilast after single oral administration of 500 µg to patients suffering from severe renal impairment (10 ≤creatinine clearance [CLCr] ≤30 mL/min/1.73 m<sup>2</sup> body surface area) vs healthy subjects (CLCr ≥80 mL/min/1.73 m<sup>2</sup> body surface area) were examined in study [FHP020]. Healthy subjects were matched to patients according to gender, age (±5 years), height (±10%) and weight (±10%). Compared with healthy subjects, the AUC<sub>∞</sub> of roflumilast and the N-oxide was lower by 21% (44.6 µg.h/L in healthy compared with 35.4 µg.h/L in impaired) and 7% (461 and 428 µg.h/L, respectively), in patients with severe renal impairment. The C<sub>max</sub> of roflumilast was also lower by 16% in renally impaired vs healthy subjects (4.26 µg/L vs 5.07 µg/L).

#### ***Impaired hepatic function***

The PK and safety of roflumilast following once daily repeated oral administrations of 250 µg roflumilast to patients with cirrhosis, Child-Pugh A and B, and to healthy subjects were

examined in study [CP-062].<sup>55</sup> For roflumilast and roflumilast N-oxide, the AUC and  $C_{max}$  increased with the degree of liver impairment. For roflumilast, the AUC ranged from 30  $\mu\text{g}\cdot\text{h}/\text{L}$  in healthy subjects to 57.7  $\mu\text{g}\cdot\text{h}/\text{L}$  in subjects with Child-Pugh B. For roflumilast N-oxide, the AUC ranged from 308 to 382  $\mu\text{g}\cdot\text{h}/\text{L}$  in healthy and moderately impaired, respectively. The AUC of roflumilast was 50% higher in Child-Pugh A and 92% higher in Child-Pugh B patients and that of roflumilast N-oxide was 23% higher in Child-Pugh A and 41% higher in Child-Pugh B patients, when compared with healthy subjects. The  $C_{max}$  of roflumilast was 2% higher in Child-Pugh A and 26% higher in Child-Pugh B patients and that of roflumilast N-oxide were 25% higher in Child-Pugh A and 40% higher in Child-Pugh B patients. The PK of roflumilast was not evaluated in patients with severe hepatic impairment.

### ***Population Pharmacokinetics***

The population PK of roflumilast and roflumilast N-oxide observed in Phase I studies in healthy subjects were examined in Study [114/2005]. The PK of roflumilast was modelled adequately with a two compartment model with first order absorption and a lag time on absorption. The influential covariates on the population mean parameters of roflumilast were:

1. clearance in males was about 19.1% greater than that in females;
2. clearance in smokers was about 30.7% greater than that in non-smokers;
3. clearance in Blacks was about 14.0% lower than that in non-Blacks/non-Hispanics, and clearance in Hispanics was about 29.7% lower than that in non-Blacks/non-Hispanics;
4. a high fat meal delayed absorption by about 30.8% or 0.1 hours; and
5. a high fat meal also reduces the absorption rate by about 69.9% or 0.16 hours<sup>-1</sup>.

The PK of the metabolite roflumilast N-oxide was modelled adequately with a one compartment model with zero order absorption and a lag time on absorption. The influential covariates on the population mean parameters of roflumilast N-oxide were:

1. clearance decreases with increasing age, and relative bioavailability decreases with age;
2. clearance in males was about 46.7% greater than that in females, and relative bioavailability in males was about 23.1% greater than that in females;
3. clearance of smokers was about 23.5% greater than that of non-smokers;
4. bioavailability in Blacks is about 43.1% greater than that in non-Blacks/non-Hispanics, and in Hispanics is about 26.6% greater than that in non-Blacks/non-Hispanics;
5. volume of distribution increases with increasing weight; and
6. a high fat meal prolonged the duration of formation by about 236%, to 7.43 hours.

These modelling based inferences on the covariates' effects on exposure were supported by data derived descriptive statistics on the non-compartmental AUC from time zero to 24 hours ( $AUC_{0-24h}$ ) at steady state.

### ***Evaluator's comments on pharmacokinetics in special populations***

The AUCs of roflumilast and roflumilast N-oxide were 26% and 18% higher, respectively, in elderly (<sup>3</sup> 65 years) than in young subjects (18 to 45 years), whereas, AUC and  $C_{max}$  were similar in middle -aged (46 to 64 years) and young subjects. Similarly,  $C_{max}$  of

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<sup>55</sup> The **Child-Pugh score** is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

roflumilast and roflumilast N-oxide were 16% and 13% higher, respectively, in elderly compared to young subjects, whereas in middle aged subjects the  $C_{max}$  of the N-oxide was 8% lower than in young subjects. In all age groups, higher systemic exposures and peak concentrations were noted in female vs male subjects for roflumilast and roflumilast N-oxide.

The  $AUC_{\infty}$  of roflumilast and roflumilast N-oxide was 21% and 7%, respectively, lower in patients with severe renal impairment vs healthy subjects. The  $C_{max}$  of roflumilast was also lower by 16% in renally impaired vs healthy subjects. The AUC of roflumilast was 50% higher in Child-Pugh A and 92% higher in Child-Pugh B patients and that of the N-oxide was 23% higher in Child-Pugh A and 41% higher in Child-Pugh B patients vs healthy subjects. The  $C_{max}$  of roflumilast was 2% higher in Child-Pugh A and 26% higher in Child-Pugh B patients and that of the N-oxide were 25% higher in Child-Pugh A and 40% higher in Child-Pugh B patients. The PK of roflumilast have not been examined in patients with severe hepatic impairment. It should also be noted that the proposed dose of 500  $\mu$ g od was not evaluated in patients with hepatic impairment.

Exposure to roflumilast is higher in females and Blacks/Hispanics, whereas, smoking reduces exposure. Exposure to roflumilast N-oxide is higher in females, the elderly and Blacks/Hispanics, whereas smoking decreases exposure. The volume of distribution increases with increasing weight and a high fat meal prolonged the duration of formation of the metabolite.

No studies examined the effects of pregnancy or lactation on the PKs of roflumilast.

## **Interactions**

### ***In vitro studies***

The possible drug interaction between roflumilast and digoxin, based on the involvement of the p-glycoprotein (P-gp) drug transporter was examined in Study [266/2002] using Caco-2 cell monolayers that constitutively express P-gp. Roflumilast did not inhibit [ $^3$ H]-digoxin transport, whereas a known P-gp inhibitor, 20  $\mu$ M verapamil fully inhibited the directional movement of digoxin, consistent with complete inhibition of P-gp.

### ***In-vivo drug interaction studies***

There were a number of studies conducted which evaluated possible interactions with other drugs. These included:

- midazolam
- a moderate CYP3A4 inhibitor, erythromycin
- a strong CYP3A4 inhibitor, ketoconazole
- a CYP 3A4 inducer, rifampicin
- cigarette smoking, a CYP1A2 inducer
- digoxin
- antacid (aluminium hydroxide/magnesium hydroxide)
- the  $\beta$ 2-agonist salbutamol
- budesonide
- theophylline
- montelukast
- warfarin
- sildenafil
- enoxacin
- cimetidine
- fluvoxamine

Results are described in the evaluator's conclusion to pharmacokinetics.

### **Exposure relevant to safety**

As mentioned previously, based on the results of ten repeated dose studies (231 subjects) where the most frequently used oral dose of roflumilast was administered (500 µg od, fasted), the median AUC of roflumilast across studies was 35.9 µg.h/L, ranging from 30.8 to 67.2 µg.h/L and the median  $C_{max}$  was 7.29 µg/L, ranging from 5.19 to 10.1 µg/L. The AUC of roflumilast N-oxide across studies was 436 µg.h/L, ranging from 351 to 717 µg.h/L. The  $C_{max}$  of roflumilast N-oxide was 24.4 µg/L ranging from 21.5 to 42.7 µg/L. The predicted effects of COPD on the AUC of both roflumilast and its N-oxide metabolite were calculated in the modelling Study [343/2008]. The predicted results were an AUC of 67.2 µg.h/L for roflumilast and 564 µg.h/L for the N-oxide metabolite which represents an approximate 1.9-fold and 1.3-fold increase in AUC for the parent drug and its active metabolite, respectively.

### **Evaluators overall conclusions**

#### ***Absorption***

The absolute bioavailability of roflumilast, following a 500 mg oral dose was estimated to be 79%. Steady state was achieved after 4 days for roflumilast and 6 days for roflumilast N-oxide. The median  $C_{max}$  for roflumilast and roflumilast N-oxide were 7.04 and 9.49 g/L, respectively, and  $t_{max}$  was 1.00 and 8.53 h, respectively. Overall, food did not appear to have a significant effect on the PKs roflumilast.

#### ***MTD and minimum effective dose***

The MTD of roflumilast was determined to be 1000 µg. In Study FHP004, a dose of roflumilast 1000 µg per day was associated with markedly greater and more pronounced AEs compared with the 500 µg dose. Based on this study it was decided that daily roflumilast doses of 500 µg should be investigated in the further clinical development. The full range of PK parameters could only be calculated for oral doses of 150 mg or greater.

#### ***Bioequivalence***

Bioequivalence between the clinical trial and the proposed marketing formulations was established.

#### ***Dose proportionality***

The AUC of roflumilast and roflumilast N-oxide increased proportionally after single and repeated roflumilast doses of 250 and 500 µg and after repeated doses of 500, 750 and 1000 µg. This was in general also true for  $C_{max}$  with the exception of roflumilast after a single roflumilast dose (Day 1) and after repeated roflumilast doses of 500 and 750 µg. Based on the results of the studies, dose proportionality can be assumed for the systemic exposure of roflumilast and roflumilast N-oxide between repeated roflumilast doses of 250 and 1000 µg.

#### ***Distribution***

The mean volume of distribution of roflumilast was 2.9 L/kg in healthy male subjects, following a 150 µg IV dose. The binding of roflumilast and roflumilast N-oxide to human plasma proteins is 99% and 97%, respectively and binding was independent of concentration up to 200 and 100 µg/L for roflumilast and roflumilast N-oxide, respectively. There was rapid uptake of oral roflumilast from the gastrointestinal tract with significant non-vascular localisation in lung, muscle (arms) and brain tissue. In the brain, the non-vascular concentration was about 8% of that of plasma, in muscle 15% and



in lung 45%. Although not confirmed in humans, roflumilast has been shown to cross the blood-brain barrier in small amounts in rats. No studies specifically examined the uptake of roflumilast into lipophilic tissues.

### **Excretion**

The plasma clearance of roflumilast after a 150 µg IV dose was 0.137 L/h/kg. The median plasma  $t_{1/2}$  following single doses of roflumilast and roflumilast N-oxide was 18.4 h and 25.7 h, respectively. Following repeated doses of roflumilast and roflumilast N-oxide the median plasma  $t_{1/2}$  was 16.6 and 29.7 h, respectively. Following IV and oral administration of a [<sup>14</sup>C]-labelled dose of roflumilast, approximately 90% of the radioactivity was recovered in urine and faeces (91.2% IV and 90.3% PO) with urinary excretion being the primary route, accounting for 70% of the [<sup>14</sup>C]-dose [FHP036].

Most (76%) of the radioactivity excreted in the urine was identified as inactive metabolites of roflumilast or their glucuronide conjugates. The remainder (24%) that corresponds to 16% of the dose was not characterised. The radioactivity recovered in faeces was not characterised. In urine, roflumilast was not detected, and roflumilast N-oxide was only detected at trace levels (less than 1%) [212/2002], suggesting that roflumilast is mainly eliminated by metabolism.

### **Metabolism**

In man, the major metabolite of roflumilast is roflumilast N-oxide, which is formed by the N-oxidation of roflumilast. Active roflumilast N-oxide is then further O-dealkylated and subsequently glucuronidated and excreted into the urine.

*In vitro* studies identified the role of CYP 3A4 and 1A2 in the metabolism of roflumilast, with some contribution of 2C19 and 1A1. In addition to roflumilast N-oxide, other phase I metabolites (M05 and the aglycone of M04) in human plasma are formed by dechlorination and O-dealkylation of roflumilast, which are also subsequently glucuronidated and excreted in the urine. The cleavage product 2, 6-dichloro-amino pyridine N-oxide (ADCP N-oxide, M09) was identified in urine (about 10% of the dose administered), however, the pathway for its formation has not been fully elucidated, but it is believed that it is most likely formed via cleavage of roflumilast N-oxide.

In plasma following IV and oral administration of [<sup>14</sup>C]-labelled roflumilast, only roflumilast and the N-oxide were observed in measurable quantities, accounting for about 58% of the total radioactive AUC. The elimination  $t_{1/2}$  of total radioactivity was mainly influenced by the  $t_{1/2}$  of roflumilast N-oxide. Aglucones of the urinary glucuronide metabolites were not quantifiable in plasma. The cleavage products ADCP and ADCP N-oxide have been found at levels near the LLOQ in plasma of a few subjects.

### **PK summary**

Based on the results of 15 single dose studies, comprising 212 subjects, following a single oral dose of 500 mg roflumilast, the median AUC of roflumilast across studies was 40.5 µg.h/L, the  $C_{max}$  was 7.04 µg/L,  $t_{1/2}$  was 18.4 h and  $t_{max}$  was 1 h. By contrast, the median AUC of roflumilast N-oxide was 415 µg.h/L,  $C_{max}$  was 9.49 µg/L,  $t_{1/2}$  was 25.7 h and  $t_{max}$  was 8.53 h. Exposure to the N-oxide metabolite was approximately tenfold higher than to the parent compound. Based on the results of ten repeat dose studies, comprising 231 subjects, following repeated oral doses of roflumilast 500 µg od, the median AUC of roflumilast was 35.9 µg.h/L, the median  $C_{max}$  was 7.29 µg/L, the median  $C_{trough}$  was 0.72 µg/L, the median  $t_{1/2}$  was 16.6 h and the median  $t_{max}$  was 1 h. For roflumilast N-oxide, the median AUC was 436 µg.h/L, the median  $C_{max}$  was 24.4 µg/L, the median  $C_{trough}$  was 14.5 µg/L, the median  $t_{1/2}$  was 29.7 h and the median  $t_{max}$  was 3 h. The estimated average time

to reach steady state for roflumilast and roflumilast N-oxide was 4 and 6 days, respectively.

### ***Effects on CYP enzymes and genetic polymorphisms***

*In vitro* studies showed that roflumilast was a weak competitive inhibitor of CYP 3A4/5. It caused little direct inhibition of CYP 2B6 and it did not appear to be an irreversible metabolism dependent inhibitor of CYP 2B6 or 3A4/5. Roflumilast was a weak inducer of CYP 2A6, 2B6 and 3A4/5 and did not induce CYP 1A2, 2C9 and 2C19.

Roflumilast N-oxide acts as a competitive inhibitor of CYP 1A2 and 2A6, an uncompetitive inhibitor of CYP 4A9/11,<sup>56</sup> a non-competitive inhibitor of CYP 2B6<sup>57</sup> and a mixed inhibitor of CYP 2C8, 2C9, 2C19 and 3A4/5. A previously unknown mutation in cytochrome CYP 3A4 in combination with a reduced enzyme activity of CYP 1A2 led to approximately 6 and 3 fold increases in AUC levels of roflumilast and roflumilast N-oxide, respectively. This increase was paralleled by a marked prolongation of elimination half-lives. However, this did not result in reporting of more frequent or more severe AEs in the subject who carried this mutation. The prevalence of a similar enzymatic defect combination in Caucasians was estimated to be less than 6 in 1 million.

### ***Interactions with commonly used medications***

There appeared to be no clinically relevant pharmacokinetic interaction between roflumilast (and roflumilast N-oxide) and the following drugs: inhaled salbutamol/formoterol; oral theophylline; digoxin; warfarin; sildenafil; budesonide; Maalox and midazolam.

Coadministration of repeated doses of erythromycin (a moderate CYP3A4 inhibitor) increased the AUC<sub>∞</sub> and C<sub>max</sub> of roflumilast by 70% and 40%, respectively compared with roflumilast alone but did not alter that of roflumilast N-oxide. By contrast, it decreased the C<sub>max</sub> of roflumilast N-oxide by 34%. Repeated doses of ketoconazole (a strong CYP 3A4 inhibitor) increased the AUC<sub>∞</sub> and C<sub>max</sub> of roflumilast by 99% and 23%, respectively, but did not alter that of roflumilast N-oxide. It also decreased the C<sub>max</sub> of roflumilast N-oxide by 38%. Repeated doses of rifampicin (a CYP 3A4 inducer) decreased the AUC<sub>∞</sub> of roflumilast and roflumilast N-oxide by 80% and 56%, respectively. It also decreased the C<sub>max</sub> of roflumilast by 68% but increased that of roflumilast N-oxide by 30%.

Repeated doses of fluvoxamine (a strong CYP1A2 inhibitor) increased the AUC<sub>∞</sub> of roflumilast and roflumilast N-oxide by 156% and 52%, respectively. Fluvoxamine did not alter the C<sub>max</sub> of roflumilast but decreased that of roflumilast N-oxide by 20%. Similarly, repeated doses of cimetidine (a CYP 1A2, 3A and 2C19 inhibitor) increased the AUC<sub>last</sub> of roflumilast by 84% and that of roflumilast N-oxide by 27%. The C<sub>max</sub> of roflumilast was also increased (46%) but that of roflumilast N-oxide was unaltered.

Repeated doses of enoxacin (a CYP 1A2 and 3A inhibitor) increased the AUC<sub>last</sub> of roflumilast and roflumilast N-oxide by 57% and 19%, respectively. Similarly, the C<sub>max</sub> of roflumilast was increased by 20%, whereas, the C<sub>max</sub> of roflumilast N-oxide was decreased by 15%.

Overall, drugs that inhibit CYP1A2 and 3A significantly increase exposure to roflumilast and caution must be taken when coadministering drugs of this class with roflumilast.

Smoking (which induces CYP1A2), decreased the AUC<sub>∞</sub> of roflumilast by 13% but that of roflumilast N-oxide was increased by 17% when compared with non-smokers. Hence

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<sup>56</sup> It binds to the complex formed between the enzyme and substrate.

<sup>57</sup> It binds to an allosteric binding site on the enzyme that prevents it from binding the substrate correctly.

overall total exposure of roflumilast and roflumilast N-oxide was not significantly altered in smokers.

Repeated doses of montelukast did not alter the PK of roflumilast and the N-oxide, whereas repeated doses of roflumilast increased the AUC and  $C_{max}$  of a single dose of montelukast by 9% and 8%, respectively. Following multiple doses of both roflumilast and montelukast, the AUC and  $C_{max}$  of montelukast increased by 28% and 32%, respectively.

### ***Limitations of the PK data***

No studies, other than simulations, examined the PK of roflumilast in the target population of COPD patients.

No studies examined the PK of roflumilast in pregnant or breast feeding mothers, subjects undergoing hormone replacement therapy or subjects of Chinese descent.

### ***Comments on the sponsor's Clinical Overview***

The authors of the report had a tendency to gloss over drug interactions and effects in special populations that significantly alter the pharmacokinetics of roflumilast and its active metabolite. For instance, study [CP-062] indicates that moderate hepatic impairment increases the subject's exposure to roflumilast and its N-oxide metabolite by 92% and 41%, respectively, but the clinical overview stated that no dose adjustment is necessary in these patients in the PI. Similarly, the modelling study [114/2005] identified that compared to men, women had significantly lower rates of clearance for both roflumilast and roflumilast N-oxide (19.1% and 46.7% lower, respectively), yet the associated increase in exposure is deemed to be of little clinical relevance in the PI and no dose adjustment is suggested for female patients.

## **Pharmacodynamics**

### **Introduction**

Ten studies, involving 145 healthy subjects (aged 19 to 78 years) and 57 subjects with COPD (aged 20 to 75 years) examined the pharmacodynamics (PD) of roflumilast.

### **Mechanism of Action**

#### ***PDE4 inhibition***

Roflumilast is a selective PDE4 inhibitor. PDE4 is the major cAMP metabolising enzyme found in inflammatory and immune cells, which include mast cells, neutrophils, eosinophils, macrophages and T-lymphocytes. Inhibitors of PDE4 are potential antiinflammatory drugs, which may be useful in the treatment of inflammatory pulmonary diseases such as COPD and asthma.

In order to estimate the combined PDE4 inhibition of the parent and metabolite, a parameter termed 'total PDE4 inhibitory activity (tPDE4i)' was developed. This parameter accounts for differences in intrinsic PDE4 inhibitory activity ( $IC_{50}$ ), unbound fraction in plasma and *in vivo* exposure (AUC) of roflumilast and roflumilast N-oxide and is calculated according an equation, the complexity of which is beyond the scope of this AusPAR. tPDE4i is exposure driven since the unbound fraction and  $IC_{50}$  of roflumilast and roflumilast N-oxide are included in the calculation as constant values. These constants were determined following *in vitro* studies using human materials. tPDE4i values were used to evaluate the PD effects of roflumilast therapy in (i) drug interaction and (ii) special population studies where potential PK alterations may differ greatly between roflumilast and roflumilast N-oxide.

### ***Other markers of antiinflammatory activity***

Neutrophils are the predominant inflammatory cells in the sputum of COPD patients and PDE4 is thought to be the most important isoenzyme in these cells. Sputum neutrophilia correlates positively with the annual FEV<sub>1</sub> decline in COPD.<sup>58</sup> Therefore it is possible that sputum neutrophils can be used as a surrogate marker when evaluating the efficacy of antiinflammatory agents in COPD. In addition, PDE4 inhibitors can inhibit interleukin 8 (IL-8) and leukotriene B4 (LTB4) production in human neutrophils *in vitro*. The PDE4 inhibitor roflumilast has also been shown to suppress the production of tumour necrosis factor  $\alpha$  (TNF $\alpha$ ), another surrogate parameter for the inhibition of inflammatory cell activation, in subjects with exercise induced asthma.<sup>59</sup> Overexpression of E-selectin, an adhesion molecule, has been observed in a variety of inflammatory disorders including asthma. E-selectin is expressed exclusively by endothelial cells after activation by cytokines (for example, TNF $\alpha$  or IL-1 $\beta$ ). After expression on the endothelium, E-selectin is released into the circulation by shedding and/or proteolytic mechanisms, therefore, the measurement of E-selectin levels in serum has also been suggested as a surrogate parameter for monitoring systemic inflammation.

Overall, biomarkers in blood, sputum and bronchoalveolar lavage fluid (BALF), and lung function variables (for example, FEV<sub>1</sub>) were used as PD parameters in clinical pharmacology studies to evaluate the potential antiinflammatory effects and improvement in lung function following roflumilast treatment. A summary of the PD variables used in the major PD studies is summarised in Table 3.

**Table 3: Pharmacodynamic variables used in clinical pharmacology studies with roflumilast**

Parameter	Study population	Subjects	Study
TNF $\alpha$ in blood after LPS challenge <i>ex vivo</i>	EIA	16	FHP003
	HV (male)	4	FHP004
	HV (male)	14	FHP009
	COPD	41	FHP030
TNF $\alpha$ in BALF after LPS challenge <i>in vivo</i>	HV (male)	37	M2-117
TNF $\alpha$ in blood after LPS challenge <i>in vivo</i>	HV (male)	37	M2-117
E-selectin in serum	COPD	37	FHP030
	HV (male)	37	M2-117
	Diabetes mellitus	91 (Rof 500), 86 (Pbo)	M2-401
Neutrophils/other cells in sputum supernatant	COPD	36	FHP030
Neutrophils/other cells in BALF	HV (male)	37	M2-117
Neutrophil elastase/IL-8 in sputum supernatant	COPD	36	FHP030
FEV <sub>1</sub>	EIA	16	FHP003
	COPD	41	FHP030

COPD=chronic obstructive pulmonary disease; EIA=exercise induced asthma; FEV<sub>1</sub>=forced expiratory volume in one second; HV=healthy volunteers

<sup>58</sup> Stanescu D, Sanna A, Veriter C, Kostianev S, Calcagni PG, Fabbri LM et al. Airways obstruction, chronic expectoration, and rapid decline of FEV1 in smokers are associated with increased levels of sputum neutrophils. *Thorax* 1996; 51: 267-271.

<sup>59</sup> Babu KS, Davies DE, Holgate ST. Role of tumor necrosis factor alpha in asthma. *Immunol Allergy Clin North Am* 2004; 24: 583-97.

## Primary pharmacology

### *Pharmacodynamics in healthy volunteers*

*In vitro*, in the absence of plasma proteins, the intrinsic PDE4 inhibitory activity of roflumilast is approximately 2.7 fold greater than of roflumilast N-oxide. *In vitro*, the loss of the des-cyclopropyl-moiety (metabolite M05) resulted in a considerable (approximate 200 fold) reduction in PDE4 inhibitory activity compared to the parent compound. Moreover, cleavage of the amide bond resulted in a complete loss of the PDE4 inhibitory activity of the resulting ADCP (2, 4 dichloro-aminopyridine) and ADCP N-oxide metabolites (M10 and M09). In contrast to the *in vitro* data, both roflumilast and roflumilast N-oxide had similar activity in inhibiting *ex vivo* LPS induced TNF $\alpha$  release from human whole blood, which is believed to reflect the *in vivo* situation.

### *Effects of food on tPDE4i*

The increase in systemic exposure to roflumilast in fed subjects was not clinically relevant as there was little difference in tPDE4i activity between fed and fasted subjects. This is believed to occur due to the concurrent reduction in exposure to roflumilast N-oxide that occurs when administering roflumilast to subjects in the fed state.

### *Bioequivalence*

The ability of two 500  $\mu$ g tablet formulations of roflumilast (Formula E vs Formula B) to inhibit PDE4 was examined in an open, randomised, four period crossover bioequivalence study [EM-056] with 2 replicated treatment sequences in 24 healthy subjects (12 female), aged between 47 and 78 years. The PKs of the two formulations were bioequivalent. Similarly, for total PDE4 inhibitory activities the 90% CI of the mean ratios of tPDE4i for the two formulations were also within the bioequivalence range of 80 to 125%.

### *Effect on TNF $\alpha$*

In study [FHP004 (128E/97)], the mean LPS-stimulated TNF $\alpha$  formation in blood samples *ex vivo* decreased during the treatment with roflumilast when compared with placebo. However, this decrease was not significant, possibly due to the high intra and inter-individual variability in the measured TNF $\alpha$  values. No influence on cardiac performance (global flow, contractility, cardiac work, pump efficiency, thoracic fluids and mean arterial pressure) was detected by impedance cardiography although these results were characterised by high levels of physiological variability. In study [FHP009], TNF $\alpha$  formation measured *ex vivo* on Day 21 was non-significantly lower following treatment with roflumilast 500  $\text{mg}$  od than following treatment with placebo or on Day 1.

### *Antiinflammatory effect following LPS challenge*

The effects of 500  $\text{mg}$  roflumilast on inflammatory cells and mediators in BALF after segmental pulmonary LPS challenge was examined in study [M2-117] in 43 healthy volunteers, aged 20 to 43 years. Following endotoxin challenge, influx of total cells (difference from baseline) in BALF of roflumilast treated subjects was 35% lower than with placebo ( $p=0.02$ ). Correspondingly, the influx of neutrophils and eosinophils in roflumilast treated subjects was 38% ( $p=0.02$ ) and 73% ( $p=0.01$ ) lower than with placebo, respectively. By contrast, endotoxin induced influx of monocytes was similar in both roflumilast and placebo treated subjects. No statistically significant differences existed between the groups pertaining to endotoxin induced influx of macrophages and lymphocytes. In addition, there were no significant differences between the treatments for any of the soluble inflammatory markers in BALF and in blood.

### ***PDs in the target population***

The antiinflammatory activity of roflumilast was investigated [FHP030] by examining the effect of 500 µg oral roflumilast over 4 weeks on sputum neutrophils in a randomised, double blind, placebo controlled, two period crossover study in 41 patients (10 female), aged 48 to 75 years, who had COPD for at least 1 year. This study represented a *post hoc* analysis of the data set contained in Study 187/2002. Relative and absolute cell counts were determined in induced sputum samples before and after 4 weeks of treatment. Measurements of spirometry and the levels of biochemical markers for inflammation in sputum supernatant and blood were also determined. In the *post hoc* analysis, the total cell count of the inflammatory cells in sputum was significantly decreased by 26% in subjects given roflumilast vs placebo. In addition, absolute numbers of sputum neutrophils and eosinophil decreased by 31% and 42%, respectively in roflumilast treated patients. In contrast to absolute cell numbers, differential cell counts for neutrophils, macrophages and lymphocytes, expressed as a percentage of total non-squamous cells, were not affected by roflumilast and placebo treatment. Levels of IL-8 and neutrophil elastase (markers for inflammation in sputum) decreased but not significantly in subjects given roflumilast vs with placebo. TNF $\alpha$  secretion in whole blood cultures following *ex vivo* stimulation by LPS (lipopolysaccharide) was significantly reduced by 11% ( $p = 0.0245$ ) in roflumilast treated subjects compared with placebo treated subjects. In contrast, E-selectin levels in blood were not different between the two treatments. Pre- and post-bronchodilator FEV<sub>1</sub> (a measure of lung function) improved significantly in subjects given roflumilast compared to placebo.

A randomised, placebo controlled, double blind, two period crossover Phase I study [FHP003 (20E/98K1)] investigated the safety, tolerability and efficacy of roflumilast in 16 subjects, aged 20 to 30 years, with exercise induced asthma following repeated dose oral administration of 500 mg roflumilast per day for 4 weeks. All subjects had moderately decreased lung function (defined as 60-70% of the normal FEV<sub>1</sub>/vital capacity) On each of the study Days 1, 14 and 28 the mean percentage fall index was lower following treatment with roflumilast (Day 1: 10.7%, Day 14: 8.1%, Day 28: 6.5%) than following treatment with placebo (Day 1: 12.3%, Day 14: 10.6%, Day 28: 11.1%). However, this difference only reached significance on Day 28 ( $P = 0.02$ ). In addition, TNF $\alpha$  formation was significantly reduced ( $p = 0.009$ ) after roflumilast vs placebo, over 4 weeks.

### ***Model based predictions of PDs in subjects with hepatic impairment***

Study [19/2009] reviewed the *in vitro* data following treatment with 500 mg roflumilast in patients with mild (Child-Pugh A) and moderate (Child-Pugh B) liver impairment. Assuming dose proportionality between roflumilast 250 and 500 µg in patients with mild and moderate liver impairment, total PDE4 inhibition, based on simulated roflumilast AUC and derived roflumilast N-oxide AUC values following Rof500 is 39% and 80% higher in patients with mild and moderate liver impairment, respectively, when compared with healthy volunteers. Total PDE4 inhibition, based on extrapolated data from study CP-062 following repeated oral doses of Rof500, is 26% and 46% higher in patients with mild and moderate liver impairment, respectively, when compared with healthy volunteers. When these total PDE4 inhibition values were compared with those of other special populations or drug interactions, the study's authors believe it is reasonable to conclude that repeated oral doses of Rof500 od can be safely applied to patients with mild (Child-Pugh A) and moderate (Child-Pugh B) liver impairment.

### **Secondary pharmacology**

The effects of roflumilast on blood pressure and heart rate were examined in an ascending single dose (10, 30, 70 and 150 µg with randomly interspersed placebo) study [FHP005]

following a short IV infusion (15 minutes) of roflumilast in 4 healthy subjects aged 26 to 31 years. For doses up to 70 µg, the mean and median values of blood pressure (BP) and heart rate (HR) were comparable between placebo and roflumilast. Following 150 mg, the diastolic BP tended to decrease between 7.5 and 30 minutes after the start of infusion, however, the mean and median values of diastolic BP were still within the normal range. Further safety parameters including ECG and clinical laboratory were comparable between the different treatments and placebo.

The cardiovascular interaction between oral roflumilast and inhaled formoterol in 27 healthy male subjects aged 21 to 44 years was examined in study [CP-059]. Roflumilast mono-treatment (Treatment A) had a minor effect on the subjects' HR, pre-ejection period (PEP), electromechanical systole (QS2), maximum velocity of the transthoracic impedance changes (dZ/dtmax), cardiac output (CO) and total peripheral vascular resistance (TPR). Formoterol in combination with roflumilast resulted in a decrease in total peripheral resistance within 10 minutes following dosing, which lasted for more than 5 hours. A compensatory rise in heart rate was observed, which subsequently led to increased cardiac output. These changes were commonly recognised effects of formoterol and a comparison of formoterol monotherapy to the combination therapy identified that most of the changes were attributable to formoterol treatment. However, all changes were small and within the physiological range.

The effect of multiple dose, orally administered roflumilast (up to 1000 µg) on cardiac repolarisation, as measured by ECG parameters, was examined in study [CP-069] in 80 healthy subjects, aged 18 to 55 years. A single 400 mg dose of moxifloxacin (used as a positive control in this study), induced a mean maximal prolongation of QTcF and QTcB of 6.79 and 6.97 milliseconds (ms), respectively, at 6 hours following drug administration. By contrast, roflumilast/roflumilast N-oxide demonstrated mean maximal time matched differences from baseline compared with placebo of -4.75 ms (QTcF) and 2.39 ms (QTcP) for the 500 and 1000 mg dose groups.

The cardiovascular PD interaction between single oral doses of 500 µg roflumilast and 100 mg sildenafil was examined in study [CP-070] in 12 healthy male subjects, aged 22 to 40 years. Serial impedance cardiography (ZCG), ECG, serial blood pressure and pulse rate were recorded. Roflumilast monotherapy had little to no cardiovascular effect. Roflumilast caused smaller time matched changes from baseline for the electrocardiographic PR interval, but no effect on QT and QTc. Sildenafil tended to lower the time averaged BP changes from baseline, without tachycardia; instead, there was a trend towards smaller minimum and average HR changes from baseline. Sildenafil was associated with a larger maximum change and a smaller minimum change in QTc, with little effect on the average time matched QTc change from baseline. The effects of the combination of 500 µg roflumilast and 100 mg sildenafil on HR, BP, ZCG/STI and QT/QTc response could not be explained by the additivity of the effects of the monotherapies (500 µg roflumilast or 100 mg sildenafil). Although there were no relevant differences in the summary measures of the time matched changes from baseline for the uncorrected QT of the combination treatment relative to placebo, the maximum and average change from baseline of the HR corrected QT intervals tended to be larger for the combination treatment, relative to the two monotherapies. Mean QTc prolongations were noted for roflumilast and sildenafil and roflumilast alone which exceeded 5 ms, however, they were below 20 ms.

### **Relationship between plasma concentration and effect**

The population PK and PD of roflumilast were examined in study [175/2008]. A computer based model was developed to determine a quantitative relationship between tPDE4i and clinical endpoints related to tolerability/safety and efficacy. Since tPDE4i was intended to

be used primarily in a tolerability/safety context, tPDE4i associated AEs (as safety/tolerability parameters) were related to tPDE4i in COPD patients (from whom sparse blood samples for PK evaluation were available). The objectives of this population analysis were (i) to develop a tPDE4i population mixed effects model based on population PK models of roflumilast and roflumilast N-oxide in healthy subjects [114/2005] and COPD patients [343/2008], (ii) to evaluate the influence of covariates on tPDE4i, and (iii) to establish a quantitative relationship between the tPDE4i and tolerability by use of logistic regression models<sup>60</sup>.

The impact of individual covariates were determined from relative tPDE4i values calculated for female, smoking, Black/Hispanic, COPD, 60 and 80 years of age compared with the reference population (male, non-smoking, non-Black/non-Hispanic, healthy, 40 year old). Of the single covariates, Black race had the greatest impact on tPDE4i, with a 42% higher mean tPDE4i than non-Black/non-Hispanic subjects. Similarly, but to a lesser extent, Hispanics were expected to have a 28% higher mean tPDE4i than non-Black/non-Hispanics. Female subjects were expected to have a 19% higher mean tPDE4 than male subjects and COPD patients were expected to have a 12% higher mean tPDE4 than healthy subjects. By contrast, smokers were expected to have a 19% lower mean tPDE4i than non-smokers/ex-smokers.

In order to determine the impact of significant subject covariates on tPDE4i, a parametric bootstrap estimation method was used. Of all the possible combinations of subject covariates, an elderly (80 year), Black, female, non-smoker suffering from COPD would be expected to have the highest mean tPDE4i of 217% when compared with the reference population. A young (40 year), non-Black/non-Hispanic, male smoker would be expected to have the lowest mean tPDE4i of 81% when compared with the reference population. Therefore, all possible patient groups would be expected to have mean tPDE4i values relative to the reference population between about 81% and 217%.

AEs were grouped by using MedDRA preferred terms (PTs).<sup>61</sup> If the given AE occurred significantly more frequently in patients treated with roflumilast compared with placebo, it was further analysed by logistic regression. Logistic regression models were successfully established for the PTs diarrhoea, nausea and headache. For both diarrhoea and headache, the AUC of roflumilast N-oxide and the tPDE4i were comparably precise in predicting the probability to develop these AEs. By contrast, the AUC of roflumilast N-oxide was better than tPDE4i in predicting nausea, whereas, the AUC of roflumilast showed a much weaker association to all AEs. However, the predicted probability to develop AEs agreed well for all 3 predictor variables in the reference population. The predicted AE probabilities using tPDE4i for a patient with tPDE4i=1.03 (geometric mean in the analysed population) are 13% (95% CI: 7.5, 18.5) for diarrhoea, 6% (95% CI: 2.6, 9.4) for nausea, and 5.1% [95% CI: 1.9, 8.6) for headache.

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<sup>60</sup> Separate population models were developed to describe the PK of roflumilast and roflumilast N-oxide. Models were built as non-linear mixed effects models and were fitted to data by NONMEM. Initially, the population PK models for parent and metabolite were built from Phase I data and subsequently extended to also describe the exposure in COPD patients. PK parameter estimates from the population PK models were then utilised to obtain the individual and population estimates for tPDE4i. Logistic models to describe the quantitative correlation between tPDE4i and AEs were fitted to the data from a phase III clinical trial with observations of both PK and AE data.

<sup>61</sup> MedDRA = Medical Dictionary for Regulatory Activities



### Pharmacodynamic interactions with other medicinal products or substances

Study [252/2008] summarised the total phosphodiesterase 4 (PDE4) inhibitory activity for roflumilast and roflumilast N-oxide from 23 clinical pharmacology studies and evaluated the following drug interactions and effects in special populations.

- ketoconazole, a strong inhibitor of CYP 3A4
- erythromycin, a moderate inhibitor of CYP 3A4
- rifampicin, a potent inducer of CYP enzymes
- a decrease in the mean tPDE4i value by 58%.
- fluvoxamine, a potent inhibitor of CYP 1A2
- theophylline, a substrate of CYP 1A2,
- cigarette smoking, an inducer of CYP 1A2
- cimetidine, a weak inhibitor of CYP 1A2 and 3A4
- an increase in the mean tPDE4i value by 47%.
- commonly used co-medications in COPD patients such as salbutamol, formoterol, budesonide, digoxin, aluminium hydroxide/magnesium hydroxide, montelukast, sildenafil and warfarin
- age and gender
- renal and hepatic impairment

Results are summarised in the evaluator's conclusion to pharmacodynamics.

### Genetic differences in pharmacodynamic response

No studies specifically examined the effects of genetic mutations on PD response. However, the mutations to CYP1A2 and CYP3A4 identified in one subject in study CP-053 and CP-054, significantly increased the exposure of the subject to roflumilast and roflumilast N-oxide, which would presumably increase tPDE4i, although it was not documented and it is not clear if it was evaluated in this subject.

### Evaluator's overall conclusions on pharmacodynamics

#### Primary PD

Differences identified between the *in vitro* and *ex vivo* estimates of relative roflumilast potency are possibly due to differences in plasma protein binding as the approximate 3-fold difference in plasma protein binding between roflumilast (1.1% unbound) and roflumilast N-oxide (3.4% unbound) may offset the 3-fold difference in the intrinsic activities. Additionally, given the differences in PK of roflumilast and roflumilast N-oxide, it appears that roflumilast N-oxide is the major contributor to circulating PDE4 inhibitory activity *in vivo*.

In healthy subjects, TNF $\alpha$  formation showed a non-significant decrease after repeated administrations of roflumilast (TNF $\alpha$  levels were measured in blood and BALF before and after *in vivo* segmental pulmonary LPS challenge in healthy subjects). In COPD patients, treatment with 500 mg roflumilast for 4 weeks significantly decreased TNF $\alpha$  (-11%) in blood, compared to placebo.

In patients with mild to moderate asthma or diabetes, statistically significant reductions in soluble E-selectin levels were shown after roflumilast; E-selectin levels were not significantly changed in COPD patients or healthy subjects. Roflumilast treatment did not show any significant reduction in levels of IL-8 and neutrophil elastase measured in sputum supernatant.

In sputum supernatant, absolute neutrophil, eosinophil and total cell numbers showed a significant decrease by 31%, 42% and 26%, respectively, following treatment with

roflumilast compared to placebo. In addition, roflumilast reduced sputum macrophage and lymphocyte numbers, however, the difference from placebo was not significant. In contrast to absolute cell numbers, differential cell counts for neutrophils, eosinophils, macrophages and lymphocytes, expressed as percentage of total non-squamous cells, were not affected by roflumilast treatment. It must be noted that absolute cell counts were only examined as a *post hoc* analysis of the data and in the original study only the differential counts were pre-specified.

In BALF, absolute neutrophils, eosinophils, and total cell numbers showed a statistically significant reduction of 38%, 73% and 35%, respectively, after roflumilast vs placebo. By contrast, absolute numbers of monocytes/macrophages and lymphocytes were not significantly lowered by roflumilast.

### ***Lung function (FEV<sub>1</sub>)***

In study FHP030, involving 41 COPD patients, there was an increase over placebo of 64 mL (post-bronchodilator FEV<sub>1</sub>) and 71 mL (pre-bronchodilator FEV<sub>1</sub>) following 4 weeks treatment with roflumilast. However, other lung function variables, for example, forced vital capacity, forced expiratory flow 25 to 75%, and peak expiratory flow, did not show any statistically significant improvement.

Roflumilast monotherapy had little to no effect on cardiac function and any changes seen were unlikely to be clinically relevant. The effects of roflumilast in combination with sildenafil on cardiac function, studied in 12 patients, could not be explained by the additivity of the effects of the individual monotherapies and mean QTc prolongations of greater than 5 ms were observed. The largest change in QTcB occurred 3 hours post dosing and based on the analysis of variance of time matched change from baseline equalled  $17.7 \pm 4.8$  ms (least squares [LS] mean  $\pm$  standard error of the mean [SEM]) with a maximum of  $39.5 \pm 5.9$  ms and minimum  $-13.2 \pm 5.5$  ms. It must be noted that it was difficult to establish the changes in QTc in individual subjects as no tables could be found in the evaluation materials that summarised change in QTc for individuals at each of the time points.

### ***Commonly Used Co-medications***

No differences in the mean total PDE4 inhibition were seen after the coadministration of salbutamol, formoterol, budesonide, theophylline, warfarin, montelukast and sildenafil compared with the mean value after roflumilast alone.

Following the coadministration of roflumilast with cimetidine (a CYP3A4/1A2 inhibitor), a 47% increase of the mean total PDE4 inhibition was observed when compared with the mean value after roflumilast alone. Similarly, after the coadministration of enoxacin (a moderate CYP 1A2 inhibitor), a 25% increase of the mean total PDE inhibition was seen when compared with the mean value after roflumilast alone.

The modelling studies suggest that a number of “at risk” groups exist in regard to higher than expected exposure to roflumilast. These include: women; the elderly; and Blacks and Hispanics.

Safety and efficacy of roflumilast have not been established in paediatric patients.

Roflumilast has not been studied in patients with severe liver impairment (Child-Pugh C). Furthermore, it is important to note that the roflumilast dose (250 µg) used in patients with mild/moderate hepatic impairment was lower than the proposed dose of 500 µg.

### ***Comment on Clinical Overview***

Although the authors of the sponsor's *Clinical Overview* discount that all of the commonly used co-medications studied are unlikely to affect the tolerability and safety of roflumilast, it must be remembered that these medications such as cimetidine (CYP1A2, 3A and 2C19 inhibitor), ketoconazole (strong CYP 3A4 inhibitor), rifampicin (CYP 3A4 inducer) and fluvoxamine (strong CYP1A2 inhibitor) cause large changes in the subject's exposure to roflumilast and roflumilast N-oxide. Therefore, as modelling studies suggest that both the AUC of roflumilast and roflumilast N-oxide are indicators of the side effect profile of these drugs, variations in roflumilast dosage may in fact be indicated when coadministered with other medications, especially in the "at risk" groups listed above.

## **Efficacy**

### **Introduction**

Over 6500 patients with COPD were evaluated in 18 Phase II and III studies; these included 6 important Phase III studies: 2 pivotal one year studies (M2-124 and M2-125), 2 supportive six month studies (M2-127, M2-128) and 2 one year supportive studies (M2-111 and M2-112).

Initial studies focused on FEV<sub>1</sub> and quality of life (St George Respiratory Questionnaire [SGRQ]) as efficacy endpoints. As the SGRQ turned out to be an insensitive endpoint to assess the treatment effect of an antiinflammatory agent such as roflumilast, the rate of mild, moderate or severe COPD exacerbations was used as primary symptomatic benefit endpoint in the 1 year studies. Later studies (Studies M2-111, M2-124, M2-125, M2-127, M2-128) and Study FK1 101 used pre-bronchodilator FEV<sub>1</sub> as primary endpoint. Post-bronchodilator FEV<sub>1</sub> was assessed as the primary endpoint in earlier studies (FK1 103, M2-107, M2-110, M2-112, M2-121) and was also used as key secondary endpoint in studies M2-111, M2-124, M2-125, and M2-128.

The pivotal studies M2-124 and M2-125 were performed in patients with severe to very severe COPD and a background of chronic bronchitis, as these were the patients who were expected to benefit most from roflumilast treatment. The primary endpoints included both COPD exacerbation rate and lung function (as measured by pre-bronchodilator trough FEV<sub>1</sub>). The supportive studies were either performed in a different patient population than the pivotal studies or used different endpoints. Among the supportive studies, special focus is on the 1 year studies (M2-111 and M2-112) and the 6 month studies M2-127 and M2-128, the latter two evaluating roflumilast in patients on maintenance treatment with long acting bronchodilators.

Pulmonary function tests were performed at each visit according to the American Thoracic Society (ATS) recommendations. Standardized spirometers were used throughout the study and the measurements were to be performed by the same technician at each visit. Measurements were performed prior to and 30 min (+ 5 min) after inhalation of 400 µg salbutamol from a metered dose inhaler (MDI) with a spacer.

### ***Evaluator's comments:***

No study was conducted to evaluate efficacy of roflumilast compared to what has become standard of care treatment for patients with COPD, that is, concomitant use of a long acting muscarinic agonist or long acting anticholinergic (LAMA) and an inhaled corticosteroid in combination with a long acting beta2-agonist (LABA).

### **Dose response studies**

The sponsor designated two of the roflumilast Phase III trials, M2-124 and M2-125, as the pivotal trials. However, to obtain a more balanced view of the efficacy of roflumilast, this

section will focus on 8 trials that span the course of the roflumilast clinical development program that are relevant to the proposed indication for “maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations”. Four of the trials (M2-124, M2-125, M2111, and M2-112) were one year (52 weeks) studies designed to evaluate the effects of roflumilast treatment on lung function and the rate of COPD exacerbations. The other trials (FK1-101, M2-107, M2-127, and M2-128) were 24-26 weeks in duration that included either a lower 250 µg dose of roflumilast or were designed to evaluate the impact of concomitant treatment with LABA or LAMA on lung function.

Due to the long effective half-lives (steady state) of roflumilast (17 h) and its active metabolite roflumilast N-oxide (3 h), a once daily dosing regimen was considered adequate. In Phase I studies, a dose of 500 µg roflumilast was established as the highest dose which demonstrated an acceptable safety and tolerability profile. An initial dose range finding study (FK1 101) evaluated efficacy of roflumilast 250 µg and 500 µg od and the optimum dose was confirmed in Study M2-107.

Study FK1 101 was a Phase II/III randomized, double blind, placebo controlled, 26 week, dose ranging and proof of concept study with administration of placebo and two doses of roflumilast (250 µg od [Rof250] and 500 µg od [Rof500]) in 516 patients with moderate to severe COPD. All of the 516 randomized patients had received at least one dose of study medication and were included in the “intent to treat” (ITT) population (placebo: 172, Rof250: 175, Rof500: 169). A total of 74 patients withdrew from the study prematurely and the most common reasons for withdrawal were non-medical reasons and AEs, with similar incidence among treatment groups. Eighty patients were excluded from the “per protocol” (PP) population due to major protocol deviations and the PP population consisted of 436 patients. The most common major protocol violations in all treatment groups were violation of exclusion criteria, use of prohibited previous and or concomitant medication and non-compliance. The median age was 60-62 years in all groups and the majority of patients were male (72%) with mean % predicted post-bronchodilator FEV<sub>1</sub> between 53% and 54% across treatment groups; mean baseline reversibility was 3-4% across all treatment groups. Baseline demographics and disease characteristics were similar in the roflumilast and placebo groups. Pre-treatment with respiratory medication was comparable between the treatment groups (most commonly inhaled short acting β<sub>2</sub>-adrenoreceptor agonists (50%) followed by xanthines). Concomitant respiratory medications were not allowed during the study with the exception of β<sub>2</sub>-agonists and inhaled anticholinergics (used by 20%, 25% and 27% of patients in the placebo, Rof250 and Rof500 groups, respectively) and oral corticosteroids which were allowed for the treatment of exacerbations and were used by 11%, 10% and 7% of the patients, respectively. The mean exposure to study drug was 169 days in the placebo group, and 163 days each in the Rof250 and Rof500 dose groups.

Within treatment ITT analyses of primary endpoint (pre-bronchodilator FEV<sub>1</sub>) showed statistically significant improvements from baseline with both doses of roflumilast; however, the within treatment difference was less marked in the PP analysis with no statistically significant difference from baseline for the 500 µg dose. Non-parametric analyses showed more pronounced effects of roflumilast. Compared with placebo, there were non-significant improvements in pre-bronchodilator FEV<sub>1</sub> with both roflumilast doses (difference vs placebo: 250 µg: 35 mL, 500 µg: 41 mL). The SGRQ total score showed some improvement from baseline in all treatment groups with no significant differences between roflumilast and placebo groups (placebo: -4.5, Rof250: -4.4, Rof500: -4.7). Improvements in post-bronchodilator FEV<sub>1</sub> were greater with roflumilast compared to placebo (ITT analysis), although between treatment difference was of borderline significance with Rof500 (p=0.0465 vs placebo); furthermore results were not robust as

PP analysis failed to show similar results. Slight, non-significant differences in favour of roflumilast were seen for most secondary lung function endpoints and blood gas analyses. The number of moderate and severe exacerbations on Rof500 was substantially decreased as compared to the 250 µg dose and placebo (25, 26 and 15 exacerbations in placebo, Rof250 and 500 µg groups, respectively). However, symptom score decreased numerically more in the placebo group than in the roflumilast groups and there was no significant difference between groups in use of rescue medication. For all other secondary endpoints, there were no differences between treatments.

M2-107 was a Phase III, randomized, double blind, 24 week study, comparing Rof250 and Rof500 od with placebo in 1411 patients with moderate to severe COPD. Overall, 1157 patients completed the treatment period and 256 randomized patients terminated the study prematurely. More patients in the roflumilast group vs placebo discontinued the study. In all three treatment groups, the most common reason for study termination was AEs; more patients withdrew due to AEs in the Rof500 group (15.1%) than in the 250 µg group (9.3%) or in the placebo group (8.2%). A total of 489 major protocol violations were observed in 343 out of 1413 patients (24.3%) The incidence of protocol violations was similar in all three treatment groups. The most common major protocol violation was 'inclusion criterion violated' (reversibility test:  $FEV_1 > 12\%$  and  $> 200$  mL).

The "full analysis set" (FAS) included 1,411 patients (placebo=280, Rof250 =576, Rof500=555). The median age was 64 years, the majority were males (n=1036; 73%) and Caucasians (1402 /1411) and the mean % predicted post-bronchodilator  $FEV_1$  was 54-55% in all treatment groups; mean baseline reversibility was 9% in all treatment groups. The baseline demographics and lung function parameters were comparable between the three treatment groups. Treatment with respiratory medication prior to study start was comparable in all three treatment groups, except for inhaled corticosteroids, which was higher in both roflumilast groups as compared to the placebo group (Rof500: 22%, Rof250: 23%, placebo: 17%). The most commonly reported previous medications were inhaled short acting  $\beta_2$ -agonists followed by inhaled short acting anticholinergics in all three treatment groups.

The ITT analyses demonstrated significant improvements in post-bronchodilator  $FEV_1$  vs placebo with both roflumilast doses (between treatment difference: 97 mL for Rof500, 74 mL for Rof250, for both  $p=0.0001$ , 2-sided). The  $FEV_1$  improvements were observed in patients with a mean post-bronchodilator baseline  $FEV_1$  of 1.5 to 1.6 L, representing an approximate 5% gain. The results of the PP analysis of post-bronchodilator  $FEV_1$  were comparable to those of the ITT analysis. The difference between the two roflumilast doses for post-bronchodilator  $FEV_1$  was 23 mL ( $p = 0.1166$ , 2-sided) favouring the 500 µg dose. In the time averaged excess AUC analysis, a statistically significant increase in post-bronchodilator  $FEV_1$  was observed with both roflumilast doses. The increase was more pronounced in the Rof500 group than in the Rof250 group.

The SGRQ total score improved with all treatments (placebo: -1.8, Rof250: -3.4, Rof500: -3.5) with the differences vs placebo approaching statistical significance for the 500 µg dose ( $p = 0.0532$ , 2-sided). Significant improvements with roflumilast were also seen for a variety of other post-bronchodilator expiratory endpoints (forced expiratory volume in the first 3 seconds ( $FEV_3$ ), forced expiratory volume in the first 6 seconds ( $FEV_6$ ), area under the expiratory curve (AEX), forced expiratory flow rate from 200 mL up to 1200 mL ( $FEF_{200-1200}$ ), forced expiratory flow at 25, 75 of vital capacity ( $FEF_{25-75}$ ), forced vital capacity (FVC) and peak expiratory flow (PEF). The inspiratory post-bronchodilator parameters tended to decrease in all groups during the course of the study with the decrease being higher in the placebo group than in the roflumilast groups. The pre-bronchodilator  $FEV_1$  showed statistically significant greater improvements over placebo

with both Rof250 and Rof500 (difference from placebo was 64 mL and 88 mL with 250 µg and 500 µg,  $p \leq 0.006$ ); other pre-bronchodilator parameters also showed similar improvements.

The proportion of patients experiencing mild, moderate or severe COPD exacerbations was lower in the Rof500 group (28.3%) compared to placebo (34.6%) and 250 µg (35.9%) groups. For all of these endpoints the Jonckheere-Terpstra test for trend revealed a  $p < 0.025$ , 1-sided, suggesting that the observed effects with roflumilast were dose related with larger improvements at the higher Rof500 dose. Statistically significant differences between the two roflumilast doses in favour of the higher dose were seen for the secondary endpoints post-bronchodilator FEV<sub>3</sub> and FEV<sub>6</sub> as well as for time to first mild, moderate or severe exacerbation. The COPD symptom score sum decreased during treatment in all three treatment groups, indicating an improvement in COPD symptoms with the change being slightly more pronounced in the Rof500 group than in the other two groups. Within treatment analysis showed that the use of rescue medication did not change substantially in the roflumilast group, while a statistically significant increase in the daily use of rescue medication was seen for the placebo group; however, there were no statistically significant between treatment differences and no statistically significant dose relationship.

#### **Pivotal studies (Studies M2-124 and M2-125).**

Two pivotal, 52 week studies compared the efficacy and safety of roflumilast 500 µg (Rof500) once daily (od) versus placebo in 3091 patients with severe to very severe COPD associated with chronic bronchitis and a history of exacerbations. Pivotal studies, M2-124 and M2-125 were identical in design and were randomized, double blind, parallel group. After a 4 week single blind placebo run-in (baseline) period, patients were randomized (1:1 randomization) to either placebo or Rof500 od. Treatment duration was 52 weeks as recommended for studies evaluating COPD exacerbations. The objectives of both pivotal studies were to investigate the effect of 500 µg roflumilast on exacerbation rate, lung function, COPD symptoms, dyspnoea, the health related quality of life and health care resource use and also to investigate the safety and tolerability of roflumilast.

#### ***Study M2-124***

Study M2-124 was conducted at 246 centres in Australia, Austria, France, Germany, Hungary, New Zealand, Romania, Russia, United Kingdom and USA from 27 February 2006 to 7 July 2008.

#### ***Inclusion/ exclusion criteria***

Patients enrolled in these studies were at least 40 years of age with a diagnosis of COPD based on the ATS/ERS consensus statement, were required to be current or former smokers (cessation at least 1 year ago) with a smoking history of at least 20 pack years and to present with chronic bronchitis (chronic productive cough for 3 months in each of the 2 years prior to study enrolment) and a history of at least 1 COPD exacerbation within the previous year (as defined by the need for oral or parenteral glucocorticosteroid intake and/or hospitalization).<sup>50</sup> Other inclusion criteria were a post-bronchodilator FEV<sub>1</sub>% predicted of  $< 50\%$ , an FEV<sub>1</sub>/FVC ratio of  $< 70\%$ . To be eligible for randomization (4 weeks after the baseline), patients had to fulfil the following criteria: no COPD exacerbation (as defined by the need for oral or parenteral glucocorticosteroid intake and/or hospitalization) during baseline period (patients with COPD exacerbations in the baseline period could be re-enrolled after resolution of the exacerbation); total cough and sputum score  $\geq 14$  during the last week directly preceding the randomization visit; no positive hemocult (guaiac) test during baseline; medication compliance  $\geq 80\%$  and  $\leq 125\%$ .

The main exclusion criteria were: unresolved COPD exacerbation at baseline, diagnosis of asthma and/or other relevant lung disease (for example, history of bronchiectasis, cystic fibrosis, bronchiolitis, lung resection, lung cancer, interstitial lung disease, and active tuberculosis), other significant medical illness or laboratory abnormality, pregnancy, current participation in a lung rehabilitation program or completion of a lung rehabilitation program within 3 months preceding the baseline visit, use of immunosuppressive medications within 4 weeks prior to baseline (for example, cyclosporin, methotrexate, TNF- $\alpha$  receptors or antibodies, gold, azathioprine); known alpha-1-antitrypsin deficiency; known infection with human immunodeficiency virus (HIV) and/or active hepatitis; diagnosis, treatment, or remission of any cancer (other than basal cell carcinoma) within 5 years prior to study start, clinically significant cardiopulmonary abnormalities (diagnosed clinically or by x-ray/CT-scans/ECG) that were not related to COPD and that required further evaluation; clinically relevant ECG findings (for example, acute or recent myocardial infarction, clinically significant arrhythmia); alcohol or drug abuse, hypersensitivity to ingredients of study medication.

#### *Evaluator's comments*

By limiting the enrolment to patients who had exacerbation in the year prior to the trial but excluding patients who had exacerbation during the run-in period, the trials have selected a special patient population (those at the highest risk of exacerbation) during a specific time frame, when highest risk patients were most likely to have exacerbation.

#### **Treatments**

Study treatment was administered orally once daily in the morning after breakfast. The following medications were not allowed throughout the study and were to be withdrawn at start of placebo, single blind, run-in period:

- short acting  $\beta$ 2-agonist, with the exception of albuterol/salbutamol supplied by sponsor and nebulised albuterol/ salbutamol if given at a constant daily dose;
- oral  $\beta$ 2-agonists;
- long acting anticholinergics (tiotropium);
- short acting anticholinergics (ipratropium) for patients receiving LABA during the study;
- combination of anticholinergics with short acting  $\beta$ 2-agonists;
- theophylline, lipoxygenase inhibitors and leukotriene antagonists;
- systemic glucocorticosteroids throughout the study with the exception of treatment for an exacerbation during the double blind (DB) treatment period.

The following medications were not allowed and were to be withdrawn at start of the 52 week, DB treatment period:

- inhaled corticosteroids;
- combinations of inhaled long acting  $\beta$ 2-agonists and inhaled corticosteroids (patients could continue with long acting  $\beta$ 2-agonists alone).

The following medications were allowed during the study:

- inhaled short acting  $\beta$ 2-agonists (albuterol/salbutamol provided by the sponsor) as rescue medication according to the patient's individual needs;
- patients already pre-treated with nebulised albuterol/salbutamol were allowed to stay on this medication as long as nebulised albuterol/salbutamol was administered at a constant daily dose and not as rescue medication;
- use of nebulised short acting  $\beta$ 2-agonists was allowed in addition to LABA or short acting anticholinergics;

- inhaled long acting  $\beta$ 2-agonists (salmeterol or formoterol) at appropriate stable dose for patients treated with long acting bronchodilators (LABA or tiotropium) on a regular basis for at least 12 months prior to the study;
- long acting  $\beta$ 2-agonists for patients pre-treated with fixed combinations (inhaled corticosteroids [ICS] + long acting  $\beta$ 2-agonists) at a constant daily dosage for at least 12 months prior to the study (fixed combination had to be stopped at start of DB period);
- long acting  $\beta$ 2-agonists or short acting anticholinergics at appropriate stable dose; LABA at appropriate stable dose for patients who have been pre-treated with tiotropium on a regular basis for fewer than 12 months prior to the study, but have been pre-treated with another long acting bronchodilator (LABA) for the remaining months of the 12 months time period;
- short acting anticholinergics at a constant daily dosage for patients not treated with long acting  $\beta$ 2-agonists during the study;
- systemic glucocorticosteroids for the management of exacerbations during the double blind treatment phase of the study;
- other drugs for the treatment of concurrent diseases (their dosages were to be kept constant throughout the study).

### ***Efficacy endpoints***

Primary endpoints were the change from baseline to end of treatment in pre-bronchodilator FEV<sub>1</sub>, and the number of moderate or severe COPD exacerbations per patient year.<sup>62</sup> Detection and documentation of COPD exacerbation were based on patient symptoms and medical management required. All patients received a paper diary to track and report their daily COPD symptoms (cough, sputum) and use of rescue medication. If, according to the investigator, an exacerbation required additional treatment, therapy with either up to 40 mg prednisolone per day (d) over 7 to 14 d or additional therapy with antibiotics in case of purulent sputum or bacterial infection was recommended and allowed.

Key secondary endpoints were post-bronchodilator FEV<sub>1</sub>, time to mortality, C-reactive protein (CRP), Transition Dyspnoea Index (TDI) focal score. Other secondary endpoints included further pre and post-bronchodilator inspiratory and expiratory lung function endpoints (for example, FVC, FEV<sub>1</sub>/FVC, FEV<sub>3</sub>, FEV<sub>6</sub>, AEX, FEF200-1200, FEF25-75, PEF, inspiratory capacity [IC], forced inspiratory volume in 1 second [FIV<sub>1</sub>], peak inspiratory flow [PIF]), COPD symptoms (cough, breathlessness, sputum production), use of rescue medication, quality of life assessments (EuroQol Questionnaire [EQ-5D], Clinical COPD Questionnaire [CCQ], Item Short-Form Health Survey [SF36], Treatment Satisfaction Questionnaire [TSQ]), TDI, morning PEF, blood gas analysis and 6-minute walking distance test.

### ***Statistical Considerations***

The primary analyses were based on the ITT analysis, which included all patients of the full analysis set (FAS). In addition, for analyses regarding 'change from baseline', at least one baseline and one post-randomization assessment had to be available. Testing for two

<sup>62</sup> COPD exacerbations were classified as follows: severe COPD exacerbation= Requiring hospitalization and/or leading to death; moderate COPD exacerbation= Requiring oral or parenteral glucocorticosteroid therapy; mild COPD exacerbation:= increase in rescue medication of 3 or more puffs/day on at least 2 consecutive days during the double-blind treatment period; CRF COPD exacerbation= COPD exacerbations as captured in the CRF by the investigator (i.e. also those events not fulfilling the primary definition, eg antibiotic-only treated events); COPD exacerbations treated with systemic steroids and/or antibiotics; COPD exacerbations treated with antibiotic therapy only.



primary endpoints was performed in a hierarchical testing strategy in order to control the overall Type I error.<sup>63</sup> All tests were performed 2-sided on the 5% significance level or 1-sided on the 2.5% level. Key secondary endpoints were tested in a hierarchical order to control the Type I error. All other secondary endpoints were considered descriptive and no adjustments for multiplicity were made.

The difference for change from baseline in pre-bronchodilator FEV<sub>1</sub> between roflumilast and placebo averaged over the entire treatment period was done using a repeated measurement analysis of covariance (ANCOVA). The dependent variable was the change from baseline to each scheduled post randomization visit with the following factors and co-variables: treatment, country (or region), smoking status, gender, age, baseline value, time and treatment by time interaction. Concomitant treatment with LABA (yes/no) was additionally included as a variable as patients were stratified by concomitant treatment with LABA.

A Poisson regression model with time in study as an offset variable was applied to analyse rates of exacerbations. The offset variable corrects for the time a patient was in the study. The dependent variable was the observed number of events.

The repeated measurement ANCOVA described above was also used for secondary lung function endpoints. The power of demonstrating a significant difference for both primary variables [the mean change from baseline during the treatment period in pre-bronchodilator FEV<sub>1</sub> and the number of COPD exacerbations requiring oral or parenteral glucocorticosteroids or hospitalization or leading to death per patient per year] was approximately 90%, assuming independence of the two variables. The power was estimated based on a mean difference of approximately 46 mL in pre-bronchodilator FEV<sub>1</sub> between the two treatments; power calculations for pre-bronchodilator FEV<sub>1</sub> (repeated measurements) were performed according to Muller & Barton.<sup>64</sup> It was also based on the following rates of exacerbations requiring oral or parenteral glucocorticosteroids or hospitalization or leading to death per patient per year (1.25 in the placebo group and a reduction of 20% with Rof500, resulting in a rate of 1.00 exacerbations per patient per year with roflumilast) and an overdispersion factor of 2.

The correction for overdispersion was estimated according to the results of a previous study with roflumilast in a comparable setting. Under the same assumptions a power of 90% would result if the placebo rate was 0.8 and the reduction with Rof500 was 25%, that is, a rate of 0.6 with roflumilast. However, the Poisson regression model had a power of 80% in the following two scenarios and with otherwise same assumptions as above: rate with placebo=0.95 and Rof500 0.76 (20% reduction) or a rate with placebo of 0.60 exacerbations and a rate of 0.45 with Rof500 (reduction of 25%). Sample size calculations for the Poisson regression model were performed according to Yee.<sup>65</sup>

#### *Evaluator's comments*

Other known bronchodilators such as tiotropium demonstrated 87-103 mL improvement in FEV<sub>1</sub> over placebo throughout a 4 year trial. Similarly salmeterol, a long acting beta agonist, demonstrated approximately 170 mL improvement in 2 hour post-dose FEV<sub>1</sub> relative to placebo. The difference of approximately 46 mL in pre-bronchodilator FEV<sub>1</sub>

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<sup>63</sup> The second primary endpoint was tested only after a statistically significant finding for the first primary endpoint. In all cases, both primary endpoints must have been proven significant and thus no adjustment of the Type I error was made.

<sup>64</sup> Muller KE, Barton CN. Approximate Power for Repeated-Measures ANOVA Lacking Sphericity. *Am Stat Association* 1989; 549-555.

<sup>65</sup> Yee KF. Poisson Regression Sample Size Estimation in Clinical Trials. *ASA Proceedings of the Biopharmaceutical Section* 1998; 114-118.

expected in this roflumilast study would provide some indication of mild bronchodilatory effect, which is what would be expected of a drug not known to have significant bronchodilatory effects.

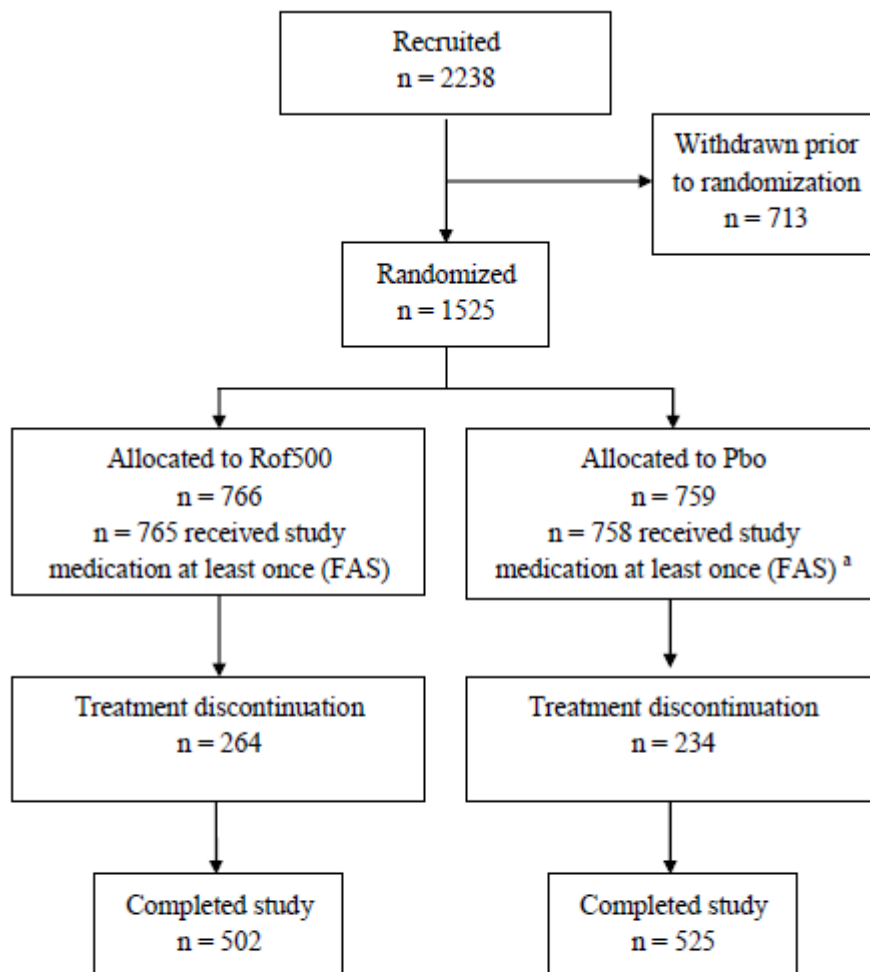
Reduction in exacerbation rate of 20% is clinically acceptable. Recently the FDA approved Spiriva (tiotropium bromide) for reduction of COPD exacerbations; the Spiriva studies demonstrated 14-20% reduction in COPD exacerbations.<sup>66</sup>

## Results

### Participant flow

Of the 1525 randomised patients, 498 patients discontinued treatment (264 and 234 in the roflumilast 500 µg and placebo groups, respectively) (Figure 2).

**Figure 2: Patient disposition in M2-124**



<sup>a</sup> One patient (patient no. 84065) was randomized twice (second patient number: 84375) and received study medication twice. As specified in the definitions of the analysis sets, the first patient number, was included in the FAS, SAF and VCS, while the second patient number, was only included in the SAF and excluded from the FAS and the VCS. Four patients randomized to Pbo received Rof500 instead (at least once) and were included in the Rof500 group for safety analyses  
n = number of patients, Pbo = placebo, Rof500 = roflumilast 500 mcg od.

<sup>66</sup> Approved USPI for Spiriva; available at:

[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/021395s029lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021395s029lbl.pdf)

The most common reason for withdrawal was patient request/unwillingness to continue (Rof vs placebo: 15.7% vs 13.2%) followed by the occurrence of an AE (15.5% vs 10.3%), especially COPD exacerbation (Rof250 vs placebo: 2.7% vs 4.1%), diarrhoea (1.8% vs 0.1%) and nausea (1.8% vs 0.3%) (Table 4).

**Table 4: Discontinuations in M2-124**

	(N = 766)	Pbo (N = 759)
	n (%) <sup>a</sup>	n (%) <sup>a</sup>
Adverse event	119 (15.5)	78 (10.3)
Patient request/Unwillingness to continue	120 (15.7)	100 (13.2)
COPD exacerbation	43 (5.6)	69 (9.1)
Predefined discontinuation criterion fulfilled	7 (0.9)	4 (0.5)
Lost to follow-up	17 (2.2)	16 (2.1)
Other	29 (3.8)	28 (3.7)
<b>Total number of patients who discontinued the study</b>	<b>264 (34.5)</b>	<b>234 (30.8)</b>
<b>Total number of early termination reasons</b>	<b>335</b>	<b>295</b>

<sup>a</sup> Percentages are based on the number of patients in the respective treatment group.

COPD = chronic obstructive pulmonary disease, N = number of patients in the respective treatment group; n = number of patients with the specified reason for termination, Pbo = placebo, Rof500 = roflumilast 500 mcg, od.

#### *Conduct of the study*

The percentages of patients with major protocol violations were comparable in the 2 treatment groups. The most frequent major protocol violation in the Rof500od group was non-compliance (9.8%), followed by “not allowed use of ICS” after randomisation (6.9%), and “not allowed use of systemic corticosteroids (CS)” after baseline (6.8%). In the placebo group, the most common violation was not allowed use of ICS after randomisation (9.6%) and non-compliance (6.2%).

#### *Baseline data*

The vast majority of randomized patients were Caucasian (97%), male (71%) aged between 40 and 92 years (median: 63 years) with slightly more patients in the age category ≤65 years (59%) compared to >65 years. All had a history of smoking with 48% being current smokers and most patients had COPD of severe (65%) or very severe (25%) intensity. The history of COPD was combined emphysema and chronic bronchitis for 72% of the patients and it was predominately chronic bronchitis for 28% of the patients. About 50% of the patients were concomitantly treated with LABA and slightly more than 40% were pre-treated with ICS. The treatment groups were comparable with respect to baseline demographics and disease characteristics. Treatment compliance was high in both groups (94%) and the mean exposure to study drug was 292 and 278 days for the placebo and roflumilast group, respectively. Approximately 60% of patients in each group took corticosteroids during the DB treatment period, including 10% taking ICS and 11% of patients in each group also took inhaled combination of corticosteroids and LABAs. Overall, the concomitant medications taken during the study were similar in the roflumilast and placebo groups.

#### *Evaluator's comments*

Both use of the prohibited CS and/or ICS and non compliance with the study drug can affect the study results and this could favour the roflumilast groups, that is more efficacy from steroid use and less side effects from noncompliance with study drug. However, it is

difficult to determine the precise impact of those violations on efficacy results. Therefore, comparing the consistency of efficacy results in the ITT and PP populations would be important. Although use of ICS and inhaled combinations of ICS and LABAs were prohibited according to study protocol, almost 10-11% of patients in each treatment group still used these drugs. The prevalent use of prohibited COPD drugs suggested that patients in the trials were under treated. This is especially important in light of the study design which seems to imply that roflumilast could be used instead of ICS in patients with severe or very severe COPD.

#### *Primary efficacy results*

Compared to placebo, pre-bronchodilator FEV<sub>1</sub> was statistically significantly ( $p \leq 0.0005$ ) increased with roflumilast by 39 mL in the ITT analysis and 47 mL in the PP analysis. Robustness of the repeated measures analysis was confirmed by the last observation carried forward (LOCF) analysis. At all treatment visits there were increases in pre- and post-bronchodilator FEV<sub>1</sub> from baseline in the Rof500 group and clearly smaller increases or decreases in FEV<sub>1</sub> from baseline in the placebo group. Statistically significant differences in LSMeans between Rof500 od and placebo ranging from 36 mL to 46 mL (pre-bronchodilator) and from 46 mL to 56 mL (post bronchodilator) were seen at all visits (ITT). The proportion of patients experiencing at least 1 COPD moderate to severe exacerbation was slightly lower in the roflumilast group (roflumilast vs placebo: 46% vs 51.3%). The frequency of patients experiencing at least 2 (and up to 6) moderate or severe COPD exacerbations was also lower in the roflumilast group (Table 5).

**Table 5: Frequency of severe or moderate COPD exacerbations (FAS)**

Number of exacerbation events	Rof500 (N = 765)	Pbo (N = 758)
	Number of patients with exacerbations n (%) <sup>a</sup>	
0	421 (55.0)	369 (48.7)
1	190 (24.8)	191 (25.2)
2	86 (11.2)	100 (13.2)
3	42 (5.5)	50 (6.6)
4	13 (1.7)	25 (3.3)
5	8 (1.0)	15 (2.0)
6	1 (0.1)	6 (0.8)
7	4 (0.5)	2 (0.3)

<sup>a</sup> Percentages are based on the number of patients in the respective treatment group.

COPD = chronic obstructive pulmonary disease, FAS = full analysis set, N = number of patients in the respective treatment group, n = number of patients with exacerbations, Pbo = placebo, Rof500 = roflumilast 500 mcg od.

However, the proportion of patients experiencing at least one exacerbation did not differ as greatly in the valid cases set (VSC) population (46.1% versus 49.0%). The rate of moderate or severe COPD exacerbations per patient per year was lower for roflumilast (1.077; ITT) than for placebo (1.266; ITT). Using the Poisson regression model with the covariates pre-specified in the protocol, the estimated reduction in rate of moderate or severe COPD exacerbations compared to placebo was statistically significant and showed superiority of roflumilast over placebo (change: -14.9%; CI: 0.737, 0.982, p-value: 0.0278; ITT). However, the PP analysis failed to show statistically significant difference between roflumilast and placebo groups, although the rate of moderate or severe COPD exacerbations per patient per year was slightly lower for roflumilast (1.007) than for

placebo (1.093), (change: -7.8%, 95% CI: 0.780, 1.089, p-value: 0.3385). The exacerbation analyses did not explicitly examine potential attenuations in treatment effect during long term treatment with roflumilast; of the four statistical models presented, the Poisson and the negative binomial models only assessed roflumilast's effect averaged over the entire course of each study, while the proportional hazards and the log rank tests only assess times to onset of exacerbations in each study, without including all exacerbation recurrences. An analysis to examine mean number of exacerbations per patient year for each time interval, similar to those used for the FEV<sub>1</sub> analyses would help interpretation of results regarding possible attenuation of efficacy following long term roflumilast treatment.

The sponsor noted that the time to first, second, third, fourth and fifth exacerbations was analysed to examine effects on exacerbations at later times during the trial period. These analyses confirmed the sustained effect of roflumilast during the pivotal trials.

#### *Key secondary efficacy results*

Post-bronchodilator FEV<sub>1</sub> of patients in the Rof500 group showed a clear increase from baseline (LSMean: 57 mL; CI: 40, 73 mL; ITT), while it remained almost the same in the placebo group (LSMean: 8 mL; CI: -9, 25 mL; ITT). Between treatment difference was statistically significantly in favour of Rof500 (LSMean: 49 mL; p-value: <0.0001; ITT). The ITT analysis was confirmed by the PP analysis. Furthermore, the LOCF ITT analysis revealed results similar to those of the repeated measurements analysis with superiority of roflumilast over placebo (treatment difference LSmMean: 35 mL; p-value: 0.0130; ITT). Although no statistically significant difference between roflumilast and placebo was observed in the PP analysis, the trend was the same as for the ITT analysis.

#### *Other secondary efficacy results*

A total of 34 patients in the FAS (17 in each treatment group) died. The time to mortality was similar for roflumilast treated (213.8 ± 118.9 days) and placebo treated patients (207.5 ± 108.5 days); hazard ratio of roflumilast/ placebo was 1.035 ± 0.357 (95% CI: 0.526, 2.034, p=0.9212). A total of 5 patients in the FAS (3 treated with Rof500 and 2 receiving placebo) died due to a COPD exacerbation during the course of the study; the mean time to mortality due to a COPD exacerbation was 294.3 days (± 63.9 days) in the roflumilast and 142.5 days (± 113.8 days) in the placebo group with a non-significant hazard ratio of 1.278 (p-value: 0.7949). Although mortality due to COPD exacerbations appears to be higher in the roflumilast group, interpretation was limited by the small number of fatal COPD exacerbations.

The mean values of natural log transformed CRP increased in both treatment groups with no significant difference between groups. An increase in TDI scores was found in both treatment groups with a statistically significant greater increase in the Rof500 group compared with placebo (LSMean: 0.233; p-value: 0.0356) in the ITT analysis, but not in the PP analysis.

Reductions in exacerbation rates were analysed for different categories of COPD exacerbations; statistically significantly greater reduction with roflumilast was observed for only 'moderate', 'moderate or severe' and 'treated with systemic steroids and/ or antibiotics'; however, the PP analysis failed to demonstrate significant difference between roflumilast and placebo group for any category of COPD exacerbations, however. The risk of experiencing any type of exacerbation was lower in the Rof500 group than in the placebo group, but the proportions of patients experiencing moderate to severe COPD exacerbations was significantly lower in the roflumilast group. Cox proportional hazards regression of 'time to first COPD exacerbation' showed a hazard ratio in favour of Rof500 for all categories of exacerbations, however the differences between treatment groups

were not statistically significant except for CRF exacerbations (hazard ratio: 0.842; p-value: 0.0118; ITT). The hazard ratio for 'time to onset of second COPD exacerbation' was in favour of Rof500 and significant compared with placebo (hazard ratio: 0.791; p-value: 0.0290; ITT).

The number needed to treat (NNT) to avoid one additional moderate or severe COPD exacerbation per patient per year was 5.29 patients (ITT) but was doubled for the PP analysis (NNT=11.63). A *post hoc* analysis to determine the NNT to keep one patient completely exacerbation free for one year was 15.74 patients (ITT) and 34.65 (PP).

Among roflumilast treated patients, a within treatment improvement was observed for all pre- and post-bronchodilator expiratory lung function secondary endpoints. Among patients in the placebo group, either a within treatment decrease or a rather small increase was observed. Between treatment differences were statistically significant (p-values <0.05; ITT) for all endpoints except for pre-bronchodilator PEF and post-bronchodilator forced expiratory flow over 25 to 75% of FVC  $FEF_{25-75}$ . There was a slight decrease in daily use of rescue medication in the roflumilast group (LSMean: -0.04 puffs/day), while there was a slight increase in the placebo group (LSMean: 0.16 puffs/day) with no statistically significant difference between groups (p=0.1030). Both treatment groups showed similar reduction in COPD symptom scores. There were no statistically significant differences in QOL measures such as EQ-5D and VAS.

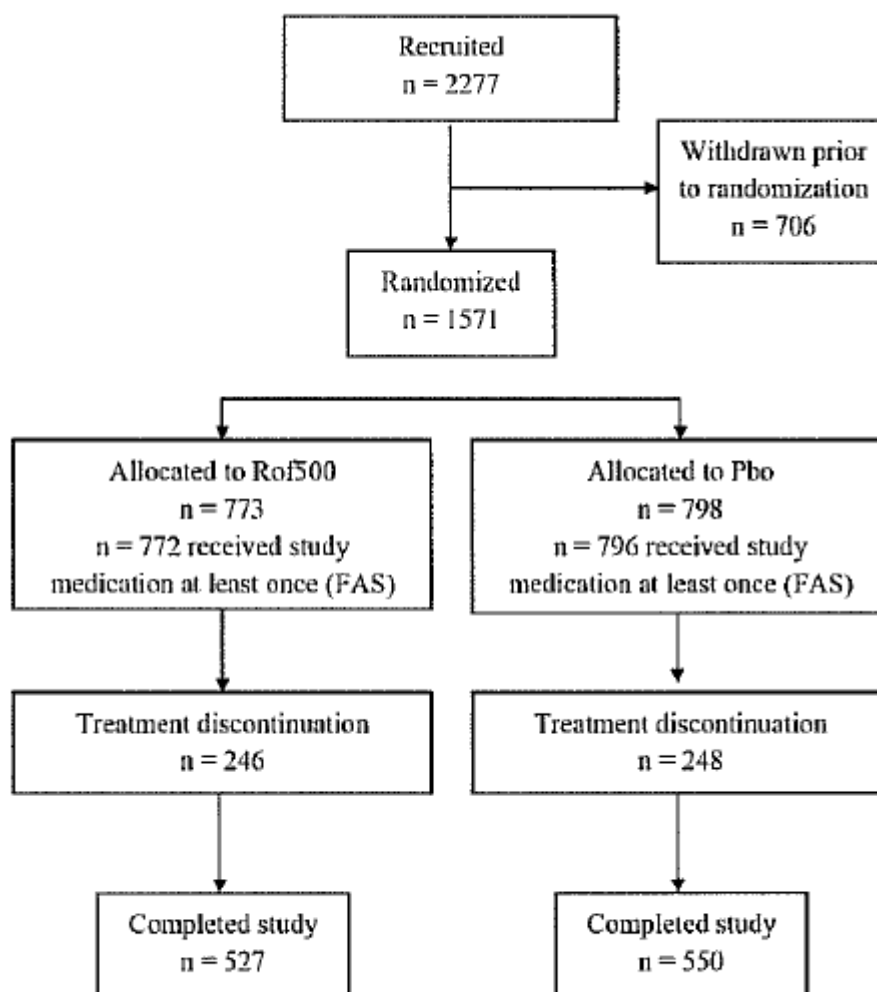
### ***Pivotal study M2-125***

Study M2-125 was conducted at 221 centres in Canada, Germany, India, Italy, Poland, South Africa, Spain and Ursiform 2/3/2006 to 29/4/2008. The study design, methods, inclusion/ exclusion criteria, efficacy endpoints and statistical analysis in this study were similar to that in study M2-124 described above.

### ***Results***

Overall, 494 patients (31.4%) discontinued treatment, 246 were patients in the roflumilast 500 µg (Rof500) od group, and 248 were patients in the placebo group (Figure 3).

Figure 3: Patient disposition in M2-125



n = number of patients. Pbo = placebo, Rof500 = roflumilast 500 mcg od.

The most common reason for withdrawal was patient request/unwillingness to continue (Rof500 vs placebo: 14% vs 13.4%) and AE (13.1% vs 10.4%), especially COPD exacerbation (3.2% vs 5.7%) and diarrhoea (1.9% vs 0%). The percentages of patients with major protocol violations were comparable in the treatment groups (roflumilast vs placebo: 31.7% vs 29.2%) and the most common reasons were non-compliance (10% vs 6.9%), not allowed use of ICS (8.2% vs 9.3%) and not allowed use of systemic corticosteroids (7.2% vs 6%).

During the treatment period, mean compliance was high among patients in both the Rof500 od group (FAS: 93.2%, VCS: 97.0%) and the placebo group (FAS: 95.7%, VCS: 98.1%). Overall, 1568 patients (roflumilast vs placebo: 772 vs 796) took at least one dose of the study medication and were included in the safety and FAS populations; however, 6 patients who were randomized to placebo received Rof500 instead and are thus included in the Rof500 group for the safety analyses; the VSC included 1093 patients (528 vs 565). The majority of the patients were Caucasian (72% and 23% were Asian), males (80%) aged between 40 and 90 years (median: 64 years) with slightly more patients in the age category  $\leq 65$  years (55%) compared to  $>65$  years. All had a history of smoking with 35% being current smokers. Patients had severe (60%) or very severe (33%) COPD; for 67% of the patients the history of COPD was combined emphysema and chronic bronchitis; for

33% it was predominately chronic bronchitis. About 50% of the patients were concomitantly treated with LABA and about 40% were pre-treated with ICS. The treatment groups were comparable with respect to baseline demographics and disease characteristics. The incidence of concomitant COPD medications before or during the treatment period was similar in both groups.

#### *Primary efficacy results*

Pre-bronchodilator FEV<sub>1</sub> increased for patients in the Rof500 group (LSMean: 33 mL; confidence interval (CI): 19, 48 mL; ITT) but decreased in the placebo group (LSMean: -25 mL; CI -39, -11 mL; ITT). A significant between treatment difference demonstrated superiority of roflumilast in improving pre-bronchodilator FEV<sub>1</sub> (LSMean: 58 mL; p-value: <0.0001; ITT). The ITT analyses were confirmed by the PP analyses. The LOCF analysis revealed results similar to those of repeated measurements analysis confirming robustness of the primary efficacy results. At all treatment visits there were increases in pre- and postbronchodilator FEV<sub>1</sub> from baseline in the Rof500 group and decreases in pre- and post-bronchodilator FEV<sub>1</sub> from baseline in the placebo group.

Statistically significant differences in LSMeans between Rof500 od and placebo ranging from 58 mL to 69 mL (pre-bronchodilator) and 61 mL to 67 mL (post-bronchodilator) were seen at all visits (ITT). Of the patients included in the FAS, 48.3% in the Rof500 od group and 54.3% in the placebo group experienced at least one moderate or severe COPD exacerbation. The frequency of patients experiencing at least 2 (and up to 9) moderate or severe COPD exacerbations was higher in the placebo group as well (Table 6). In the VCS, a similar pattern was observed. The rate of moderate or severe COPD exacerbations per patient per year was lower for Rof500 (rate: 1.210; ITT) than for placebo (rate: 1.485; ITT). The estimated reduction in rate of moderate or severe COPD exacerbations compared to placebo was statistically significant and showed superiority of roflumilast over placebo (change: -18.5%; CI: 0.710, 0.935; p-value: 0.0035; ITT). The ITT analysis was confirmed by the PP analysis.

**Table 6: Frequency of severe or moderate COPD exacerbations (FAS)**

Number of exacerbation events	Rof500 (N = 772)	Pbo (N = 796)
	Number of patients with exacerbations n (%) <sup>a</sup>	
0	399 (51.7)	364 (45.7)
1	198 (25.6)	200 (25.1)
2	91 (11.8)	112 (14.1)
3	48 (6.2)	56 (7.0)
4	24 (3.1)	30 (3.8)
5	8 (1.0)	18 (2.3)
6	3 (0.4)	7 (0.9)
7	1 (0.1)	5 (0.6)
8	0 (0.0)	2 (0.3)
9	0 (0.0)	2 (0.3)

<sup>a</sup> Percentages are based on the number of patients in the respective treatment group.

COPD = chronic obstructive pulmonary disease, FAS = full analysis set, N = number of patients in the respective treatment group, n = number of patients with exacerbations, Pbo = placebo, Rof500 = roflumilast 500 µg od.



### *Key secondary efficacy results*

As with pre-bronchodilator FEV<sub>1</sub>, post-bronchodilator FEV<sub>1</sub> of patients in the Rof500 od group increased (LSMean: 44 mL; CI: 30, 59 mL; ITT). In contrast, post-bronchodilator FEV<sub>1</sub> of patients in the placebo group decreased (LSMean: -17 mL; CI: -31, -3 mL; ITT). A statistically significant between treatment difference demonstrated superiority of roflumilast in improving post-bronchodilator FEV<sub>1</sub> (LSMean: 61 mL; p-value: <0.0001; ITT). The ITT analysis was confirmed by the PP analysis. The LOCF confirmed the results although the increase in roflumilast group was lesser (LSMean: 15 mL; CI: -3, 32 mL; ITT) but the decrease in the placebo group was greater (LSMean: -33 mL; CI: -50, -15 mL; ITT); superiority of roflumilast over placebo was demonstrated (LSMean: 47 mL; p-value: <0.0001; ITT).

A total of 50 patients (25 in each treatment group) died. The time to mortality was slightly shorter for roflumilast treated patients than for placebo treated patients: the mean time to mortality was 201.0 days ( $\pm$  116.9 days) in the roflumilast and 214.6 days ( $\pm$  137.3 days) in the placebo group; the hazard ratio was not statistically significantly different between Rof500 od and placebo (hazard ratio: 1.213+0.350; 95% CI: 0.689, 2.137, p-value: 0.5028). Since there was no statistically significant treatment difference for the key secondary endpoint 'time to mortality due to any reason', the following key-secondary endpoints were tested in an exploratory manner only. The mean CRP levels increased in both groups with slightly non-significantly greater increase in the roflumilast group. An increase in TDI scores was found in both treatment groups with statistically significant greater improvement in the Rof500 group compared with placebo (LSMean: 0.286; p-value: 0.0059; ITT). The PP analysis supported these results. The risk of experiencing a clinically relevant improvement was slightly higher in the Rof500 od group (risk: 0.322; responders: n=287) than in the placebo group (risk: 0.294; responders: n=264). The risk ratio for the 2 treatment groups was 1.093, indicating a slightly favourable outcome for the Rof500 od group, which was not statistically significant (p-value: 0.1490; ITT).

### *Other secondary efficacy results*

The mean rate of COPD exacerbations decreased numerically with Rof500 od vs placebo (ITT). The largest effect of roflumilast was seen for severe exacerbations, with a reduction of -22.9%, although this effect was not statistically significant due to the relatively small rates in that category. The risk of experiencing any type of exacerbation was lower in the Rof500 od group than in the placebo group. In the ITT population, the results were statistically significant except for categories with relatively low numbers of patients experiencing at least one exacerbation (that is, severe exacerbations and exacerbations treated with antibiotics only). Cox proportional hazards regression for time to onset of first exacerbation showed a hazard ratio in favour of Rof500 od for all categories of exacerbations, however the differences between treatment groups were not significant except for mild exacerbations (hazard ratio: 0.849; p-value: 0.0379; ITT). However, the hazard ratio for 'time to onset of second moderate or severe exacerbation' was statistically significantly in favour of Rof500 thus demonstrating a long lasting treatment effect (hazard ratio: 0.793; p-value: 0.0214; ITT).

The duration of COPD exacerbations for all different categories was summarized in two different ways: firstly as the mean number of COPD exacerbation days per patient, and secondly as the mean duration of COPD exacerbations per patient. Concerning moderate or severe exacerbations, results were in favour of roflumilast for both parameters.

The NNT to avoid one additional moderate or severe COPD exacerbation per patient per year was 3.64 patients (ITT) and 3.12 (PP); the NNT to keep one patient completely exacerbation free for one year was 16.79 patients (ITT) and 18.23 patients (PP).

A total of 19 patients in the FAS (9 treated with Rof500 and 10 receiving placebo) died due to a COPD exacerbation during the study. The mean time to mortality due to a COPD exacerbation was 188.6 days ( $\pm$  106.9 days) in the roflumilast and 173.6 days for placebo ( $\pm$  103.2 days). The hazard ratio was 1.102 and not statistically significant (p-value: 0.8334), although there were small numbers of fatal COPD exacerbations.

Differences in LSMeans between Rof500 od and placebo ranging from 58 mL to 69 mL (pre-bronchodilator) and 61 mL to 67 mL (post-bronchodilator) were seen at all visits.

There was an increase in daily use of rescue medication in the placebo group (LS Mean: 0.55 puffs/day; 95% CI: 0.35, 0.74; ITT). The difference between patients treated with Rof500 and patients receiving placebo was statistically significant (LSMean: -0.43; p-value: 0.0003; ITT). The COPD symptom score sums tended to decrease in both treatment groups indicating an improvement in COPD symptoms which was slightly larger, but not statistically significant, in the Rof500 group compared to the placebo group. The quality of life measures (EuroQOL) did not show any significant difference between the treatment groups.

### **1 year studies (M2-111 and M2-112)**

All supportive efficacy studies focused on lung function and quality of life as endpoints. Exacerbations were evaluated as endpoints in almost all studies but the definition as well as the methods of analysis evolved over time. These studies were similar in design to the pivotal studies but included a slightly different patient population. Patients in Studies M2-111 and M2-112 were not required to have a history of exacerbations and chronic bronchitis as in the pivotal studies. The definitions of moderate and severe exacerbations as well as the primary endpoint, rate of exacerbations differed from that of the pivotal studies; exacerbations were captured differently in study M2-111 and study M2-112 as compared to the pivotal studies, M2-124 and M2-125. An exacerbation free period of at least 10 days was required for separate exacerbations in study M2-111, while at least one exacerbation free day was required to separate exacerbations in study M2-112.

#### **M2-111**

M2-111 was a Phase III, double blind, randomized, parallel group, 52 week study (with a 4 week single blind placebo baseline period) conducted at 188 centres located in Canada (13), France (12), Germany (14), Poland (10), South Africa (15), and the USA (124) from 9 December 2003 to 2 December 2005. The inclusion/ exclusion criteria were similar to those described for the pivotal studies.

The co-primary endpoints were the change from baseline in pre-bronchodilator FEV<sub>1</sub> and number of moderate (treated with oral or parenteral glucocorticosteroids) or severe (leading to hospitalization and/or death) COPD exacerbations per patient per year. The key secondary endpoints were post-bronchodilator FEV<sub>1</sub>, rate of exacerbations requiring oral or parenteral glucocorticosteroid therapy or leading to hospitalization and/or death in a variety of subgroups, frequency of exacerbations by severity and frequency of different types of exacerbations. Other secondary endpoints included various pre- and post-bronchodilator inspiratory and expiratory lung function parameters, mortality, COPD symptom score, use of rescue medication, Baseline/Transition Dyspnoea Index (BDI/TDI) focal and component scores. The LOCF method was applied to replace missing values for the endpoint-analysis of efficacy.

#### **Results**

Of the 1176 randomized patients, 1173 received at least one dose of study medication and were included in the FAS (Rof vs placebo: 567 vs 606). A total of 288 randomized patients were excluded from the VCS due to major protocol violations with similar incidence in

roflumilast (26.6%; 151/568) and placebo (23%; 140/608) groups. The frequency of withdrawal from the study was slightly higher in the roflumilast treatment group (38%; 216/568) compared with the placebo group (30.8%; 187/608) and the most common reasons for study termination were AEs (Rof vs placebo: 19.9% vs 11.0%) and patients' request or unwillingness to continue (16.4% vs 12.7%). Treatment compliance was high with a mean between 94% and 99% (median 99% to 100%) during both baseline and treatment periods in each treatment group (FAS and VCS). The majority of patients were male (67%) and Caucasian (93%) with median age of 65 years and suffered from severe (65%) or very severe (24-27%) COPD. Both treatment groups had similar baseline demographic and lung function data (VCS or PP population also had similar characteristics to the FAS population). Inhaled short acting  $\beta$ 2-agonists, ICS and inhaled short acting anticholinergics were the most commonly used concomitant medications for COPD with similar incidence in both treatment groups.

#### *Primary efficacy results*

A statistically significant greater improvement in pre-bronchodilator FEV<sub>1</sub> was seen in the roflumilast treatment group compared with placebo (difference in LSMeans: 36 mL, 95% CI: 6 to 57 mL; p = 0.0160, 2-sided, ITT, confirmed by PP analysis). Differences in LSMeans ranging from 21 to 45 mL between Rof500 and placebo were seen at all visits. The Poisson regression revealed that the rate of moderate exacerbations treated with systemic glucocorticosteroids or severe exacerbations per patient per year was non-significantly lower in the Rof500 compared with the placebo group (0.623 vs 0.720, ITT); the reduction compared with placebo was -13.5% in the ITT and -16.4% in the PP analysis. Based on the non-parametric Wilcoxon rank sum test (done to confirm robustness of results), the frequency of moderate steroid treated exacerbations or severe exacerbations per patient per year decreased statistically significantly with roflumilast compared with placebo (46% reduction, 2-sided p = 0.0132, ITT, confirmed by PP).

#### *Secondary efficacy results*

Since superiority of Rof500 od to placebo was not shown for the primary endpoint of moderate/severe COPD exacerbations per patient per year in the primary Poisson regression analysis, confirmatory hypothesis testing was stopped and key secondary variables were analysed only in an exploratory manner.

Post-bronchodilatory FEV<sub>1</sub> showed statistically significant greater increase with Rof500 compared with placebo (difference=38 mL, 95% CI: 18 to 58 mL, p=0.0002, ITT confirmed by PP analysis). The number of moderate/ severe exacerbations in roflumilast treated patients showed a small increase (+8.6%) compared with placebo (2-sided p = 0.6466) in patients with 'very severe' COPD at baseline. In patients with a history of chronic bronchitis with or without emphysema, roflumilast treatment showed a non-significant 19% reduction in the frequency of moderate/ severe exacerbations compared with placebo (2-sided p = 0.1036).

Compared with placebo, roflumilast treatment showed a statistically significantly greater reduction in moderate/severe exacerbations in patients with mean baseline cough score  $\geq 2$  (-38.5%, 2-sided p = 0.0261) and mean baseline sputum score  $> 2$  (-38.5%, 2-sided p=0.0323). In patients with a history of  $\geq 1$  exacerbation in the year prior to baseline, roflumilast treatment produced a non-significant reduction in moderate/severe exacerbations compared with placebo (0.910 and 1.018 moderate/ severe exacerbations per patient per year with roflumilast and placebo, respectively, resulting in a -10.6% reduction; one-sided p = 0.2107); however, patients with no history of COPD exacerbations in the past years showed slightly greater reduction (-13.3%).

The change from baseline in pre-bronchodilator FEV<sub>1</sub> was statistically significantly better in roflumilast treated patients who had severe COPD at baseline, had received prior treatment with ICS, had no history of COPD exacerbation in past year and were ex-smokers; however, roflumilast treatment was not associated with statistically better improvement in pre-bronchodilator FEV<sub>1</sub> in patients with mean baseline cough and sputum score  $\geq 2$ . Compared with placebo, roflumilast treated patients had 10% lower rate of 'moderate/severe' and 13.6% lower rate of 'mild/moderate/severe' COPD exacerbations per patient per year; the differences between treatments were not significant. Superiority of roflumilast to placebo was shown for most pre- and post-bronchodilator expiratory lung function parameters with the following exceptions: for pre- and post-bronchodilator slow vital capacity (SVC) and expiratory reserve volume (ERV), for pre-bronchodilator FEF<sub>25%</sub> and PEF, as well as for post-bronchodilator FEF<sub>75%</sub>, the differences between treatments were in favour of roflumilast but not statistically significant. The number of patients experiencing exacerbations was statistically significantly lower in the Rof500 group compared with placebo; the duration of COPD exacerbations was comparable in the roflumilast and placebo groups.

An increase in TDI scores from baseline and thus an improvement in dyspnoea was observed for both treatments with the improvement was significantly greater than placebo for the TDI focal score and all component scores. Furthermore, the number of patients with a clinically relevant improvement in TDI (that is, an increase in focal score of  $\geq 1$  unit) were statistically significantly greater in the roflumilast group compared with placebo (38.6% vs 30.9%,  $p = 0.0063$ ). Compared with placebo, roflumilast treated patients showed an improvement in quality of life (corresponding to a decrease in SGRQ total score) which was statistically greater for the total score, the impact score and the symptoms score.

For the activity score, the difference between treatments was in favour of roflumilast but not statistically significant. The number of patients with or without a clinically relevant improvement in SGRQ total score, that is, a decrease of  $\geq 4$  units was similar in the roflumilast (36.5%; 183/444) and placebo (33.3%; 185/533) groups. Morning PEF derived from patients' diaries improved with roflumilast (2.6 L/min) and deteriorated with placebo (-0.4 L/min) with statistically significant difference in favour of Rof500 ( $p = 0.0404$ , 2-sided, ITT, confirmed by PP). Daily use of rescue medication did not change over the treatment period in roflumilast treated patients, but increased in placebo treated patients statistically significant treatment difference in favour of roflumilast (difference in LSMeans: -0.5 puffs/d,  $p = 0.0002$ , one-sided, ITT).

The COPD symptom scores (breathlessness, cough, sputum production and score sum) tended to decrease during the study in both treatment groups, indicating an improvement in COPD symptoms. However, the differences between Rof500 and placebo did not favour roflumilast and in fact favoured placebo for sputum production. The number of patients who died during the study was similar in the Rof500 group (1.9%; 11/567) and the placebo group (2%; 12/606), with no statistically significant difference between groups ( $p = 0.5647$ , Fisher's exact test).

The mean time to study discontinuation was shorter in the roflumilast treatment group (273 days) compared with the placebo group (303 days), with a 40% higher risk of early discontinuation with roflumilast when compared with placebo and a statistically significant difference between the treatment groups in favour of placebo for time to study withdrawal (Cox-proportional hazards regression hazards ratio 1.4, two-sided  $p = 0.0003$ , ITT, not confirmed by PP). The two sample log rank test revealed similar results ( $p = 0.0017$ , ITT). Both the two sample log rank test and the Cox proportional hazards regression revealed statistically significantly shorter times to study discontinuation due to

AEs for patients treated with roflumilast compared with placebo treated patients (both  $p < 0.0001$ , ITT, confirmed by PP). The time to study discontinuation due to a COPD exacerbation was comparable in the roflumilast treatment group and the placebo group (median: 161 and 162 days, respectively).

#### *Evaluator's comments*

Modest improvements in LSMeans of pre-bronchodilator FEV<sub>1</sub> ranging from 21 to 45 mL in favour of Rof500 compared with placebo were seen at all visits. The primary Poisson regression analysis for rate of moderate/ severe COPD exacerbations failed to reveal statistically significant differences between Rof500 and placebo. The Wilcoxon rank sum test was done only to confirm robustness of results and showed statistically significant greater reduction in exacerbation rate with roflumilast; however, these results should be interpreted with caution as the Poisson regression model is more appropriate than the Wilcoxon rank sum test because it corrects for subject heterogeneity and standardizes the patients' individual length of time in the study in a more accurate way.

The number of patients experiencing exacerbations was lower in the Rof500 group compared with placebo although this should be interpreted with caution due to the fact that early dropouts occurred more frequently in the roflumilast group and the effect of the different rate of withdrawal was not considered in this analysis. Roflumilast treatment was associated with significantly greater reduction in the incidence of moderate/ severe exacerbations in patients with mean baseline cough and sputum score  $\geq 2$ ; prior treatment with ICS, history of COPD exacerbation in past year or chronic bronchitis (with or without emphysema) did not have any significant impact on roflumilast induced reduction in exacerbation rate.

Roflumilast treatment showed significantly greater benefit in the change from baseline in pre-bronchodilator FEV<sub>1</sub> in subgroups of patients with history of emphysema, no exacerbations in past year, study completers, 'severe' COPD severity, prior treatment with ICS and ex-smokers; patients with mean baseline cough and sputum score  $> 2$  did not show significantly greater improvement in pre-bronchodilator FEV<sub>1</sub> following roflumilast treatment, which was in contrast to the significant benefit in this subgroup of patients for moderate/ severe COPD exacerbation rates.

Compared with placebo, treatment with Rof500 od showed statistically significant greater improvement in TDI total score, morning PEF and SGRQ total score. There was no difference between treatment groups for mortality or COPD symptom scores. However, roflumilast treated patients had a 40% greater risk of early discontinuation compared with placebo, especially due to AEs although incidence of discontinuations due to COPD exacerbations was similar in roflumilast and placebo groups.

#### **M2-112**

M2-112 was a Phase III, double blind, randomized, parallel group, 52 week study (with a 4 week single blind placebo baseline period) conducted at 159 centres in Australia (11), Austria (7), Canada (21), France (17), Hungary (7), Italy (9), Netherlands (12), Poland (9), Portugal (4), Russian Federation (9), South Africa (13), Spain (16), Switzerland (9), and United Kingdom (15) from 24 January 2003 to 27 October 2004. The study design, inclusion/ exclusion criteria, list of prohibited medications and allowed concomitant medications was similar to that discussed for study M2-111 above. There was a stratification of patients according to smoking status and treatment with ICS.

The co-primary endpoints were the change from baseline in post-bronchodilator FEV<sub>1</sub> and number of moderate (treated with oral glucocorticosteroid and/or antibiotics) or severe (leading to hospitalization) COPD exacerbations per patient per year. The key secondary

endpoint was the change in total score of St. George's Respiratory Questionnaire (SGRQ). Other secondary endpoints included various pre- and post-bronchodilator inspiratory and expiratory lung function parameters, COPD symptom score, the use of rescue medication, Baseline/Transition Dyspnoea Index (BDI/TDI) focal and component scores. The LOCF method was applied to replace missing values for the endpoint-analysis of efficacy. The study had a power of at least 82% to be successful in both primary parameters, assuming independence of the two variables; this was based on a 20% reduction in frequency of exacerbations with expected mean of 1.0 and 0.8 exacerbations in the treatment period per patient under placebo and roflumilast, respectively) and the change of post-bronchodilator FEV<sub>1</sub> (improvement in roflumilast compared to placebo in group means of 50 mL and a common standard deviation of 250 mL).

### Results

Overall, 1513 patients received at least one dose of study medication and were included in the FAS (Rof vs placebo: 760 vs 753). A total of 1134 patients completed the treatment period and 380 randomized patients withdrew from the study prematurely; roflumilast-treated patients (217/761, 29%) discontinued study participation more frequently than placebo treated patients (163/753, 22%). In the Rof500 treatment group, the most common reason for withdrawal for the study was AEs, whereas patients in the placebo group withdrew most frequently from the study due to non-medical reasons. Overall, treatment compliance was 98%-99% in both groups.

A total of 464 randomized patients were excluded from the VCS due to major protocol deviations. The incidence of protocol violations was similar in both treatment groups (Rof vs placebo: 32.5% vs 28.8%). The most common major protocol violation was 'non-compliance' with nearly double as many patients in the Rof500 treatment group (16.0%) violating this criterion compared to the placebo group (8.8%).

The majority of patients were male (76%) and Caucasian (99%) with a median age of 65 years and both groups had similar baseline disease characteristics. Essential (primary) hypertension was the most frequently recorded disease other than COPD in both treatment groups. The incidence of concomitant respiratory medications was similar in both treatment groups with ICS, inhaled short acting anticholinergics and inhaled short acting  $\beta_2$ -agonists being most common.

The ITT last value analysis showed that the increase in post-bronchodilator FEV<sub>1</sub> was statistically significantly greater in the roflumilast group compared with the placebo group (difference in LSMeans: 39 mL, 95% CI: 16 to 62 mL, p=0.0005 ITT) with similar results for the PP analysis. Statistically significant differences ranging from 45 to 70 mL between Rof500 and placebo were seen at all visits. Furthermore, repeated measure analysis confirmed the statistically significant difference between Rof500 and placebo groups (difference in LSMeans: 48 mL, p < 0.0001, ITT and PP analysis). Based on the Wilcoxon rank sum test, the frequency of moderate or severe exacerbations per patient per year decreased numerically with roflumilast compared with placebo. The same effect could be seen for the frequency of moderate and mild exacerbations, but not for severe exacerbations. The difference between Rof500 and placebo was not statistically significant. Similar results were observed for moderate/severe exacerbations in the Poisson regression analysis with a non-significant 7% reduction with roflumilast compared with placebo.

A pre-specified analysis which considered only exacerbations that were treated with oral glucocorticosteroids also failed to show any significant difference in the rate of moderate or severe exacerbations by the Poisson regression analysis although the Wilcoxon rank sum test did show statistically significantly greater reduction in moderate exacerbations

with roflumilast ( $p = 0.0294$ , 2-sided, ITT). The mean number of observed moderate/severe exacerbations and of moderate/mild exacerbations was lower in the roflumilast group but the mean number of observed severe exacerbations was comparable between the treatment groups.

The key secondary variable SGRQ total score failed to show significant differences between the roflumilast and placebo groups. The individual component scores of SGRQ also failed to show any difference between groups.

The pre-bronchodilator FEV<sub>1</sub> increased with roflumilast treatment but decreased with placebo leading to a statistically significant difference in LSMeans of 36 mL (95% CI: 14 to 59 mL,  $p = 0.0009$ ). Statistically significant differences between roflumilast and placebo were also found for FEV<sub>3</sub> and FEV<sub>6</sub> in the ITT analysis and for FVC in the PP analysis. Furthermore, there were statistically significant between treatment differences in favour of roflumilast observed for the parameters AEX, FEF200-1200, FEF25-75, FEF25, and FEF50.

Morning PEF showed similar improvements from baseline in both treatment groups with no statistically significant between treatment differences. The decrease in the COPD symptom score sum (and the dyspnoea, cough and sputum scores), indicating an improvement of COPD symptoms was non-significantly greater in the Rof500 group than the placebo group. The daily use of rescue medication was increased in both treatment groups with no significant difference between the two.

#### *Evaluator's comments*

The primary efficacy endpoint of post-bronchodilator FEV<sub>1</sub> showed statistically significantly greater improvement with Rof500 od compared with placebo. However, the co-primary endpoint of rate of moderate/severe exacerbations failed to show any significant difference between treatment groups. Although the study report claims that the pre-specified analysis of rate of exacerbations requiring oral glucocorticoid therapy showed that roflumilast was associated with a statistically significantly greater reduction in rate of moderate exacerbations, this was only true for the Wilcoxon rank sum analysis. The Poisson regression model analysis failed to demonstrate any significant difference between treatments in the incidence of moderate/severe exacerbations requiring oral glucocorticoid therapy.

Roflumilast showed statistically significant improvement in pre-bronchodilator FEV<sub>1</sub> and other expiratory lung function parameters showed significant improvements with roflumilast treatment. However, the key secondary endpoint of SGRQ total score failed to show any significant improvement with roflumilast. Roflumilast treatment did not have any significant effect on morning PEF, COPD symptom score and use of rescue medication. Overall, this study showed very little evidence of symptomatic improvement; the pre- and post-bronchodilator FEV<sub>1</sub> did show significant improvements with roflumilast over placebo, although these appeared to be driven by reductions in placebo group rather than any significant increase in the roflumilast group.

#### **Six month studies**

Studies M2-127 and M2-128 were randomized, double blind, 24 week studies, comparing the benefit of roflumilast (500 µg od) in 1676 patients with moderate to severe COPD when added to maintenance treatment with long acting bronchodilators, either salmeterol (50 µg twice daily in M2-127) or tiotropium (18 µg od in M2-128). On this background of long acting bronchodilator therapy, patients were randomized to receive roflumilast or placebo. The duration of the double blind treatment period was 24 weeks after a single blind run-in phase of 4 weeks in duration. The main focus of these studies was to evaluate

if roflumilast adds additional benefit on lung function beyond the effects of long acting bronchodilators. These studies included patients with moderate as well as severe COPD (FEV<sub>1</sub> of 40-70% predicted) and were not required to have a history of chronic bronchitis with sputum production and/or COPD exacerbations. Patients were required to be current or former smokers with a smoking history of at least 10 pack years, have a post-bronchodilator FEV<sub>1</sub> % predicted between 40 and 70%, and an FEV<sub>1</sub>/FVC ratio of <70%.

In Study M2-128 patients were additionally required to present with chronic bronchitis at study enrolment. To be eligible for randomization, patients were required to use  $\geq$ 28 puffs rescue medication during the week preceding randomization in study M2-128. Rescue medication (salbutamol) was allowed on an as needed basis during the entire run-in and treatment period. Other COPD treatment with the exception of the underlying long acting bronchodilators had to be withdrawn prior to study start. Concomitant systemic glucocorticosteroids were only allowed for the treatment of exacerbations; ICS were not allowed during the treatment period.

#### *Evaluator's Comments*

Although LABA combined with ICS is a commonly used therapeutic option in treatment of COPD, these studies prohibited use of ICS which seemed to imply that roflumilast could be used instead of ICS as add-on to bronchodilator therapy in the treatment of COPD.

The primary endpoint was the change in pre-bronchodilator FEV<sub>1</sub> from baseline to end of treatment in both studies. The primary endpoint, mean change in pre-bronchodilator FEV<sub>1</sub> from baseline (V2) to each post-randomization visit during the treatment period, was analysed using a repeated measurements ANCOVA model including treatment, baseline value, age, sex, smoking status, country and time, as well as a treatment by time interaction. Using the primary analysis model of the repeated measurements ANCOVA, the sample size had 90% power to detect a difference of 50 mL (SD=240 mL) in pre-bronchodilator FEV<sub>1</sub> (with a one-sided significance level of 2.5% or 2-sided of 5%).

Key secondary endpoints included COPD exacerbations (mild, moderate or severe), the TDI focal score, and the Shortness of Breath Questionnaire (SOBQ) in Study M2-127, and post-bronchodilator FEV<sub>1</sub> and moderate or severe exacerbations in Study M2-128. Secondary endpoints in both studies included a variety of further lung function endpoints, further exacerbation analyses, TDI (component scores), symptom score, use of rescue medication, and CRP, as well as SOBQ and TDI focal score in Study M2-128.

A total of 1,679 patients were included in the supportive 6 month studies M2-127 and M2-128 and treatment discontinuation was higher in study M2-127 (18% to 23%) as compared to study M2-128 (11% to 17%) with higher incidence in the roflumilast than in the placebo group. Adverse events as reason for discontinuation were also reported by more roflumilast treated patients compared with placebo patients in study M2-127 (Rof: vs placebo: 16.5% vs 9.6%) and in study M2-128 (8.9% vs 5.4%). However, discontinuation due to a COPD exacerbation was more common in placebo treated patients in study M2-127 (Rof vs placebo: 3% vs 6%) and in study M2-128 (1% vs 2%).

Demographic characteristics were comparable in the two treatment groups in each of the two individual studies. Patients were between 40 and 91 years old with a median age of 65 years in both studies, the proportion of patients being older than 65 years was between 47% and 49%. The majority of patients (64% to 72%) were male and Caucasian (>95%) and the mean body mass index (BMI) was 27 kg/m<sup>2</sup> or 28 kg/m<sup>2</sup>, indicating overweight patients. Baseline lung function was well comparable in both treatment groups and across both studies. Pre-bronchodilator FEV<sub>1</sub> was 1.4 or 1.5 L corresponding to mean % predicted values of 47% to 49%. Post-bronchodilator FEV<sub>1</sub> was 1.5 L or 1.6 L



corresponding to mean % predicted values of 50% or 51%, indicating patients with moderate to severe COPD, as requested by the protocol. Reversibility was 6% in both studies. About 30-35% had severe COPD and 65-70% had moderate COPD in study M2-127. Study M2-128 also involved patients with similar baseline demographics and disease severity.

Previous respiratory medication used within the 4 weeks prior to study entry was comparable between roflumilast and placebo groups. Between individual studies, previous respiratory medication was comparable in frequency for short acting  $\beta$ 2-agonists (SABAs) (49% to 62%), combination of  $\beta$ 2-agonists and short acting muscarinic agonists or short acting anticholinergics (SAMAs) (14% to 20%), as well as for combinations of corticosteroids and LABAs (39% to 41%). SAMAs, LABAs and ICS were more frequently reported by patients in study M2-127 compared to patients in study M2-128. Intake of tiotropium for at least 3 months prior study to entry was an inclusion criterion in study M2-128 but not study M2-127, and almost all patients in Study M2-128 reported a long acting anticholinergic as previous medication while only about 35% of patients in study M2-127 reported such medication. Concomitant medication was comparable in nature and frequency in both treatment groups and across studies. The most frequently used medication were short acting  $\beta$ 2-agonists, taken by almost all patients, followed by corticosteroids (14% to 22% of patients). Other medications were only rarely used in both studies.

### **Study M2-127**

This study was conducted at 135 centres in Austria (11), Belgium (14), Canada (25), Germany (16), Spain (12), France (13), UK (14), Italy (8), Netherlands (10) and South Africa (12) from 28 April 2006 to 3 July 2007. The FAS included 933 patients (placebo: 467, Rof: 466). The median age was 65 years, 618 patients (66%) were male, and the mean % predicted post-bronchodilator FEV<sub>1</sub> was 55% in both groups. The mean exposure to study drug was 153 and 142 days for the placebo and roflumilast group, respectively. Treatment compliance was 94-96%. The incidence of protocol violations was similar in both groups (Rof vs placebo: 22.9% vs 21.2%)

Roflumilast given to patients on salmeterol maintenance treatment significantly increased the pre-bronchodilator FEV<sub>1</sub> (primary endpoint) by 49 mL as compared to placebo (95% CI: 27, 71 mL, 2-sided p-value = <0.0001). The difference in FEV<sub>1</sub> between treatments was statistically significantly in favour of roflumilast over placebo at each of the study visits during the 24 week treatment period.

The rate of COPD exacerbations (mild, moderate, or severe) was lower for roflumilast (1.9) than placebo (2.4) with a reduction of 20.7% for roflumilast in the ITT analysis. However, the ratio of the exacerbation rates was not statistically significant (Rof/placebo rate ratio: 0.79, 95% CI: 0.58, 1.08; p = 0.1408, 2-sided). A *post hoc* analysis showed that the rate of 'moderate or severe' exacerbations was significantly reduced by 36.8% (p = 0.0315, 2-sided), although separate categories of mild, moderate or severe failed to show significant difference between treatment groups. Analysis of proportion of patients experiencing at least one COPD exacerbation showed reduced risk with roflumilast compared with placebo for all categories of COPD exacerbations except 'mild' and 'severe'. There were no observed treatment differences for the key secondary endpoints TDI focal score and SOBQ.

Post-bronchodilator FEV<sub>1</sub> improved for both groups during the treatment period, but with statistically significantly greater improvement in the roflumilast group compared with placebo (LSMean of roflumilast – placebo: 60 mL, 95% CI: 38, 82 mL, one-sided p-value <0.0001, ITT) and at all other visits during the 24 week treatment period. The other pre-

bronchodilator and post-bronchodilator lung function parameters also showed favourable results for roflumilast. The time to onset of a 'moderate' or 'moderate/severe' exacerbation was delayed for roflumilast compared to placebo with a hazards ratio of 0.6 each ( $p < 0.02$ , 2-sided). There were neither substantial nor clinically meaningful differences between treatments for all other secondary endpoints including TDI component scores, COPD symptom scores or use of rescue medication. There was significantly increased risk of withdrawal due to AE in the roflumilast group although withdrawal due to COPD exacerbation was similar in both groups.

### **Study M2-128**

The study was conducted at 85 centres in Austria (4), France/ United Kingdom (33), Germany (17), Hungary (11), and Italy/ Spain (20) from 5 January 2007 to 31 January 2008. The sample size of 350 patients per treatment group provided power of approximately 90% assuming a between treatment difference of 50 mL (SD=230 mL) in the primary endpoint (mean change in pre-bronchodilator FEV<sub>1</sub> from baseline over 24 weeks of treatment) using the repeated measurements ANCOVA model with a two sided significance level of 5.0% (equivalent to a one sided significance level of 2.5%). The incidence of protocol violations was similar in both treatment groups (Rof vs placebo: 18.3% vs 18.8%) and treatment compliance was 96% in both groups. The FAS included 743 patients (placebo: 372, Rof: 371). The median age was 65 years, 529 patients (71%) were male, and the mean % predicted post-bronchodilator FEV<sub>1</sub> was 56% in both treatment groups. The mean exposure to study drug was 158 and 150 days for the placebo and roflumilast group, respectively.

Compared with placebo, roflumilast given to patients on a background of tiotropium maintenance treatment significantly increased pre-bronchodilator FEV<sub>1</sub> by 80 mL (primary endpoint,  $p = 0.0001$ , 2-sided) in the ITT and 76 mL in the PP analysis. This was confirmed in the LOCF analysis which showed a statistically significant difference in pre-bronchodilator FEV<sub>1</sub> between treatments in favour of roflumilast compared with placebo (LSMean: 110 mL, 95% CI: 69, 150 mL, 2-sided  $p$ -value  $< 0.0001$ , ITT), confirming the repeated measurements analysis. The post-bronchodilator FEV<sub>1</sub> also showed a statistically significant improvement over placebo of 81 mL (key secondary endpoint,  $p = 0.0001$ , 2-sided). The pre- and post-bronchodilator FEV<sub>1</sub> was significantly greater with roflumilast compared with placebo at all visits during the 24 week treatment period.

Although the rate of moderate or severe exacerbations (key-secondary endpoint) was reduced by 23.2% with roflumilast compared to placebo, the difference was not statistically significant ( $p = 0.1957$ , 2-sided). The rate of COPD exacerbations for all severity grades combined (mild, moderate, or severe) was lower among patients treated with roflumilast (1.8) than among those treated with placebo (2.2) although the difference was not statistically significant (rate ratio: 0.835, 95% CI: 0.568, 1.227; 2-sided  $p$ -value = 0.3573). The proportion of patients with COPD exacerbations (mild, moderate or severe) was statistically significantly reduced for roflumilast compared to placebo, although it appears that this was driven mainly by significant reduction in the 'mild' group only (with no significant difference between groups for moderate or severe exacerbations).

Improvements in all secondary lung function endpoints were larger in roflumilast than in placebo treated patients. There were no significant differences between roflumilast and placebo groups for the other secondary endpoints of TDI, SOBQ and COPD symptom scores. The sponsor indicated that this interpretation was incorrect. Roflumilast has shown a statistical significant benefit in the secondary endpoints for dyspnoea as assessed by BDI/TDI and SOBQ. Roflumilast showed statistically significant greater reduction in use of rescue medication compared to placebo. There was a significantly increased risk of

withdrawal due to AE in the roflumilast group, although the risk of withdrawal due to COPD exacerbation was non-significantly lower in the roflumilast group.

## **Supportive studies**

### ***Effect of withdrawal- study FK1 103***

Study FK1 103 was a randomized, double blind, 24 week study, comparing Rof500 od with placebo in 581 patients with COPD. In addition, the study evaluated the effects of roflumilast withdrawal, that is, patients received roflumilast for 12 weeks followed by treatment with placebo for an additional 12 weeks (Rof-pbo). Hence, there were 3 treatment groups: Rof 500 (n=200); Rof 500/placebo (n =195) and placebo (n=186). Primary endpoints were the changes from baseline to end of treatment in post-bronchodilator FEV<sub>1</sub> and SGRQ total score. Compared to placebo, 24 weeks treatment with Rof500 od increased post-bronchodilator FEV<sub>1</sub> non-significantly by 39 mL. There was no treatment effect of roflumilast on the SGRQ total score (placebo: -2.9, Rof500: -2.6). Slight, nonsignificant differences in favour of roflumilast were seen for most secondary lung function endpoints (exception PEF).

For all other endpoints there were no remarkable differences between treatment groups. In another comparison between patients who continued on roflumilast with those who were withdrawn from roflumilast treatment and received placebo for last 12 weeks, no statistically significant changes were observed in the roflumilast group (Rof 500) for the expiratory post-bronchodilator parameters. By contrast, in the withdrawal group (roflumilast/placebo), statistically significant decreases were observed for FEV<sub>1</sub>, FEV<sub>2</sub>, FEV<sub>3</sub>, and FEV<sub>25-75</sub> after withdrawal of roflumilast. The PP endpoint analysis showed similar results except for PEF, which increased slightly in the roflumilast group but decreased in the withdrawal group (roflumilast/ placebo); Although all between treatment differences were positive indicating better results in the roflumilast group, no statistically significant differences between the treatment groups were found in the ITT endpoint analysis. In the PP endpoint analysis, a statistically significant difference between the groups in favour of roflumilast was found for FEV<sub>1</sub>.

### ***Evaluator's comments***

Overall, withdrawal of roflumilast after 12 weeks of treatment led to a statistically significant decline in post-bronchodilator FEV<sub>1</sub> over a period of approximately 4 to 8 weeks (mean decline observed was 49 mL at 12 weeks); a decline was not observed in patients on continuous treatment with roflumilast. Despite withdrawal of drug, the post-bronchodilator FEV<sub>1</sub> levels in the withdrawal arm remained above placebo levels. The study duration was too short to evaluate effect of withdrawal on symptomatic endpoints such as COPD exacerbation.

### ***Effect of roflumilast on hyperinflation parameters – M2-121***

Study M2-121 was a Phase IIIb, randomized, double blind, 24 week study (conducted in 2004-2005), comparing roflumilast 500 µg od with placebo focussing primarily on parameters indicative for hyperinflation. Hyperinflation is the result of a misbalance of static forces and/or dynamic lung components, displayed by increased RV (residual volume), increased FRC (functional residual capacity) and decreased IC. Several recent clinical studies focusing on hyperinflation parameters indicated a high correlation of those parameters to patient focused outcomes.<sup>67,68,69</sup> The main inclusion criteria for this study

<sup>67</sup> O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation and endurance during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158:1557–65.

<sup>68</sup> Newton MF, O'Donnell D, Forkert L. Response of lung volumes to inhaled salbutamol in a large population of patients with severe hyperinflation. *Chest* 2002;121:1042–50.

were a history of COPD for at least 12 months as defined by the GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria 2003; age  $\geq 40$  years; FEV<sub>1</sub>/FVC ratio (post-bronchodilator)  $\leq 70\%$ ; FEV<sub>1</sub> (post-bronchodilator)  $\leq 65\%$  of predicted; FRC (post-bronchodilator)  $\geq 120\%$  of predicted and clinically stable COPD disease within 4 weeks prior to baseline. Primary endpoints were the change from baseline to end of treatment in post-bronchodilator FEV<sub>1</sub> and change from baseline to end of treatment in post-bronchodilator FRC as measured by body plethysmography (FRC<sub>pl</sub>). The TDI focal score and the residual volume (RV) were defined as key secondary endpoints. Additional secondary endpoints included a variety of lung function endpoints from spirometry as well as body plethysmography, pulse oximeter oxygen (SpO<sub>2</sub>) saturation, TDI (other than focal score), clinical COPD questionnaire (CCQ), and exacerbations.

The FAS included 600 patients (placebo: 299, Rof: 301). The median age was 65 years in both treatment groups, 448 patients (75%) were male, and the mean % predicted post-bronchodilator FEV<sub>1</sub> was 47% (placebo group) and 46% (roflumilast group). The mean post-bronchodilator FEV<sub>1</sub> at baseline was 1.3 L. The mean exposure to study drug was 146 and 135 days for the placebo and roflumilast group, respectively. Roflumilast treatment significantly increased the primary endpoint post-bronchodilator FEV<sub>1</sub> with a between treatment difference of 36 mL, favouring roflumilast ( $p = 0.0061$ ). A non-significant between-treatment difference of 37 mL in favour of placebo was seen for the second primary endpoint FRC.

For the key secondary endpoints, there was no significant change in TDI or small, non-significant improvements in RV in favour of roflumilast. Results of secondary lung function endpoints showed small improvements in favour of roflumilast reaching statistical significance for pre- and post-bronchodilator FEV<sub>1</sub>/FVC and SVC, as well as pre-bronchodilator FEV<sub>1</sub>, FVC, FEF<sub>25-75</sub>, RV/TLC, and SVC.15. No clinically relevant improvements in CCQ were seen and there were no differences in the rate of exacerbations between treatment groups. The time to onset of first steroid treated moderate or severe exacerbation was 61 days in the placebo and 67 days in the roflumilast group.

### **Clinical studies in special populations**

Subgroup analyses were performed to assess the consistency of treatment effects across subpopulations defined by gender, age, race, disease severity, geographic region, smoking status, disease characteristics, concomitant SAMAs, concomitant ICS, concomitant LABAs, and pre-treatment with ICS. Subgroup analyses were only performed if at least 25 patients were within the respective strata. All subgroup analyses were performed in an exploratory manner. Therefore, no adjustment for multiplicity of the significance level  $\alpha=0.05$  was needed. Subgroup analyses were performed on the integrated ITT analysis for change in pre-bronchodilator FEV<sub>1</sub> in the following 4 groups: (i) the pivotal studies pool, (ii) M2-111 and M2-112 studies pool, (iii) 1 year studies pool and (iv) the 6 month studies pool; all the above study pools except the 6-month study pool were used for analysis of moderate/severe exacerbation rates.

#### ***Effect of gender, age and race***

In both male and female patients, fewer moderate/severe exacerbations occurred in the roflumilast compared to the placebo group; however, the treatment effect of roflumilast was lower in female (% change: -5.7 to -12.0) compared to male patients (% change: -18.7 to -19.7). Between treatment differences in pre-bronchodilator FEV<sub>1</sub> were in favour of

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<sup>69</sup> Celli B, ZuWallack R, Wang S, Kesten S Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes Chest 2003;124:1743-8.

roflumilast in both male and female patients in all four integrated analyses. Compared to placebo, the treatment effect of roflumilast was lower in female (between treatment difference: 19 mL to 59 mL) compared to male patients (57 mL to 68 mL). In both age groups ( $\leq 65$  years and  $> 65$  years), results were in favour of roflumilast with fewer moderate or severe exacerbations in the roflumilast compared with placebo group in all three integrated analyses. In the M2-111+M2-112 studies pool, the treatment effects were comparable in both subgroups. In the pivotal studies and 1 year studies pool, the treatment effect of roflumilast tended to be higher in patients older than 65 years (% change: -19.7 to -21.2) compared to younger patients (% change: -15.3 to -15.7). Between treatment differences in pre-bronchodilator FEV<sub>1</sub> were in favour of roflumilast in both age subgroups and in all four integrated analyses. The difference between roflumilast and placebo was comparable between subgroups and was about 50 mL in the pivotal, M2-111+M2-112, and 1 year studies pool and about 65 mL in the 6 month studies pool.

A meaningful comparison by race for moderate or severe exacerbations and FEV<sub>1</sub> was only possible for Asians and Caucasians in the pivotal studies pool. In both subgroups, roflumilast provided a better control of moderate or severe exacerbations than placebo with a more pronounced treatment effect of roflumilast in Whites. For other subgroups and integrated analyses, there were either too few patients for any meaningful comparison or the model used could not calculate estimates. For both subgroups and integrated analyses, the treatment differences between roflumilast and placebo for pre-bronchodilator FEV<sub>1</sub> were consistently in favour of roflumilast. A slightly more pronounced treatment effect of roflumilast was observed in Whites (treatment differences of 49 mL to 66 mL) compared to Asians (treatment differences of 38 mL to 40 mL).

### ***Disease severity***

In all subgroups based on COPD severity and all integrated analyses, roflumilast provided better control of moderate or severe exacerbation than placebo, with the exception of moderate COPD in the pivotal studies pool. While the treatment effect of roflumilast was comparable in subgroups with severe or very severe COPD, the effect was substantially smaller in patients with moderate severity of COPD.

Independent of disease severity, the treatment differences between roflumilast and placebo for pre-bronchodilator FEV<sub>1</sub> were consistently in favour of roflumilast in all integrated analyses. In the pivotal studies pool, improvements over placebo were comparable in the subgroups of patients with moderate or severe COPD and lower in patients with very severe COPD. In the M2-111+M2-112 and 1 year studies pool, fairly comparable improvements were seen for patients with moderate or very severe COPD and larger improvements were seen in patients with severe COPD. In the 6 month studies pool, improvements were fairly comparable between all three subgroups.

### ***Geographic region***

Subgroup analyses by geographic region including North America (USA and Canada), Europe, and 'other' countries ("rest of the World", ROW) were performed for the pivotal and 1-year studies pool. In patients of all geographic regions, roflumilast provided better control of moderate/ severe exacerbations compared with placebo. The percent reduction in moderate or severe exacerbation with roflumilast vs placebo was between -11.3% and -13.2% in Europe, while in North America and ROW the percent reduction was between -20.7% to -25.8%. In all geographic regions, the between treatment differences for pre-bronchodilator FEV<sub>1</sub> were consistently in favour of roflumilast.

### ***Smoking status***

In both former and current smokers, roflumilast provided better control of moderate or severe exacerbations than placebo with a consistent reduction between -14.3% and -18.4% across subgroups and integrated analyses. Independent of smoking status (current or former smoker), the treatment differences between roflumilast and placebo for pre-bronchodilator FEV<sub>1</sub> were consistently in favour of roflumilast in all integrated analyses. The between treatment differences were fairly comparable between subgroups with a trend towards larger improvements in former smokers in the pivotal, M2-111+M2-112, and the 1 year studies pool. In the 6 month studies pool, a trend towards larger improvements was observed in current smokers.

### ***Disease characteristics***

Disease characteristics ('emphysema only' or 'bronchitis with or without emphysema', the latter referred to as 'bronchitis' in this analysis) were not collected in the 6 month studies. In the pivotal studies, patients with emphysema were excluded. Thus, subgroup analyses by disease characteristics were performed only for the M2-111+M2-112 studies pool and the 1 year studies pool. A reduction of -1.1% to -3.2% for moderate or severe exacerbations with roflumilast treatment was observed in patients with "emphysema only", while in those diagnosed with 'bronchitis' (which is the target population for roflumilast), the reduction was -20.3% to -26.2%. In both subgroups ('emphysema only' and 'bronchitis' patients), the treatment differences between roflumilast and placebo for pre-bronchodilator FEV<sub>1</sub> were consistently in favour of roflumilast. The treatment effects of roflumilast on pre-bronchodilator FEV<sub>1</sub> in patients with "emphysema only" were 60 mL to 61 mL compared to 46 mL to 48 mL in patients with 'bronchitis'.

### ***Concomitant short acting anticholinergics***

SAMAs were allowed in most of the studies. Studies M2-127 and M-128 did not allow such medication and in the two pivotal studies, patients receiving LABAs were not allowed to take SAMAs. Study M2-128 was explicitly performed to evaluate the effect of roflumilast in patients who were concomitantly on maintenance treatment with long acting anticholinergics (tiotropium). The rate of moderate or severe exacerbations was generally better controlled with roflumilast as compared to placebo in both subgroups based on concomitant SAMA use and in all three integrated analyses. Comparing the treatment effects between subgroups, there was no consistent trend in the integrated analyses. The treatment effect tended to be larger in patients 'not taking SAMAs' in the pivotal studies pool, while it was substantially larger in patients 'taking SAMAs' in the M2-111+M2-112 pool, and it was comparable between subgroups in the 1 year studies pool. Independent of concomitant SAMA use, the difference between roflumilast and placebo treatment for pre-bronchodilator FEV<sub>1</sub> was in favour of roflumilast in all integrated analyses. The between treatment differences were fairly comparable between subgroups ranging from 42 mL to 66 mL. In the M2-111+M2-112 pool, the treatment effect of roflumilast appeared larger in patients without concomitant SAMA use (65 mL) compared to those using concomitant SAMAs (42 mL).

### ***Concomitant ICS use***

Concomitant ICS were only allowed in Studies M2-111 and M2-112 and therefore the corresponding subgroup analysis was performed for the M2-111+M2-112 studies pool only. The treatment effect of roflumilast on the rate of moderate or severe exacerbation was larger in patients concomitantly treated with ICS than in patients not using ICS (-18.8% vs -7.7% reduction). There were no relevant differences in the treatment effect of roflumilast compared to placebo on pre-bronchodilator FEV<sub>1</sub> in the two subpopulations. In particular, treatment difference between roflumilast and placebo in pre-bronchodilator

FEV<sub>1</sub> was +53 mL and +49 mL in patients with or without concomitant ICS treatment, respectively. Pre-treatment with ICS was analysed in the pivotal studies pool only. The patients in the pivotal studies did not take ICS during the study. Independent of ICS pre-treatment, roflumilast provided better control of moderate or severe exacerbation than placebo. The treatment effects were comparable in the two subpopulations based on ICS pre-treatment. Moderate or severe exacerbations were reduced by 19.3% or 16.8% in patients with or without ICS pre-treatment, respectively. Treatment difference between roflumilast and placebo in pre-bronchodilator FEV<sub>1</sub> was +47 and +49 mL in patients with or without ICS pre-treatment, respectively.

### ***Concomitant inhaled long acting beta-agonists***

Concomitant LABAs were only allowed in the pivotal Studies M2-124 and M2-125 and the corresponding subgroup analysis was therefore performed for the pivotal studies pool only. Independent of LABA treatment, roflumilast provided better control of moderate or severe exacerbations than placebo. The reduction of moderate or severe exacerbations with roflumilast compared to placebo was higher in patients on concomitant LABAs (-20.7%) than in patients not using concomitant LABAs (-14.6%). There were no differences in the treatment effects of roflumilast on pre-bronchodilator FEV<sub>1</sub> in the two subpopulations based on concomitant LABA treatment. In particular, roflumilast increased pre-bronchodilator FEV<sub>1</sub> vs placebo by 46 mL and 50 mL in patients with or without concomitant LABA treatment, respectively.

### **Analysis performed across trials (pooled analyses and meta-analysis)**

For integrated analyses and for subgroup analyses, the studies were pooled based on study design, treatment duration, and patient population. Integrated analyses and re-analyses were performed only for the comparison of Rof500 vs placebo. The roflumilast 250 µg dose and the withdrawal arm of Study FK1 103 were not included in the integrated analyses.

### ***Pivotal studies integrated analysis***

A total of 3,096 patients were included and randomized in the two pivotal studies. The protocols for Studies M2-124 and M2-125 were identical. The percentage of patients discontinuing prematurely (around 30%) was comparable between treatment groups, both within the individual studies, and among studies and within the pooled analysis. No major differences in nature or frequency of previous respiratory medication were observed between patients in either treatment group or between studies and the pooled analysis. The most frequently used previous medications were short acting β<sub>2</sub>-agonists (SABAs, documented for 60% to 66% of patients) followed by inhaled combinations of corticosteroids and LABAs (34% to 44% of patients).

Compared with placebo, the annual rate of moderate or severe exacerbations was significantly reduced with roflumilast by 14.9% in Study M2-124 and 18.5% in Study M2-125. A substantial reduction was also seen for severe exacerbations, for moderate exacerbations, and those exacerbations characterized by systemic steroid and/or antibiotic use, demonstrating robust results within and across both studies. The negative binomial regression model also demonstrated a significant reduction in the number of moderate or severe exacerbations with roflumilast versus placebo of -15.0% (M2-124) and -18.5% (M2-125), confirming results of the Poisson regression model described above. The NNT to avoid one moderate or severe exacerbation per patient per year was 5.3 (M2-124) and 3.6 (M2-125). The hazards ratio for time to first moderate or severe exacerbation was 0.88 (M2-124) and 0.89 (M2-125) in favour of roflumilast. For the time to second moderate or severe exacerbation an even lower hazards ratio of 0.79 in favour of roflumilast in both studies was observed.

The duration of exacerbations was summarized in two different ways: the number of exacerbation days per patient and the average duration of exacerbations per patient. The latter is identical to the number of exacerbation days in case the patient experienced only one exacerbation otherwise this reflects the average duration of any exacerbation a patient experienced during the treatment period. The median number of (moderate or severe) exacerbation days experienced by patients in the roflumilast arms was 19 or 20 days vs 21 or 22 days in the placebo group across studies and the pooled analysis. Thus, patients in the roflumilast group experienced a moderate or severe exacerbation on fewer days (2 to 3 days less) than patients treated with placebo. The median duration of each moderate or severe exacerbation was comparable among treatment groups in the two studies and the pooled analysis and was 10 or 11 days. Treatment effects with roflumilast were independent of concomitant LABA treatment in both studies, that is, results in patients with or without concomitant use of LABAs were similar for both primary endpoints.

Beneficial effects of roflumilast on the key secondary endpoints, post-bronchodilator FEV<sub>1</sub> and the TDI focal score were also seen in both studies. There were no apparent differences between treatments for mortality due to any reason and CRP. Superiority of roflumilast over placebo with ( $p < 0.05$ , 2-sided) was shown for all (M2-125) or most (M2-124) secondary lung function endpoints (pre- and post-bronchodilator FVC, FEF<sub>25-75</sub>, FEV<sub>3</sub>, FEV<sub>6</sub>, FEV<sub>1</sub>/FVC, FEV<sub>1</sub>/FEV<sub>6</sub>, PEF). Roflumilast was superior ( $p < 0.05$ , 2-sided) for all TDI component scores in both studies and use of rescue medication in Study M2-125. Time to study withdrawal tended to be shorter in roflumilast treated than placebo treated patients in both studies. No apparent differences between treatments were observed for mortality due to COPD exacerbation, symptom scores, or the EuroQoL in both studies, as well as for use of rescue medication in Study M2-124.

### ***One year studies pool***

A total of 2,690 patients were included and randomized in the supportive 1 year studies M2-111 and M2-112. The percentage of patients reporting an AE as reason for discontinuation was generally higher in the roflumilast (14% to 20%) compared to the placebo group (7% to 11%). Discontinuation due to an exacerbation was comparable between treatment groups and was reported for 4% to 6% of roflumilast recipients and for 3% to 6% of placebo recipients. Baseline lung function was comparable in both treatment groups. The majority of patients had severe (63-68%) or very severe (23-28%) COPD.

Although excluded by the protocols, there was a limited number of patients with mild (<1%) or moderate (6% to 11%) COPD in both studies, as the disease severity for inclusion was only assessed at study start and not re-confirmed at randomization. Concomitant respiratory medication in nature and frequency was well comparable in both treatment groups in both individual studies and pooled analyses and fairly comparable across studies and pooled analyses with exception of inhaled SABAs, which were allowed as rescue medication and were used by around 95% of patients in Study M2-111 (>96%), while only around 15% of patients in Study M2-112 used such medication.

### ***Results***

Compared to placebo, roflumilast reduced the rate of moderate or severe exacerbations by 14.0%, 15.2%, and 14.3% in Study M2-111, Study M2-112, and the integrated analysis, respectively. Results of Studies M2-111 and M2-112 were also comparable to those observed in the 1 year studies pool and pivotal studies. The largest effect of roflumilast treatment was observed on mild exacerbations in Study M2-111 (-24.2%) and moderate exacerbations in Study M2-112 (-19.4%). Results of Studies M2-111 and M2-112 were also



comparable to those observed in the pivotal studies and 1 year studies pool with exception of severe exacerbations, for which there was a larger treatment effect of roflumilast in the pivotal studies (pooled -18.1%) compared to Studies M2-111 and M2-112 (pooled: 2.2%). The proportion of patients with exacerbations, the time to first exacerbation, exacerbation duration, and number of exacerbation days in the integrated 1 year studies were similar to those observed for the pivotal studies.

Pre-bronchodilator FEV<sub>1</sub> was the primary endpoint in Study M2-111 and was included as secondary endpoint in Study M2-112 (for which post-bronchodilator FEV<sub>1</sub> was the primary endpoint). In each of the individual studies and both integrated analyses roflumilast was superior to placebo in terms of pre-bronchodilator FEV<sub>1</sub> with comparable differences of 42 mL to 57 mL. In both individual studies and integrated analyses, pre-bronchodilator FEV<sub>1</sub> decreased in the placebo and increased in the roflumilast treatment group. Post-bronchodilator FEV<sub>1</sub> was the primary endpoint in Study M2-112 and was included as key secondary endpoint in Study M2-111 (for which pre-bronchodilator FEV<sub>1</sub> was the primary endpoint roflumilast) showed superiority for roflumilast compared to placebo in each of the individual studies and both integrated analyses with differences of 42 mL to 60 mL.

Results for the 6 month integrated analysis should be interpreted with caution due to different study designs, patient populations and efficacy endpoints used in the individual studies.

#### **Evaluator's overall conclusions on clinical efficacy**

Over 6500 patients with COPD were evaluated in 18 Phase II and III studies. While generally similar in design, there were some notable differences between the Phase III studies. Studies M2-111 and M2-112 evaluated a broad population of patients with severe COPD while M2-124 and M2-125 required patients to have recent histories of chronic bronchitis (cough and sputum production) and COPD exacerbations. Additionally, studies M2-124 and M2-125 allowed concomitant treatment with LABAs (50% of the patients in each study took LABAs) but prohibited the use of inhaled corticosteroids and LAMAs during the treatment period. Conversely, studies M2-111 and M2-112 allowed the use of inhaled corticosteroids however prohibited use of LABAs and LAMAs altogether. The 6 month studies evaluated efficacy of roflumilast 500 µg in patients on background therapy with salmeterol (M2-127) or tiotropium (M2-128). The differences in study design and use of concomitant medications used to treat COPD make inter-study comparisons difficult.

Both the dose ranging studies (FK-101 and M2-107) showed a trend suggesting a higher response for the 500 µg dose, compared to the 250 µg dose for the primary and most secondary lung function endpoints, although results were not as robust in study FK1 101. Statistically significant differences between the two roflumilast doses in favour of the higher dose were seen in Study M2-107 for the secondary endpoints post-bronchodilator FEV<sub>3</sub> and FEV<sub>6</sub> as well as for time to first mild, moderate or severe exacerbation. However, only the 500 µg dose of roflumilast was associated with reduction in incidence of COPD exacerbations and 250 µg roflumilast failed to show any improvement over placebo for clinical endpoints such as SGRQ, exacerbations, symptom score and use of rescue medication. The 500 µg dose was selected as the optimal dose for further clinical development by the sponsor, although data supporting this was equivocal; based on the general lack of separation in efficacy parameters between the 250 and 500 µg doses, dose selection for the roflumilast program appears to have been arrived at by selection of the maximally tolerated dose.

It should be noted that in no study was the efficacy of roflumilast evaluated compared to what has become standard of care treatment for patients with COPD, concomitant use of a

LAMA and an inhaled corticosteroid in combination with a LABA. In the pivotal studies, prevalent use of prohibited COPD drugs (ICS and inhaled combinations of ICS and LABA by almost 10-11% of patients in each treatment group) suggested that patients in these studies were under-treated.

The year long studies (M2-124, M2-125, M2-111, and M2-112) were specifically designed to assess the effect of roflumilast on the rate of COPD exacerbations. The definition of an exacerbation in Study M2-112 differed slightly from the other 3 studies as it included exacerbations requiring antibiotics treatment (moderate) and exacerbations leading to death were added post-protocol (severe).

The first two studies of one year duration (M2-111 and M2-112) failed to demonstrate a statistically significant reduction in the rate of moderate or severe exacerbations. Although both studies did show significant improvement in pre-bronchodilator FEV<sub>1</sub>, the effects were not maintained after Week 20 in this patient population. The sponsor noted that this was incorrect: the primary analysis (repeated measures) showed significant results for all visits. These earlier trials used GOLD rather than ATS/ERS definition for COPD and included COPD patients with both chronic bronchitis and emphysema. It should be noted that the study population in M2-111 had more reversibility than M2-112 and other trials discussed above (approximately 160 mL in M2-111 versus ≤100 mL in others). *Post hoc* analyses were then used to define a more responsive patient population (those with chronic bronchitis and a history of cough, sputum production, and recent exacerbations) which was carried forth in the year long studies designated as pivotal (M2-124 and M2-125)

The pivotal studies presented in this application used lung function (pre-bronchodilator FEV<sub>1</sub>) and a symptomatic benefit endpoint (rate of COPD exacerbations) as primary endpoints, which complied with regulatory guidance. Airflow limitation in COPD is usually progressive over time and the amount of observed COPD exacerbations also varies during the seasons of the year; hence, the study duration of one year was considered appropriate. The intervention driven type of definition for 'exacerbations' raises concerns because the decision to intervene may be a subjective decision by a health care provider that can vary depending on local practices. It is acknowledged that there is no consensus on definitions for exacerbations and the sponsor appears to have taken adequate precautions to gather as much information as possible.

Both pivotal studies demonstrated superiority of Rof500 treatment over placebo for both primary endpoints. Compared to placebo, roflumilast improved the pre-bronchodilator FEV<sub>1</sub> by about 39mL in study M2-124 and by 58mL in study M2-125. It should be noted that in both studies, the mean pre-bronchodilator FEV<sub>1</sub> of enrolled patients was 1 L, and therefore these changes represent a mild, mean gain in airflow of about 4 to 6% over baseline. Furthermore, the patients presented with irreversible airways obstruction (increase of 10% to 12% after inhalation of 400 µg salbutamol).

Using the Poisson regression model, the reduction in rate of moderate/severe COPD exacerbation was statistically significantly greater (by 15-18%) in the roflumilast group compared with placebo. The results were consistent and robust in study M2-125 but not so in study M2-124. Analysis according to exacerbation severity in the ITT population indicated that COPD exacerbations of all severities decreased in roflumilast groups in both trials. However, there were no statistically significant differences between treatments for severe exacerbations in either trial and for mild exacerbations in trial M2-124. The differences in moderate or severe exacerbation rate (co-primary endpoint) between roflumilast and placebo were driven by reduction in the rate of moderate exacerbations, which was based on use of systemic steroid prescribed by the investigators according to their clinical judgments.

The effect of roflumilast on improvement in pre- and post-bronchodilator FEV<sub>1</sub> was maintained throughout the 1 year study. However, similar evidence for long term maintenance of reduction of exacerbations was not unequivocal. The exacerbation analyses provided did not examine potential attenuations in treatment effect during long term treatment with roflumilast; of the four statistical models presented, the Poisson and the negative binomial models only assessed roflumilast's effect averaged over the entire course of each study, while the proportional hazards and the log rank tests only assessed times to onset of exacerbations in each study, without including all exacerbation recurrences. An analysis to examine mean number of exacerbations per patient year for each time interval, similar to those used for the FEV<sub>1</sub> analyses would help interpretation of results regarding possible attenuation of efficacy following long term roflumilast treatment.

Roflumilast efficacy results in the pivotal studies were observed independent of concomitant treatment with LABA. Results of key secondary endpoints post-bronchodilator FEV<sub>1</sub> and TDI focal score, as well as additional secondary endpoints provided some supportive evidence for efficacy of roflumilast in the studied COPD population. However, it is important to note that use of prohibited ICS (alone or in combination with LABA) and non-compliance with the study drug can confound interpretation of efficacy results and could favour roflumilast with more efficacy from steroid use and less side effects from non-compliance with roflumilast.

Both the 6 month studies (M2-127 and M2-128) demonstrated statistically significant improvements over placebo for the primary efficacy endpoint of pre-bronchodilator FEV<sub>1</sub> following treatment with Rof500 od in patients with moderate to severe COPD on a background therapy of LABA (salmeterol) or tiotropium. Similar to the results of the one year studies described above, modest increases (3-5%) in pre-bronchodilator FEV<sub>1</sub> were observed compared to placebo in both studies, 49 and 80 mL for studies M2-127 and M2-128, respectively. However, both the 6 month studies failed to show any significant improvement in any symptomatic endpoints of COPD exacerbation rate, SGRQ, SOBQ, TDI or COPD symptom score.

The sponsor indicated that this interpretation was incorrect. Roflumilast has shown a statistical significant benefit in the secondary endpoints for dyspnoea as assessed by BDI/TDI and SOBQ. Roflumilast treatment was associated with significant reduction in use of rescue medication only in study M2-128 in patients on background tiotropium treatment. Furthermore, in both studies, roflumilast treatment was associated with an increased risk of withdrawal due to AEs, although the risk of withdrawal due to COPD exacerbation was similar in roflumilast and placebo groups.

Compared with placebo, the treatment effect of roflumilast was lower in females, patients aged <65 years and Asians. In the pivotal studies pool, the reduction in rate of moderate/severe COPD exacerbations with roflumilast was comparable in the subgroups of patients with severe or very severe COPD; however, the effect was substantially smaller in patients with moderate severity of COPD. Independent of disease severity, the treatment differences between roflumilast and placebo for pre-bronchodilator FEV<sub>1</sub> were consistently in favour of roflumilast in all integrated analyses.

Smoking status and geographic region did not affect efficacy of roflumilast. Independent of concomitant SAMA, LABA or ICS use, the treatment difference between roflumilast and placebo for pre-bronchodilator FEV<sub>1</sub> and reduction of moderate/severe COPD exacerbations favoured roflumilast, although the reduction in exacerbation rate tended to be larger in roflumilast treated patients taking concomitant SAMAs, LABA and ICS.

## Safety

### Introduction

From 1996 through 2008, more than 24,000 subjects were enrolled in 114 clinical studies investigating oral roflumilast, of whom more than 14,000 were exposed to roflumilast at a variety of dose levels. Within the clinical program, the safety and tolerability of roflumilast tablets was investigated in healthy volunteers, as well as in patients with COPD and asthma, and in a limited number of patients with allergic rhinitis, arthritis and diabetes. This section of clinical safety mainly focuses on COPD, which is the proposed indication for roflumilast in this submission. Over 6500 patients with COPD were evaluated in 18 Phase II and III studies. Safety assessments conducted throughout the Phase III program included assessment of AEs, clinical laboratory studies, vital signs, physical examinations, ECGs, and 24 Holter monitoring (in a subset of patients). The majority of placebo controlled COPD and asthma studies were combined in safety analysis pools (Table 7).

**Table 7: Pooling strategy**

Indication	Group	Analysis	Studies
<b>Safety pools</b>			
COPD	Pivotal COPD studies pool	Pooled (integrated) analysis	M2-124, M2-125
COPD	COPD safety pool	Pooled (integrated) analysis	FK1 101, FK1 103 <sup>a</sup> , M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-124, M2-125, M2-127, M2-128, IN-108
COPD	COPD study duration pools:	Pooled (integrated) analysis	
	1-year studies pool		M2-111, M2-112, M2-124, M2-125
	6-month studies pool		FK1 101, FK1 103 <sup>a</sup> , M2-107, M2-110, M2-121, M2-127, M2-128
	3-month studies pool		M2-118, M2-119, IN-108
Asthma	Asthma safety pool (placebo-controlled asthma studies)	Pooled (integrated) analysis	FK1 003, FK1 004, FK1 011, FK1 020, FK1 021, FHP031, M2-012, M2-013, M2-014, M2-023

<sup>a</sup>Study FK1 103 evaluated withdrawal of 500 µg roflumilast after 12 weeks of treatment *versus* continued treatment for 24 weeks *versus* placebo in patients with COPD. Data from the withdrawal arm were not included in the pooled analysis.

During the clinical development program of roflumilast, 65 Phase I studies were completed, in which more than 1,000 healthy adult subjects were exposed to roflumilast. Single oral doses of roflumilast administered ranged from 100 to 5000 µg. The maximal tolerated dose (MTD) of roflumilast was found to be a dose of 1000 µg. In Study FHP004, a dose of roflumilast 1000 µg per day was associated with markedly more, and also more pronounced AEs as compared with the 500 µg dose. Based on that study it was decided that daily roflumilast doses of 500 µg should be investigated in the further clinical development. Most of the clinical pharmacology studies were conducted with Caucasian subjects, however, in some studies Black, Hispanic, and Japanese subjects also participated. Safety was also evaluated in special patient populations with renal impairment (500 µg) and mild/moderate hepatic impairment (250 µg). Safety and tolerability of roflumilast treatment was also compared in children and adolescents with mild to moderate bronchial asthma, as well as in young, middle aged and elderly healthy adults.

*Evaluator's comments*

It is important to note that although the pooled groups included studies with similar study design, the demographics, disease characteristics and concomitant medications were quite different for various studies included in the 'COPD safety pool' and the '1 year' and '6 month' studies pool. Only the pivotal studies pooled analysis had similar study design, patient/disease characteristics and concomitant medications.

**Patient exposure**

Over 6500 COPD patients were exposed to roflumilast in 18 phase II and III COPD trials, 5766 of the patients received at least one 500 µg dose, 797 patients received at least one 250 µg dose. Among those who received the proposed dose of 500 µg, 1232 patients were treated for ≥1 year, 1081 for 6 months to <1 year, 2081 for 3 to < 6 months and 1370 for <3 months. The total number of patients included in the 2 main study pools was: 'COPD safety pool' (N=12,054; Rof500 group N=5,766) and 'pivotal COPD studies pool' (N=3,092, Rof500 group N=1,547).

In the pivotal trials (M2-124 and M2-125), 1547 patients were treated with 500 µg of roflumilast with 721 (46%) of them treated for the full 52 week treatment period. However, in the 'COPD safety pool', only 21.4% of roflumilast treated patients were treated for >52 weeks with the majority (36.1%; 2081/5766) being treated for ≥13 to <26 weeks. In all COPD treatment duration pools, the mean exposure time per patient was also slightly higher in the placebo group than in the Rof500 od group (Table 8).

In the pivotal COPD studies and COPD 1 year studies pools, approximately 70% of patients completed the studies, while about 30% discontinued prematurely, and in both pools, slightly more Rof500 od patients discontinued than placebo patients. The demographic characteristics were generally comparable for the Rof500 od and placebo treatment groups in the pivotal COPD studies and COPD safety pools, as well as in the three COPD treatment duration pools. Across the COPD pools, the median age ranged from 61 to 65 years (35% to 45% of the patients were older than 65 years) and 39% to 48% were current smokers. With the exception of the COPD 3 month studies pool, about 70% to 75% of patients were male in each treatment group of each COPD pool. In the COPD 3 month studies pool, about 90% of the patients in each treatment group were male. The mean BMI in the pivotal COPD, COPD safety, COPD 1 year studies and 6 month studies pools ranged between 25.7 and 26.9 kg/m<sup>2</sup>, indicating a slightly overweight patient population.

Baseline disease severity was generally comparable for the Rof500 od and placebo treatment groups within the pivotal COPD studies and COPD safety pools, as well as within the COPD study duration pools. In accordance with the study design of the studies included in each COPD pool, the pivotal COPD studies and COPD 1 year studies pools included higher overall proportions of patients with very severe or severe COPD, while the remaining pools included more patients with severe or moderate COPD. As a consequence of the different study designs, inhaled LABA was more frequently used in the pivotal COPD studies pool than in the COPD safety pool, while the reverse was true for ICSs.

Table 8: patient drug exposure: pivotal COPD and COPD safety pools

Exposure to study drug	Pivotal COPD studies pool <sup>a</sup>		COPD safety pool <sup>b</sup>		
	Placebo (N=1545)	Rof500 (N=1547)	Placebo (N=5491)	Rof250 (N=797)	Rof500 (N=5766)
	n (%) <sup>c</sup>	n (%) <sup>c</sup>	n (%) <sup>c</sup>	n (%) <sup>c</sup>	n (%) <sup>c</sup>
<1 week	24 (1.6)	36 (2.3)	53 (1.0)	13 (1.6)	119 (2.1)
≥1 week to <4 weeks	48 (3.1)	90 (5.8)	162 (3.0)	23 (2.9)	370 (6.4)
≥4 weeks to <13 weeks	132 (8.5)	164 (10.6)	710 (12.9)	100 (12.5)	883 (15.3)
≥13 weeks to <26 weeks	113 (7.3)	90 (5.8)	2045 (37.2)	549 (68.9)	2081 (36.1)
≥26 weeks to <52 weeks	468 (30.3)	446 (28.8)	1167 (21.3)	112 (14.1)	1081 (18.7)
≥52 weeks	760 (49.2)	721 (46.6)	1354 (24.7)	0 (0.0)	1232 (21.4)
Mean ET per patient (days) [mean ± SD]	293.1 ± 120.6	279.9 ± 134.0	226.5 ± 119.0	148.8 ± 47.9	206.6 ± 125.8
Median ET per patient (days)	363	363	173	168	169
Total ET (patient years)	1240	1186	3405	325	3261

<sup>a</sup>Includes studies M2-124, M2-125.

<sup>b</sup>Includes studies FK1 101, FK1 103, IN-108, M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-124, M2-125, M2-127, M2-128.

<sup>c</sup>Percentages are based on N.

COPD = chronic obstructive pulmonary disease, ET = exposure time, N = number of patients in treatment group, n = number of patients with data available, Rof250 = 250 µg roflumilast once daily, Rof500 = 500 µg roflumilast once daily

Source data: [289/2008, Tables 1.3.1, 1.3.3, 2.3.1, 2.3.3]

## Adverse events

In the pivotal COPD and overall COPD studies safety pool, the overall incidence of AEs was slightly higher in the Rof500 od group than in the placebo groups; AEs judged to be treatment related (judged by the investigator) and AEs leading to study discontinuation were also more frequent under Rof500 than under placebo (Table 9). While the incidences in the System Organ Class (SOC) of *Infections and Infestations* were similar between treatment arms, the incidences of *Gastrointestinal Disorders* and AEs related to *Investigations* were higher in the Rof500 group compared to the placebo group. In contrast, *Respiratory, Thoracic and Mediastinal Disorders* occurred more frequently under placebo than under Rof500. In all treatment groups, COPD (exacerbation) was the most frequent AE, followed by diarrhoea or weight decreased in Rof500 groups and by nasopharyngitis in placebo groups (Table 10).

### Evaluator's Comments:

In the pivotal studies M2-124 and M2-125, COPD exacerbations were considered as an efficacy variable rather than an adverse reaction to the study medication. Therefore, COPD exacerbations in these studies were documented in the efficacy sections of the case report form (CRF). Only those COPD exacerbations that met the criteria for a serious adverse event (SAE) were additionally recorded in the AE section of the CRF, thus non-serious COPD exacerbations were not to be documented as AEs. This may account for the lower incidence of COPD (exacerbations) in the pivotal COPD studies pool compared to the COPD safety pool.

Table 9: Overview of frequencies of patients with AEs

	N	ET	Patients with AEs [n (%)] <sup>a</sup>				
			All AEs	AEs related to study drug	Deaths	Serious AEs	AELW
<b>Pivotal COPD studies pool</b>							
Placebo	1545	1240	963 (62.3)	73 (4.7)	40 (2.6)	336 (21.7)	177 (11.5)
Rof500	1547	1186	1040 (67.2)	225 (14.5)	42 (2.7)	301 (19.5)	219 (14.2)
<b>COPD safety pool</b>							
Placebo	5491	3405	3447 (62.8)	294 (5.4)	86 (1.6)	782 (14.2)	503 (9.2)
Rof250	797	325	484 (60.7)	52 (6.5)	7 (0.9)	57 (7.2)	71 (8.9)
Rof500	5766	3261	3873 (67.2)	1003 (17.4)	84 (1.5)	781 (13.5)	824 (14.3)
<b>COPD 1-year studies pool</b>							
Placebo	2904	2392	2052 (70.7)	186 (6.4)	72 (2.5)	600 (20.7)	313 (10.8)
Rof500	2874	2205	2121 (73.8)	510 (17.7)	65 (2.3)	564 (19.6)	454 (15.8)
<b>COPD 6-month studies pool</b>							
Placebo	2232	936	1246 (55.8)	90 (4.0)	13 (0.6)	168 (7.5)	174 (7.8)
Rof250	751	315	467 (62.2)	52 (6.9)	7 (0.9)	55 (7.3)	69 (9.2)
Rof500	2515	979	1537 (61.1)	424 (16.9)	17 (0.7)	193 (7.7)	340 (13.5)
<b>COPD 3-month studies pool</b>							
Placebo	355	77	149 (42.0)	18 (5.1)	1 (0.3)	14 (3.9)	16 (4.5)
Rof250	46	10	17 (37.0)	0 (0.0)	0 (0.0)	2 (4.3)	2 (4.3)
Rof500	377	77	215 (57.0)	69 (18.3)	2 (0.5)	24 (6.4)	30 (8.0)

<sup>a</sup>Percentages of patients with at least one event in the category.

AE = adverse event, AELW = AEs leading to study withdrawal, COPD = chronic obstructive pulmonary disease, ET = number of patient years of exposure, N = number of patients in treatment group, n = number of patients with at least one event in the category, Rof250 = 250 µg roflumilast once daily, Rof500 = 500 µg roflumilast once daily

**Table 10: Patients with frequent ( $\geq 2\%$  in any treatment group) AEs by SOC and PT: pivotal COPD studies and COPD safety pools**

System Organ Class Preferred Term (MedDRA)	Pivotal COPD studies pool		COPD safety pool		
	Placebo (N=1545) (ET=1240)	Rof500 (N=1547) (ET=1186)	Placebo (N=5491) (ET=3405)	Rof250 (N=797) (ET=325)	Rof500 (N=5766) (ET=3261)
	n (%) <sup>a</sup>	n (%) <sup>a</sup>	n (%) <sup>a</sup>	n (%) <sup>a</sup>	n (%) <sup>a</sup>
<b>All AEs</b>	<b>963 (62.3)</b>	<b>1040 (67.2)</b>	<b>3447 (62.8)</b>	<b>484 (60.7)</b>	<b>3873 (67.2)</b>
<b>Infections and infestations</b>	<b>422 (27.3)</b>	<b>424 (27.4)</b>	<b>1508 (27.5)</b>	<b>188 (23.6)</b>	<b>1492 (25.9)</b>
Nasopharyngitis	97 (6.3)	92 (5.9)	346 (6.3)	50 (6.3)	364 (6.3)
Bronchitis	64 (4.1)	56 (3.6)	192 (3.5)	25 (3.1)	177 (3.1)
Upper respiratory tract infection	59 (3.8)	49 (3.2)	234 (4.3)	32 (4.0)	219 (3.8)
Pneumonia	31 (2.0)	42 (2.7)	110 (2.0)	5 (0.6)	104 (1.8)
Influenza	38 (2.5)	39 (2.5)	132 (2.4)	16 (2.0)	145 (2.5)
<b>Gastrointestinal disorders</b>	<b>188 (12.2)</b>	<b>319 (20.6)</b>	<b>587 (10.7)</b>	<b>104 (13.0)</b>	<b>1271 (22.0)</b>
Diarrhoea	49 (3.2)	130 (8.4)	143 (2.6)	39 (4.9)	585 (10.1)
Nausea	30 (1.9)	62 (4.0)	79 (1.4)	18 (2.3)	297 (5.2)
<b>Investigations</b>	<b>181 (11.7)</b>	<b>281 (18.2)</b>	<b>584 (10.6)</b>	<b>55 (6.9)</b>	<b>811 (14.1)</b>
Weight decreased	44 (2.8)	157 (10.1)	101 (1.8)	6 (0.8)	394 (6.8)
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>327 (21.2)</b>	<b>265 (17.1)</b>	<b>1607 (29.3)</b>	<b>197 (24.7)</b>	<b>1476 (25.6)</b>
COPD <sup>b</sup>	204 (13.2)	157 (10.1)	1271 (23.1)	169 (21.2)	1142 (19.8)
Dyspnoea	28 (1.8)	28 (1.8)	120 (2.2)	18 (2.3)	84 (1.5)
<b>Musculoskeletal and connective tissue disorders</b>	<b>144 (9.3)</b>	<b>181 (11.7)</b>	<b>445 (8.1)</b>	<b>62 (7.8)</b>	<b>590 (10.2)</b>
Back pain	35 (2.3)	50 (3.2)	117 (2.1)	22 (2.8)	176 (3.1)
<b>Nervous system disorders</b>	<b>90 (5.8)</b>	<b>150 (9.7)</b>	<b>304 (5.5)</b>	<b>45 (5.6)</b>	<b>615 (10.7)</b>
Headache	25 (1.6)	51 (3.3)	110 (2.0)	28 (3.5)	266 (4.6)
Dizziness	16 (1.0)	30 (1.9)	65 (1.2)	9 (1.1)	139 (2.4)
<b>Metabolism and nutrition disorders</b>	<b>60 (3.9)</b>	<b>104 (6.7)</b>	<b>186 (3.4)</b>	<b>19 (2.4)</b>	<b>311 (5.4)</b>
Decreased appetite	7 (0.5)	36 (2.3)	22 (0.4)	4 (0.5)	125 (2.2)
<b>Psychiatric disorders</b>	<b>55 (3.6)</b>	<b>98 (6.3)</b>	<b>164 (3.0)</b>	<b>22 (2.8)</b>	<b>344 (6.0)</b>
Insomnia	20 (1.3)	37 (2.4)	50 (0.9)	11 (1.4)	148 (2.6)
<b>Vascular disorders</b>	<b>80 (5.2)</b>	<b>76 (4.9)</b>	<b>229 (4.2)</b>	<b>20 (2.5)</b>	<b>196 (3.4)</b>
Hypertension	48 (3.1)	38 (2.5)	136 (2.5)	12 (1.5)	95 (1.6)

<sup>a</sup>Percentages of patients with at least one event in the category.

<sup>b</sup>The preferred term COPD refers to COPD exacerbation. Note, in the pivotal COPD studies only COPD exacerbations fulfilling the criterion of a serious AE were to be recorded in the AE section.

AE = adverse event, COPD = chronic obstructive pulmonary disease, ET = number of patient years of exposure, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients in treatment group, n = number of patients with at least one event in the category, Rof250 = 250 µg roflumilast once daily, Rof500 = 500 µg roflumilast once daily

Compared to placebo, patients treated with Rof500 od showed higher incidence of weight decreased, diarrhoea, nausea, headache, decreased appetite, back pain, dizziness and insomnia. In contrast, the incidence of COPD (exacerbation), hypertension, bronchitis and



upper respiratory tract infection (URTI) was higher in the placebo group compared with the Rof500 group in both COPD pools. In the pivotal COPD studies pool, the incidence of pneumonia was slightly more frequent for patients in the Rof500 treatment group than in the placebo group; however, the incidence of pneumonia was balanced between the two treatment groups in the larger COPD safety pool. The incidences of the most frequent AEs in the COPD study duration pools (1 year, 6 months and 3 months) generally followed similar patterns of distribution as those observed for the aforementioned COPD pools

In both the pivotal COPD studies pool and the COPD safety pool, treatment related AEs (based on the investigator's causality assessment) occurred most frequently in the SOCs of *Gastrointestinal Disorders, Investigations, Nervous System Disorders, and Metabolism and Nutrition Disorders*. For these SOCs, the proportion of AEs was higher in the Rof500 group than in the placebo group. In the two pools, weight decreased, diarrhoea, nausea and headache were among the most frequent treatment related AEs in both treatment groups and occurred more frequently under Rof500 than placebo.

Limited dose ranging was performed in the clinical trials with only 2 doses, 250 and 500 µg once daily, being evaluated in COPD patients. While evaluation of the 250 µg dose of roflumilast was limited, there appears to be a dose dependent increase in GI, weight loss and psychiatric AEs associated with the 500 µg once daily dose of roflumilast. The prevalence of AEs, treatment related AEs, deaths, SAEs and discontinuations due to AEs was similar or slightly less in the Rof500 group compared with the placebo group.

### ***Intensity of AEs***

For approximately half of the patients with AEs in all treatment groups and COPD pools, the AEs were rated as moderate. The majority of AEs assessed as related to study medication in all treatment groups and COPD pools were mild or moderate in intensity. AEs related to *Respiratory, Thoracic and Mediastinal Disorders* and *Infections and Infestations* were generally most often reported as severe. COPD (exacerbation) was the most frequent severe AE in all roflumilast and placebo groups. Incidences of diarrhoea or nausea were usually mild or moderate in intensity.

In the pivotal COPD studies pool, apart from COPD (exacerbations), severe pneumonia was frequently documented for both treatment groups, as expected for the study population. While severe COPD (exacerbations) occurred in a larger proportion of patients in the placebo group than in the Rof500 od group (10.7% vs 8.0%), severe pneumonia occurred in a smaller proportion of patients in the placebo group than in the roflumilast group (0.9% vs 1.4%). Except for COPD (exacerbation) and pneumonia, the incidences of severe AEs were generally balanced in the Rof500 and placebo groups.

In the COPD safety pool, the incidence of most frequent 'severe AEs' was similar for the Rof500 and placebo groups, with the exception of COPD (severe exacerbation) which was more frequently reported in the placebo (6.3%) than in the Rof500 group (5.3%). The difference in the incidence of severe pneumonia was smaller (placebo: 0.8%, Rof500: 1.0%). Diarrhoea was the only severe AE occurring with a clearly higher incidence under Rof500 (0.8%) compared with placebo (<0.1%).

### ***Time to onset, duration and outcomes of AEs***

Across both COPD pools, most AEs in the Rof500 and placebo treatment groups occurred after at least 4 weeks of study treatment (between 72.4% and 87.3% of AEs). In both COPD pools, the proportions of AEs during the first 4 weeks of treatment were higher with Rof500 vs placebo, while the proportions of AEs with later onset were higher with placebo. Times to onset of AEs generally followed the same trends in the roflumilast and placebo arms of the COPD 1 year, 6 month and 3 month studies pools. In the pivotal COPD

studies pool, the time to onset for COPD (exacerbations) was longer in the Rof500 group compared with placebo, although this was not observed in the 'COPD safety pool'. In both pools, the AEs of weight decreased, diarrhoea, as well as nausea and headache were more often experienced at the beginning of the study (<4 weeks) in patients treated with Rof500 od compared to placebo treatment. In the pivotal studies M2-124 and M2-125, Kaplan-Meier estimates of frequent AEs such as nausea, diarrhoea and headache showed that the risk of experiencing the AEs was higher for patients in the Rof500 od group compared to the placebo group throughout the study; however, the risk of experiencing the event was not constant over time, but higher in the first period of the study. There was no evidence of any increasing risk over time in this analysis. In all treatment groups, the majority of AEs ( $\geq 78\%$ ) resolved during the course of the study. Similar to the overall analysis of AEs, the vast majority of treatment related AEs ( $\geq 79\%$ ) in all treatment groups in the pivotal COPD studies and COPD safety pools resolved during the course of the study.

### ***Exposure adjusted AE incidence***

The exposure time adjusted AE incidence is given by the AE incidence per 1000 patient years of exposure.<sup>70</sup> In the pivotal COPD studies and COPD safety pools, the exposure time adjusted incidences of decreased weight, diarrhoea, nausea, headache, dizziness, decreased appetite and insomnia were higher in the Rof500 group compared with placebo, while the incidences of COPD (exacerbation) and hypertension were higher in the placebo group. A higher exposure time adjusted incidence of urinary tract infection (UTI) was observed in the Rof500 group compared to the placebo group (25.3 vs 9.7 per 1000 patient years of exposure) in the pivotal COPD studies pool.

However, in the COPD safety pool, the difference between roflumilast and placebo in the incidence of UTI was smaller (22.7 vs 16.7 per 1000 patient years of exposure). In the pivotal COPD studies pool, pneumonia occurred more frequently in the Rof500 group compared with placebo (35.4 vs 25.0 per 1000 patient years of exposure). However, the incidence was similar for the COPD safety pool (31.9 vs 32.3 per 1000 patient years of exposure). Comparing the COPD 1 year, 6 month, and 3 month studies pool, a decline in exposure time adjusted overall incidence of AEs with increasing treatment duration was observed in the Rof500 group, indicating an accumulation of AEs during the first weeks of roflumilast treatment and a decline in AE rate with longer treatment duration.

### ***AEs of special interest***

#### ***Infections***

There was no difference between the overall incidence of infections in the Rof500 group compared with placebo in the pivotal COPD studies pool (27.4% vs 27.3%) or the COPD safety pool (25.9% vs 27.5%). Similarly, the overall incidence of infection AEs leading to death, SAEs, events leading to study discontinuation, or events related to the study medication, were not appreciably different between Rof500 and placebo. Some infections did occur at higher incidence rates in the roflumilast group compared with placebo, including viral URTI, acute sinusitis, UTI and gastroenteritis. On the other hand, incidence rates for several infections were lower in the roflumilast group than in the placebo group (URTIs, lower respiratory tract infections, bacterial infections, fungal infections).

In the pivotal COPD studies pool, roflumilast treated patients had a higher incidence of abdominal/gastrointestinal infections (1.4% vs 0.6%) and urinary infections (2.3% vs

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<sup>70</sup> In order to adjust for the different durations of treatment exposure in the COPD pools, AEs were also analysed on the basis of exposure time adjusted incidences: the number of patients with an event observed at least once for the respective treatment or dose was divided by the total exposure time in years of patients with the same treatment or dose and multiplied by 1000.

1.4%) compared with placebo. However, the difference between roflumilast and placebo was less in the COPD safety pool for both abdominal/gastrointestinal infections (1.1% vs 0.9%) and urinary infections (1.7% vs 1.5%). Additionally, because COPD patients are prone to pneumonia, these events were analysed separately and showed no appreciable differences between roflumilast and placebo.<sup>71</sup> In the pivotal studies pool, the overall rate of pneumonia was slightly higher in the roflumilast group (3%; 46/1547) compared with placebo (2.3%; 36/1545). In the COPD safety pool, the incidence rate of 'pneumonia of some sort' was slightly lower in the roflumilast group compared to placebo (1.9% vs 2.2%). In the COPD safety pool, there was one patient with pneumococcal sepsis and two patients with atypical pneumonia in the 500 µg roflumilast group compared with no reports in placebo. In the pivotal studies pool, there were no reports of pneumococcal sepsis or atypical pneumonia; one placebo treated patient reported pneumonia *Klebsiella* compared with none reported with roflumilast.

In the COPD safety pool, the majority of infections (61.4%) lasted between 1 and <4 weeks, less than one week (24.7%), and 4 to <13 weeks (10.4%) in the Rof500 group, with similar results observed in the placebo group (62.8% between 1 and <4 weeks, 24.1% <1 week and 9.9% between 4 to <13 weeks). Similar results were seen for the pivotal COPD studies pool. In the COPD safety pool, there was no appreciable difference in the incidence of mild (Rof vs placebo 10.7% vs 11.2%), moderate (12.9% vs 14.0%), and severe infections (2.3% vs 2.3%). A similar pattern was seen in the pivotal COPD studies pool for mild (11.2% vs 10.3%), moderate (13.6% vs 15.0%), and severe (2.6% vs 2.1%) infections.

The overall rate of infection SAEs was similar in the roflumilast and placebo groups in the pivotal studies pool (Rof vs placebo: 2.7% vs 2.6%) with similar results in the COPD studies pool (Rof vs placebo: 2% vs 2.3%). Overall, incidence of study discontinuation due to 'infections' and 'pneumonia' events was low with similar incidence between roflumilast and placebo in the pivotal studies pool [roflumilast vs placebo: infections: 0.8% and 0.8%; pneumonia, (0.3% vs 0.5%)] with similar results in the COPD safety pool ['infections' (Rof vs Placebo: 0.8% vs 1%) and 'pneumonia' (0.3% vs 0.5%)]. Overall, there was no difference in the incidence of fatal 'infections' AEs. In the COPD safety pool, 13 (0.2%) patients on Rof500 experienced a fatal event compared with 15 (0.3%) on placebo with majority of reported deaths due to pneumonia [Rof: 10 (0.2%) vs placebo: 10 (0.2%)]. Similar results were observed in the pivotal COPD studies pool, with fatal 'infections' in 6 (0.4%) of patients on Rof500 compared with 3 (0.2%) on placebo with majority due to pneumonia [4 (0.3%) vs 3 (0.2%)]. Severe systemic illness (invasive fungal infections, opportunistic bacterial and viral infections, tuberculosis) known to occur with the use of TNF-α inhibitors were not observed with roflumilast.

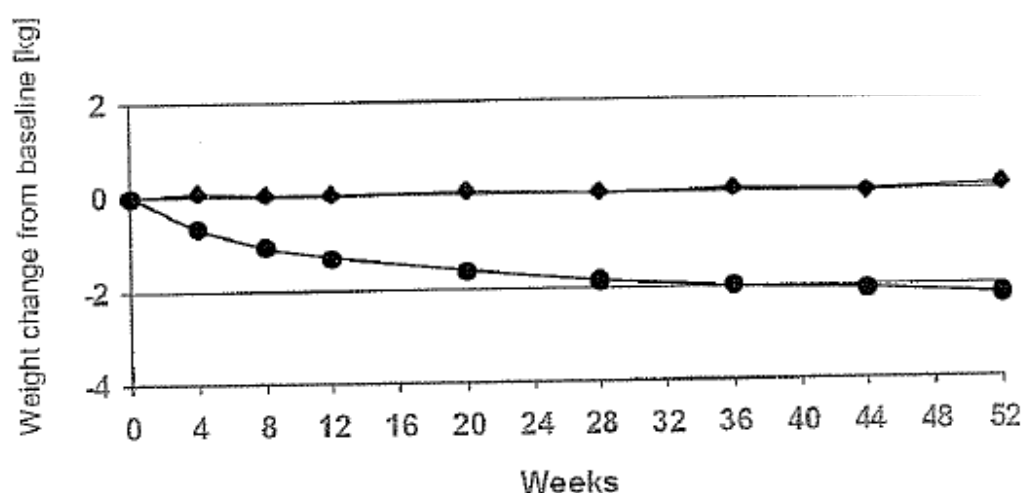
#### *Decreased weight*

In Study M2-128, bioimpedance measurements were conducted in addition to the regular weight measurements. In pivotal studies M2-124 and M2-125 as well as the 6 month studies M2-127 and M2-128, weight was evaluated at baseline and at regular intervals through the study. However, in studies M2-111 and M2-112, weight was only assessed at baseline, Week 20 and end of study. In the pivotal COPD studies pool, 62% of roflumilast treated patients lost weight during the 1 year treatment period, compared to 38% in the placebo group with similar results in the 1 year and 6 month pooled data. In the pivotal studies pool, the incidence of mild (0 to ≤5%), moderate (>5 to <10%) or severe (≥10%)

<sup>71</sup> Not all events of pneumonia were reported as 'pneumonia', but using several different terms, e.g. 'lung infections', 'bacterial infections'. Therefore, a set of terms reflecting pneumonia was selected for the analysis of pneumonia.

weight loss was much higher in the roflumilast treated patients (35.2%, 20.1% and 7.1% with mild, moderate and severe weight loss, respectively) compared with placebo (27.5%, 8.3% and 1.9%, respectively). The incidence of a clinically relevant weight decrease (defined as a decrease of >5% during first month or >10% at any visit after the first month) was also higher in the roflumilast group compared with placebo (12.2% vs 4.2%). Patients treated with roflumilast showed a statistically significantly greater mean decrease in weight from baseline compared to placebo (Rof: -2.09 kg vs Placebo: +0.08 kg; treatment difference= -2.14 kg; 95% CI: -2.40, -1.88 kg, p-value: <0.0001). The decline in mean body weight from baseline was most pronounced during the first 8 weeks of roflumilast treatment with smaller reductions from Month 6 to the end of treatment (Week 52). There was no change of mean body weight in the placebo arm over the 1 year treatment period (Figure 4).

**Figure 4: Mean changes from baseline in body weight, by time: pivotal COPD studies pool**



SAF = safety set

In the pivotal COPD studies pool, 159 patients experienced 163 AEs 'weight decrease' in the roflumilast group compared to 44 patients with 44 AEs 'weight decrease' in the placebo group. For about half of the patients in the roflumilast group (53.5%), the investigators assessed the AEs 'weight decrease' as related to study medication, compared to 40.9% in the placebo group. The majority of AEs of 'weight decrease' were of mild or moderate intensity (>98%) and only a few patients (4 patients treated with roflumilast compared to 1 patient treated with placebo) discontinued the study prematurely due to the AE 'weight decrease'. Two (0.1%) patients in the roflumilast group experienced a serious AE 'weight decrease' (none with placebo).

Patients were also analysed stratified into two categories (1) baseline BMI <20 and a weight decrease  $\geq 5\%$  from baseline to at least one post baseline visit, and (2) baseline BMI  $\geq 20$  and a weight decrease  $\geq 10\%$  from baseline to at least one post baseline visit. A total of 291 patients with either weight decrease according to category 1 or category 2 were identified. Of the 291 patients, 216 (out of 1547 patients, 14.0%) were in the roflumilast treatment group, compared to only 75 (out of 1545 patients, 4.9%) in the placebo treatment group. Analysed by category, 118 were in the first category (Rof: 81 patients [5.2%], placebo: 37 [2.4%]) and 173 in the second category (Rof: 135 patients [8.7%], placebo: 38 [2.5%]).

When splitting the pivotal COPD studies pool population by BMI categories, it was found that the number of roflumilast treated patients experiencing weight decrease was more evident in overweight patients with 47.8%, 61.2%, 62.7% and 70.3% of underweight, normal weight, overweight and obese patients experiencing weight loss. In the placebo group, the percentage of obese patients with weight decrease was also higher than the percentage of underweight patients with weight decrease. When the pivotal COPD studies pool was analysed by COPD severity, the proportions of roflumilast treated patients with mild to moderate weight decrease were similar in patients of the different COPD severity categories.

The ANCOVA analysis of measured body weight changes was used for the comparison of treatment groups adjusted for covariates. The following factors were identified for the pivotal COPD studies pool: roflumilast treatment ( $p < 0.0001$ ), age above 65 years ( $p < 0.0001$ ), presence of an AE 'weight decrease' during baseline ( $p = 0.0295$ ), and country pools Canada ( $p = 0.0116$ ) and Italy/Spain ( $p = 0.0009$ ). The risk of losing weight also seemed to be greater in females but without reaching statistical significance ( $p = 0.065$ ). The experience of either a GI AE (pivotal COPD studies pool:  $p = 0.0052$ , COPD safety pool:  $p < 0.0001$ ), or a metabolism and nutrition AE (both pools  $p < 0.0001$ ), or a psychiatric AE (pivotal COPD studies pool:  $p = 0.0101$ , COPD safety pool:  $p < 0.0001$ ) during roflumilast treatment was associated with the occurrence of the AE 'weight decrease'. There was no association between weight decrease and occurrence of COPD exacerbations in the pivotal COPD studies pool. Patients in the pivotal studies M2-124 and M2-125 and the two 6 month supporting studies M2-127 and M2-128 that had reported an AE 'weight decreased' (218 patients in the roflumilast groups and 51 patients in the placebo groups) were asked to participate in a 3 month follow up, with weight measurements done at 1 and 3 months after the end of treatment.

Overall, 126 patients from the pivotal studies (including 12 patients without AE 'weight decreased', on recommendation of the investigator) and 30 patients from the 6 month studies (including 9 patients without AE 'weight decreased') consented to take part in this follow up. In the pooled 1 year M2-124/M2-125 studies, patients in both the roflumilast and the placebo groups with Weight Decrease Follow-up Questionnaire most frequently experienced a weight gain during the follow up period (Roflumilast: 74 patients, 81.3%; placebo: 15 patients, 42.9%), after having experienced a weight decrease during the active treatment period. Within the 3 months of the follow up period, patients in the roflumilast group regained on average half of the weight they had lost during the 12 months of active treatment (mean weight decrease: 6 kg,  $N = 91$ ; mean weight gain: 3.2 kg,  $N = 90$ ). The results for roflumilast in the pooled M2-124/M2-125 studies were confirmed by the analysis of the pooled M2-127/M2-128 studies although the duration of the active treatment period was shorter (6 months) and less patients were included (mean weight decrease: 6.1 kg,  $N = 28$ ; mean weight gain: 2.8 kg,  $N = 28$ ).

#### *Bioimpedance data from study M2-128*

During all visits mean FFMI (fat free muscle mass index) remained almost constant for patients in the placebo group compared to a slight decrease in the roflumilast group (LSMean: -0.299; 95% CI: [-0.475, -0.122] vs placebo: LSMean: 0.012; 95% CI: [-0.160, 0.184]). There was a statistically significant decline in FFMI among patients receiving roflumilast compared to placebo (difference in LSMeans: -0.311, 95% CI: -0.532, -0.090,  $p$ -value: 0.0059), which occurred predominantly during the first 4 weeks of treatment tending to plateau thereafter.

*Evaluator's comments*

Overall, 62% of COPD patients treated with roflumilast had weight loss compared to only 38% of placebo treated patients. The risk of weight loss following roflumilast treatment did not appear to be increased in underweight patients or those with 'very severe' COPD. A variety of BMI phenotypes are represented and weight decrease associated with roflumilast therapy was observed in all BMI subgroups. After discontinuation of roflumilast, about 80% of patients who took part in a 3 month follow up investigation regained body weight, suggesting that weight decrease is reversible upon treatment cessation. An association between weight loss and the incidence of depression or anhedonia was not specifically evaluated.

*Cardiac AEs*

The grouping 'cardiac events of interest' were defined as AEs contained within the four MedDRA High Level Group Terms (HLGTs) of the SOC *Cardiac Disorders* listed below. These four HLGT were chosen for the conduct of the detailed analyses because they contain the majority of cardiac adverse events at the MedDRA preferred term (PT) level. HLGTs for 'cardiac events of interest' included *Cardiac arrhythmias*, *Coronary artery disorders*, *Heart failures* and *Myocardial disorders*. Individual case reports of all patients who had at least one 'cardiac adverse event leading to death' were reviewed in a blinded fashion by an external Independent Cardiovascular Adjudication Committee, comprised of three cardiologists. Individual case reports of all patients in the roflumilast treatment groups who had a supraventricular arrhythmia event ('atrial fibrillation', 'atrial flutter', or 'arrhythmia supraventricular') were reviewed by a medical expert to determine the cause of the event. Analysis of cardiac safety was based on data from the COPD safety pool, which consists of 14 clinical studies, and the pivotal COPD studies pool (M2-124 and M2-125).

In the COPD safety pool, the rate of patients with cardiac AEs of interest was slightly lower for the Rof500 than the placebo group (5.2% vs 5.7%) overall as well as for all of the adverse event subcategories: cardiac adverse events leading to death (0.4% vs 0.5%), cardiac serious adverse events (1.8% vs 2.1%), cardiac adverse events related to study medication (0.2% vs 0.3%), and cardiac adverse events leading to study discontinuation (0.9% vs 1.0%). In the pivotal COPD studies pool, the results followed a similar trend as in the COPD safety pool, with the exception of slightly higher incidence of cardiac adverse events leading to death with Rof500 (1.0% vs 0.7%). In the pivotal and COPD safety pool, the incidence of cardiac arrhythmias was slightly higher in the roflumilast group, while that of the other 3 AEs of interest were similar in roflumilast and placebo groups.

In the COPD safety pool, the intensity of cardiac AEs of interest was mild or moderate for the majority of patients on Rof500 (73.1%) or placebo (65.7%). Similar results were observed for patients in the pivotal COPD studies pool. In the COPD safety pool, the majority of events lasted between <1 week and up to 4 weeks (54.9% in the Rof500 and 55.4% in placebo group). In the roflumilast group, the event 'cardiac arrhythmia' lasted less than 1 week for 32.4% of events, compared with 19.8% of events in the placebo group. Similar results were obtained for the pivotal COPD studies pool. Kaplan- Meier analysis of time to onset of the first 'cardiac adverse event of interest' showed no notable difference within the first six months between roflumilast and the placebo groups. During the second six month period, the incidence of events was lower for the roflumilast than for the placebo group. This was observed for both the COPD safety pool and the pivotal COPD studies pool.

In the COPD safety pool, the rate of 'cardiac arrhythmias' was slightly higher in the roflumilast group than in the placebo group (3.5% vs 3.1%), especially that of 'atrial

fibrillation' (0.8%, N = 48 vs 0.6%, N = 31); this difference was more pronounced in the pivotal COPD studies pool (1.1%, N = 17 vs 0.5%, N = 7). However, review of the individual case records revealed that for more than two thirds of patients the events had identifiable comorbidities.

In the pivotal studies group, incidence of death due to cardiac AEs was slightly higher in roflumilast group compared with placebo (1% vs 0.7%), mainly due to higher incidence of cardiac arrhythmias. In the COPD safety pool, 56 patients had cardiac AEs leading to death (representing all treatment groups) with similar rate in the Rof500 and placebo group (0.4% vs 0.5%). None of these events were assessed by the investigator or the sponsor as related to treatment with study drug. Furthermore, an external independent adjudication committee review was performed in a blinded fashion of all individual case reports for patients in roflumilast and placebo treatment groups who died.

The results of the committee's review showed that of the 56 deaths, non-cardiovascular events accounted for 14 deaths (9 in the roflumilast group and 5 in the placebo group); 3 death cases in the placebo group were not assessed due to insufficient data. All cardiovascular categories of deaths were balanced between the roflumilast and placebo treatment groups, including death due to 'arrhythmia', for which a total of 3 fatal cases was established (1 patient from the Rof500 group and 2 from the placebo group).

In the COPD safety pool, there was a slightly lower rate of patients with cardiac SAEs in the Rof500 group than in the placebo group (1.8% vs 2.1%) with similar findings for the pivotal COPD group (2.3% vs 2.9%); however, the incidence of cardiac arrhythmias, especially atrial fibrillation was slightly higher in the roflumilast group. Overall, the incidence of discontinuations due to cardiac AEs was similar in the Rof500 and placebo groups (0.9% vs 1.0%); compared with placebo, patients in the roflumilast group showed slightly lower incidence of discontinuation from *Coronary artery disorders* (roflumilast vs placebo: 0.3% vs 0.5%) and *Heart failures* (0.3% vs 0.4%), but slightly higher incidence of discontinuations due to *Cardiac arrhythmias* (0.4% vs 0.2%).

#### *Tumours*

In the COPD safety pool, at least one tumour AE was documented by 170 of the 12,054 patients (overall rate: 1.4%) with a slightly higher incidence in the roflumilast treatment group compared with the placebo group (1.5% vs 1.3%). The observed tumours were mostly solid tumours (175 tumours out of 185 tumours events overall) and lung cancers constituted the largest proportion of all solid tumours (50 tumours). Haematological tumours were observed only in a small number of patients (10 tumours). None of the tumour AEs were assessed as related to the study medication by either the investigator or the sponsor and tumour AEs led to study discontinuation in 0.7% of the patients (0.8% vs 0.7%).

Furthermore, the rates of tumour AEs for patients treated with roflumilast or placebo also varied between studies. The confidence interval for the Cox proportional hazard ratio of each study indicated that any imbalance between roflumilast and placebo was not statistically significant; for example, in the two 1 year studies (M2-111 and M2-112), the rate of patients with tumours was higher for roflumilast than for placebo (2.3% vs 1.5%), whereas it was same for both treatment groups (1.9%) in both the pivotal COPD studies (M2-124 and M2-125). Of the more frequent tumour AEs (occurring in >0.1% of patients in any treatment group), 'lung cancer' and 'prostate cancer' occurred more frequently in the roflumilast treatment group than in the placebo group (0.5% vs 0.3%, and 0.2% vs 0.1%, respectively). In contrast, the rate of patients with 'other and not further specified neoplasms' (0.2% vs 0.1%) or 'other gastrointestinal neoplasms' (0.2% vs <0.1%), was higher in the placebo group than in the roflumilast group and respectively). 'Skin

neoplasms' occurred at equal rates in the roflumilast and placebo groups (0.2%). The exposure time adjusted incidence of tumour AEs was higher in patients treated with roflumilast compared with placebo (roflumilast vs placebo: 27.3 vs 21.1) with a higher incidence in the roflumilast group for 'lung cancer' (9.2 vs 5.0), 'prostate cancer' (3.9 vs 2.1), and 'colon and rectal cancer' (2.5 vs 0.6). However, the incidence of tumour AEs was lower for patients in the roflumilast compared with placebo for 'other and not further specified neoplasms' (2.2 vs 3.8) and 'other gastro-intestinal neoplasms' (1.4 vs 3.8%).

In the pivotal COPD pool, 58 of the 3,092 patients experienced at least one tumour event (29 patients in each treatment group). Of the tumour types that showed a difference in incidence of >1 patient per 1,000 patient years between the roflumilast and placebo treatment groups, higher exposure time adjusted incidences were observed in roflumilast treated patients for 'lung cancer' (roflumilast vs placebo: 9.3 vs 5.6), 'prostate cancer' (4.2 vs 1.6), and 'colon and rectal cancer' (4.2 vs 0.0). However, roflumilast treated patients showed a lower incidence of 'skin neoplasms' (0.8 vs 4.0) 'other and not further specified neoplasms' (3.4 vs 4.0), 'other gastro-intestinal neoplasms' (0.8 vs 4.0), 'neoplasms of the urinary tract' (2.5 vs 4.0), and 'gynaecologic neoplasms' (0.0 vs 2.4).

#### *Evaluator's comments*

The occurrence of tumours is largely related to the demography and morbidity of the patients, and the results discussed above suggest that tumours observed in the COPD studies with roflumilast were related to the disease/comorbidities in the target population and not to treatment with roflumilast.

#### *Mesenteric vasculitis*

Mesenteric vasculitis was discussed during an application for marketing authorization for the phosphodiesterase 4 (PDE4) inhibitor cilomilast due to nonclinical findings also seen with other PDE4 inhibitors. A thorough review and analysis of mesenteric vasculitis were performed for roflumilast, despite the fact that there were neither clinical findings with cilomilast, nor nonclinical findings with roflumilast, nor was mesenteric vasculitis recorded as an adverse drug reaction during the clinical development of roflumilast. Mesenteric vasculitis most commonly manifests itself clinically as ischaemic colitis, which occurs in about 60% of patients with gastrointestinal ischaemia.

In the COPD safety evaluation for roflumilast, ischaemic colitis was used as a representative clinical condition for mesenteric vasculitis. In five clinical studies with roflumilast (M2-124, M2-125, M2-110, M2-111, M2-023), results of systematic haemoccult testing and follow up GI investigations (colonoscopy) to detect gastrointestinal bleeding did not reveal any findings that were consistent with or indicative of ischaemic colitis. The search identified two patients with suspected ischaemic colitis (one patient receiving placebo and one patient receiving Rof500 once daily for more than 24 weeks). For the roflumilast treated patient, intestinal polypectomy performed 2 months prior to the event was identified as a likely cause of the event. The incidence of haemoccult positive tests was 1.7% (13/769) and 0.8% (6/755) in Rof500 and placebo groups, respectively in study M2-124; in study M2-125, incidence was 1.3% (10/788) and 1.3% (10/790), respectively. In study M2-110, eight subjects (4 placebo and 4 roflumilast treated subjects) had objective evidence of GI blood loss and had follow up evaluations. Of the 4 placebo treated subjects, 2 were haemoccult positive tests, 1 had a bloody bowel movement and the other had a rectal bleed. Of the 4 roflumilast treated subjects, 2 were haemoccult positive tests, 1 had blood clots in stool, and the other had rectal bleeding. Only 1 subject had event or follow up diagnoses (oesophagitis and gastritis in a roflumilast treated subject) that was considered treatment related. In study M2-111, 54 patients had at least one positive haemoccult finding during the study treatment period with slightly higher incidence in the



roflumilast treatment group (5.5%; 31/567) compared with the placebo group (3.8%; 23/606). In study M2-023, a small number of patients had positive haemoccult findings with Rof500 (4.0%; 12/302), roflumilast 250 µg (2.4%; 7/290) and placebo (3.2%; 9/283).

#### *Psychiatric AEs*

Psychiatric AEs were not specifically elicited nor actively sought. Stable patients with psychiatric illness were not excluded from the Phase III studies. However, patients who were not able to follow study procedures (language problems, psychological disorders) were excluded from the studies.

AEs related to the *Psychiatric Disorders* SOC were more common in patients who received Rof500 compared to those who received the 250 µg dose or placebo. There was a total of 403 (6%) psychiatric AEs reported in patients who received Rof500 once daily compared to 190 (3%) events in the placebo group. The incidence of insomnia, anxiety and depression related AEs in the Rof500 group were 2-3 times greater compared to those in placebo.

The occurrence of three completed suicides and two suicide attempts in COPD patients treated with roflumilast compared to no suicides/suicide attempts in patients receiving placebo was of significant concern. Of the three completed suicides, 2 were in patients receiving Rof500 and the third was in a patient receiving 250 µg. In none of the three completed suicide cases (all males) did the patient have a prior history of depression. In two of the cases the patient had reportedly discontinued roflumilast approximately 20-21 days prior to the suicide event. With regard to the suicide attempts, both females had prior psychiatric histories (depression in one patient and previous suicide attempt in the other) and both patients were receiving roflumilast at the time of the suicide attempt.

In order to assess whether the incidence of psychiatric AEs was consistent across other disease clinical development programs, *Psychiatric Disorders* AEs were reviewed for COPD studies conducted by a different sponsor in Japan and in asthma and "other" disease indications that roflumilast has been studied (diabetes, allergic rhinitis, rheumatoid arthritis and osteoarthritis). Review of these data showed an approximately twofold increase in *Psychiatric Disorders* AEs in patients receiving 500 µg of roflumilast once daily was persistent across studies in different patient populations and appears to be dose related. The types of AEs reported in these studies were consistent with those reported in the COPD population (insomnia, anxiety, depression).

#### **Serious AEs and deaths**

Deaths were infrequent with little difference observed between treatment arms and no death was considered treatment related by either the investigator or the sponsor. In the COPD safety pool, there were 177 deaths (84, 7 and 86 in the roflumilast 500 µg, 250 µg and placebo groups, respectively). The overall incidence of fatal AEs, as well as the incidence of fatal AEs by SOC and PT was generally comparable for the roflumilast and the placebo groups in both COPD pools. In the Rof500 od group and the placebo group, most AEs leading to death were related to *Respiratory, Thoracic and Mediastinal Disorders*, followed by *Cardiac Disorders*. COPD (exacerbation) was the most frequently documented AE leading to death in both treatment arms and was balanced between arms. Other AEs that led to death were also generally balanced between treatment groups, with infrequent numbers of death for each category. Three additional deaths occurred after the SAE follow up period of 30 days (2 patients in study M2-124 and 1 patient in study M2-127). No AEs leading to death were documented for these patients and therefore they were not included in the analysis of fatal AEs. In addition to deaths occurring in pooled COPD analysis, 3

patients died in the unpooled open label study FK1 102 and 2 patients in the withdrawal arm of study FK1 103.

The incidence of SAEs was low and similar for the Rof500 and placebo groups. The most frequent SAEs in both COPD pools were *Respiratory, Thoracic and Mediastinal Disorders and Infections and Infestations* and *Cardiac Disorders*. In all treatment groups, COPD (exacerbation) was the most frequent SAE, followed by pneumonia. In the pivotal COPD studies pool and in the COPD safety pool, atrial fibrillation occurred at a higher rate in the Rof500 group (0.4 to 0.6%) than in the placebo group (0.1 to 0.2%). However, the overall rate of cardiac SAEs was comparable for the two treatment groups due to a higher occurrence of acute myocardial infarction and cardiac failure in the placebo group.

Overall, in both pools, roflumilast was associated with more SAEs as a result of bronchitis, pneumonia, atrial fibrillation, intractable diarrhoea, acute pancreatitis, prostate cancer and acute renal failure. In contrast, the placebo group had more COPD related events, cerebrovascular events and lower respiratory tract infections. In the COPD safety pool, a total of 10 SAEs in 8 patients (0.1%) in the placebo group, 1 SAE in 1 patient (0.1%) in the Rof500 od group, and 17 SAEs in 14 patients (0.2%) in the Rof500 group were considered treatment related by the investigator. In the Rof500 group, serious gastrointestinal disorders were most frequently judged to be treatment related. No trend was observed for treatment related SAEs in the placebo group. A comparable distribution of SAE incidences under Rof500 od and placebo was generally observed in the COPD 1 year, 6 month and 3 month study duration pools, with the exception of the COPD 3 month studies pool, where the incidence of SAEs was low overall, but somewhat higher under Rof500 od than under placebo.

#### *Evaluator's comments*

Nearly half of the deaths in the COPD studies (84 of 177) occurred in the 52 week pivotal trials M2-124 and M2-125 and mortality rate was similar in the roflumilast (2.6%) and placebo groups (2.7%). Cardiac disorders and COPD were the most common AEs reported in patients who died during treatment. Although there were no overall difference in mortality between the Rof500 groups and the placebo groups, more roflumilast treated patients, compared to placebo, died of cardiac arrest (7 versus 1), suicide (3 versus 0) and acute pancreatitis (2 versus 0). These findings were consistent with the overall higher incidence of atrial fibrillation, depression and acute pancreatitis observed among roflumilast treated patients in the COPD safety pool.

For the COPD safety pool, the incidence of SAEs was 13.5% and 14.2% in the Rof500 and placebo groups, respectively. The SAE rates were higher in the pivotal studies pool (19.5% and 21.7% respectively) likely as a result of the more severe COPD population evaluated in these studies. COPD exacerbations and pneumonia were the most frequent SAEs in all treatment groups. In both pools, the Rof500 group reported more SAEs as a result of bronchitis, pneumonia, atrial fibrillation, intractable diarrhoea, acute pancreatitis, prostate cancer and acute renal failure. In contrast, the placebo group had more COPD related events, cerebrovascular events and lower respiratory tract infections.

#### **Laboratory findings, vital signs, ECG and pregnancies**

Across the studies included in the COPD safety pool, laboratory values were obtained from different laboratories without harmonization of normal ranges. Therefore only analyses of normal and abnormal laboratory values were performed for the overall population in the pivotal COPD studies and COPD safety pools.

For haematology parameters, the frequency of shifts to values outside the alert range was similar in the pivotal COPD studies pool and the COPD safety pool and comparable for the

Rof500 and placebo groups, with the exception of haemoglobin; more patients in the Rof500 group than in the placebo group presented with changes in haemoglobin from within normal ranges at baseline to below the lower limit of the alert range (LLAR) at the end of treatment. For biochemical parameters, more patients in the placebo group than in the Rof500 group presented with changes in gamma glutamyltransferase (GGT) and glucose to above the upper limit of the alert range (ULAR).

Blood pressure and pulse rate were comparable between treatment groups and generally stable over time in both the pivotal COPD pool and the COPD safety pool. The frequency of shifts to values outside the alert range was low (<1% in any treatment group) in both COPD pools. There were no notable differences between the Rof500 and placebo groups. For both double blind pivotal studies, 12-lead ECGs were collected at baseline, Weeks 28 and 52 and the final visit for all patients who had received at least one dose of study medication. Patients were excluded from participation in the studies if any ECG abnormality of concern was identified at the baseline visit. About a third of the patients in both the Rof500 od and placebo groups entered the study with abnormal (not clinically relevant) ECG findings, and  $\leq 3\%$  with abnormal, clinically relevant ECG findings. Less than 1% of the patients in each treatment group had shifted from normal or abnormal (not clinically relevant) to abnormal, clinically relevant ECG at the end of treatment. The overall assessment of ECG readings at last visit versus baseline did not reveal any clinically significant findings following roflumilast treatment.

### **Safety in special populations**

#### ***Effect of intrinsic factors (age, gender, race, COPD severity) on roflumilast safety***

Across the COPD pools, extent of exposure for all treatment groups within a subgroup generally followed comparable trends to those observed for the overall COPD pools. Compared by subgroup, female patients tended to present with slightly lower mean and total exposure times than male patients. Similarly, patients >65 years of age, patients from North America, patients with increasing COPD severity (exception: COPD safety pool), and patients with SAMA or LABA use (pivotal COPD studies pool only) presented with lower mean exposure times per patient. No difference in mean exposure times was documented for the majority of COPD pools stratified by race or smoking status.

The demographic characteristics were generally comparable for the Rof500 od and placebo treatment groups in each subgroup. Across the subgroups, in both treatment groups, male patients, Asian and Other (race) patients, former smokers, and patients with concomitant SAMA use presented more frequently with very severe COPD at baseline than female patients, Black or African American or Caucasian patients, current smokers, or patients without concomitant SAMA use. Severe COPD at baseline was documented more frequently for patients >65 years of age and European patients than for patients  $\leq 65$  years of age and North American or ROW patients, while the reverse was true for very severe COPD. Safety results in the Rof500 and placebo treatment groups were mostly the same in the subgroups as they were in the overall study population. The following differences between subgroups were, however observed:

#### ***Gender***

Females generally reported higher rates of all AEs, treatment related AEs and AEs leading to withdrawal than males, but lower rates of deaths and serious AEs. However, across all AE categories, the differences between the roflumilast and placebo arms remained consistent for female and male patients.

### *Age*

AE rates in all AE categories were higher in older patients (>65 years of age) compared to younger patients (≤65 years of age), but again, with consistent trends for differences between roflumilast and placebo treatment.

### *COPD severity*

In both the Rof500 and placebo treatment groups, the death rate was higher in patients with very severe COPD compared to patients with less severe COPD, which was expected. In both treatment arms, SAE rates increased with increasing COPD severity but, in contrast to patients with severe and very severe COPD, patients with moderate COPD reported slightly more SAEs in the Rof500 group than in the placebo group. Moreover, in patients with moderate COPD, the rate of patient withdrawal due to AE was higher in the Rof500 group compared with placebo, although interpretation was limited by the low number of patients in this subgroup.

### *Race*

In Asian patients, lower rates of overall AEs, treatment related AEs and SAEs were seen in both the Rof500 od and placebo treatment groups, compared to Caucasian patients. The number of patients included in the subsets Black or African American and Other (race) were too small for meaningful interpretations.

### *Overall*

Similar to the overall study population, in all subgroups, most frequent AEs in the Rof500 od and placebo treatment groups were infections of the respiratory tract, respiratory disorders, or gastrointestinal disorders. Across all subgroups, the most frequent AEs in the Rof500 od group were COPD (exacerbation), weight decreased and diarrhoea, while the most frequent AEs in the placebo group were COPD (exacerbation), nasopharyngitis and bronchitis. The subgroup analyses showed that trends concerning differences between the Rof500 od group and placebo treatment groups in subgroups were comparable to those in the overall study population. Few noteworthy differences were seen between the subgroups. In both treatment groups, COPD (exacerbation) rates increased with increasing disease severity and with increasing age; COPD (exacerbation) rates were lower in female than in male patients. In contrast, in the Rof500 od group, the rates of weight decreased and diarrhoea were higher in female than in male patients. In Asians, pyrexia was documented as second most common AE in the placebo group.

In all subgroups of the pivotal COPD studies pool, COPD (exacerbation) was the most common fatal AE in both treatment groups, followed by respiratory failure and cardiac failure/arrest, except in females with placebo treatment, where only five deaths occurred, none of which was reported to be due to COPD (exacerbation). Pneumonia was only observed as frequent fatal AE in male patients, patients with very severe COPD, and White patients, with the respective rates being comparable for the Rof500 od and placebo groups. In the pivotal COPD studies pool, COPD (exacerbation) was the most frequent SAE in both treatment groups of all subgroups, generally followed by pneumonia. In each subgroup, the incidence of COPD (exacerbations) that met the criteria for an SAE was higher in the placebo group compared with Rof500, while the incidence of serious atrial fibrillation and serious diarrhoea was higher in the Rof500 group. The rates of other frequent SAEs were comparable between the subgroups. The rates of serious COPD (exacerbations) in both treatment arms increased with increasing COPD severity, with higher age and were higher in males compared to females, with differences between the Rof500 od and placebo arms remaining consistent.

Across the subgroups of the pivotal COPD studies pool, COPD (exacerbation) was also the most frequent AE leading to withdrawal in the Rof500 od and placebo treatment groups (exception: patients with moderate COPD and roflumilast treatment), generally followed by pneumonia in the placebo group and by diarrhoea and nausea in the Rof500 od group. Across the subgroups, the incidence of COPD (exacerbations) leading to withdrawal was higher in the placebo group compared with Rof500 (except for Other [race] patients), whereas the incidence of diarrhoea and of nausea leading to withdrawal was higher in the Rof500 group. In both treatment groups, the rates of COPD exacerbations leading to withdrawal increased with increasing disease severity and with higher age. Unlike for the other race categories, the second most common AE leading to withdrawal in Asians was cardiopulmonary failure instead of diarrhoea. In the COPD safety pool, the differences between Rof500 and placebo treatment groups were generally similar in the subgroups compared to the overall population. The differences between subgroups were comparable to those observed for the subgroup analyses of patients in the pivotal COPD studies pool.

### ***Effect of extrinsic factors (geographic region and smoking) on safety***

Trends concerning differences between the Rof500 od and placebo treatment groups were, on the whole, the same in the subgroups as they were in the overall study population. The following differences between subgroups were observed:

#### ***Geographic region***

In North America, the overall AE rates in both treatment arms were higher than in Europe or ROW, although the magnitudes of difference between the roflumilast and placebo arms remained consistent. In the Rof500 od group in North America, the rate of treatment related AEs and AEs leading to withdrawal was also higher than in the other regions.

#### ***Smoking status***

Across all AE categories, AE rates in both treatment arms were higher in former compared to current smokers. The differences between Rof500 and placebo treatment were generally comparable for current and former smokers, with the exception of SAEs (higher rates of SAEs in former smokers in placebo group compared with roflumilast 500 µg group), while the rates were balanced in current smokers. Similar results were observed for the COPD safety pool.

### **Safety related to drug-drug interactions and other interactions**

Limited dose ranging was performed in the clinical trials with only 2 doses, 250 and 500 µg once daily. While evaluation of the 250 µg dose of roflumilast was limited, there appears to be a dose dependent increase in GI, weight loss and psychiatric adverse events associated with the 500 µg once daily dose of roflumilast. The prevalence of AEs, treatment related AEs, deaths, SAEs and discontinuations due to AEs was similar or slightly less in the Rof250 group compared with the placebo group.

For the COPD studies, safety was analysed in subgroups stratified by concomitant use or non-use of LABA and SAMA. Trends concerning differences between the Rof500 and placebo treatment groups were the same in the subgroups and the overall study population. As seen for the overall population, in all subsets the incidence of all AEs, AEs judged to be causally related, and AEs leading to withdrawal was higher under Rof500 than under placebo, while the opposite was true for SAEs. Rates of all types of AEs were higher in patients with, compared to patients without concomitant SAMA use, with the differences observed between roflumilast and placebo generally remaining at the same order of magnitude. Similar findings were observed for SAEs, AEs leading to withdrawal and deaths in patients with concomitant LABA use compared to patients without LABA use.

In patients with Rof500 treatment and concomitant SAMA or LABA use, COPD (exacerbation) was the most frequent AE, while in patients with Rof500 treatment but without concomitant SAMA or LABA use documented 'weight decreased' and diarrhoea as most frequent AEs. Regardless of whether LABA or SAMA were taken or not, COPD (exacerbation) was the most common fatal AE in both the Rof500 od and placebo treatment groups of subgroups in the pivotal COPD studies pool, mostly followed by respiratory failure and cardiac failure/arrest. The rates for these most common fatal AEs were generally comparable for the Rof500 od and placebo groups and no differences were detected between the subgroups. In all subsets, the rate of COPD (exacerbations) that met the criteria for a SAE was higher in the placebo group compared with the Rof500 group, while the rate of serious atrial fibrillation and serious diarrhoea was higher in the Rof500 group. Serious pneumonia occurred with comparable incidence in both treatment arms, with the exception of patients with concomitant LABA use, where more patients in the Rof500 group than in the placebo group had serious pneumonia. Rates of serious COPD (exacerbations) were higher in concomitant SAMA or LABA users compared to SAMA or LABA non-users, with the differences between roflumilast and placebo remaining consistent. In all subgroups of the pivotal COPD studies pool, COPD (exacerbation) was the most frequent AE leading to withdrawal in both treatment groups, followed by diarrhoea and nausea in the Rof500 group. In the placebo group, pneumonia was the second most common AE leading to withdrawal in patients with concomitant LABA or SAMA use, while nausea was the second most common AE leading to withdrawal in patients not taking concomitant LABA or SAMA. Throughout the subgroups, COPD (exacerbations) leading to study discontinuation were more frequent in patients receiving placebo than in patients receiving Rof500 od group, with comparable differences between the treatment arms in all subsets. The AE profile in combination therapy with salmeterol or tiotropium (M2-127 and M2-128) was shown to be consistent with previous roflumilast studies.

### **Discontinuations due to AEs**

Across all the treatment groups, between 8.9% and 14.3% of the patients experienced AEs which led to their withdrawal. For both COPD pools, the overall frequencies of AEs leading to withdrawal were slightly higher in the Rof500 group than in the placebo group. COPD (exacerbation) was the most frequently documented AE leading to withdrawal in the Rof500 and the placebo groups of both COPD pools, with slightly higher incidence in the placebo group compared with the roflumilast 500µg group. Other frequent AEs leading to premature study discontinuation in the placebo group were pneumonia and dyspnoea. Diarrhoea and nausea leading to withdrawal occurred at higher rates in the Rof500 group than in the placebo group. In addition, headache more frequently led to study withdrawal in the Rof500 group than in the placebo group in the COPD safety pool.

In all five COPD pools, of all the AEs leading to withdrawal, about 10-20% of those in the placebo group and 40-50% of those in the Rof500 group were assessed as being related to study treatment by the investigator. The most frequent treatment related AEs leading to withdrawal in the Rof500 group across all COPD pools were diarrhoea (1.6% to 2.5% of all patients per treatment group), nausea (0.5% to 1.7%) and headache (0.4% to 0.7%). Other AEs leading to withdrawal frequently considered related to Rof500 treatment were tremor, dizziness, insomnia, weight decreased, abdominal pain and decreased appetite. In the placebo groups, the investigator most often assessed nausea (up to 0.4% of patients) and dyspnoea (up to 0.2%) as treatment related AEs leading to withdrawal. The majority of AEs leading to withdrawal in all treatment groups and COPD pools were moderate or severe. The rates of AEs leading to withdrawal showed a similar general pattern in the COPD 1 year and 6 month studies pools. The overall rates of AEs leading to withdrawal were low for all treatment groups in the COPD 3 month studies pool.

### **Evaluator's overall conclusions on clinical safety**

Over 6500 COPD patients were exposed to roflumilast in 18 Phase II and III COPD trials, 5766 of the patients received at least one 500 µg dose, 797 patients received at least one 250 µg dose. Among those who received the proposed dose of 500 µg, 1232 patients were treated for ≥1 year, 1081 for 6months to <1 year, 2081 for 3 to < 6months and 1370 for <3 months. Hence, the number of patients (and duration of treatment) evaluated for safety complied with guidelines for drugs required for chronic illness.

Approximately two thirds of patients in the COPD safety pool (roflumilast 500 µg: 67.2%, placebo 62.8%) had at least one treatment emergent AEs. The AEs reported at a higher frequency in the roflumilast 500 µg group, in order of descending prevalence were diarrhoea, weight loss, nausea, headache, back pain, insomnia, dizziness decreased appetite, depression and anxiety. AEs that occurred at a higher rate in the placebo group included COPD, URTI and hypertension. Nasopharyngitis was common in both groups at equal rates

Limited dose ranging was performed in the clinical trials in COPD patients with 250 and 500 µg once daily. While evaluation of the 250 µg dose of roflumilast was limited, there appears to be a dose dependent increase in GI, weight loss and psychiatric AEs associated with 500 µg. The prevalence of AEs, treatment related AEs, deaths, SAEs and discontinuations due to AEs was similar or slightly less in the Rof250 group compared with the placebo group.

The majority of AEs were mild to moderate and most occurred after at least 4 weeks on treatment (72-87%); however, the proportion of AEs during the first 4 weeks of treatment were higher in the Rof500 group compared with placebo, while the proportions of AEs with later onset (after 13 weeks) were higher under placebo compared with roflumilast 500 µg. Most AEs (>78%) resolved during the course of the study.

Among the almost 12,000 patients included in the COPD safety pool, there were 177 deaths, 84 in the Rof500 group, 86 in the placebo group and 7 in the Rof250 group. Cardiac disorder and COPD were the most common fatal AEs. While there were no overall differences in mortality between the Rof500 and the placebo groups, more roflumilast treated patients, compared to placebo, died of cardiac arrest (7 versus 1), suicide and suicide attempt (3 and 2 versus 0) and acute pancreatitis (2 versus 0).

For the COPD safety pool, the SAE rates were 13.5% and 14.2% for the Rof500 and the placebo groups, respectively. However, the Rof500 group reported more severe cases of bronchitis, pneumonia, atrial fibrillation, intractable diarrhoea, acute pancreatitis, prostate cancer and acute renal failure. In contrast, the placebo group had more COPD related events, acute respiratory failure, coronary artery disease and thromboembolic events.

The overall dropout rate for patients receiving roflumilast was approximately 28% compared to about 23% for patients who received placebo. For nearly all Phase II and III trials included in the development program, the Rof500 groups had higher early withdrawal rate than the placebo groups, largely driven by the higher number of AEs that ultimately led to early withdrawal (Rof vs Placebo: 14.3% vs 8.9%). This is contrary to the findings from most other COPD drug trials, in which the dropout rates were usually higher for the placebo group because of lack of effect from the placebo treatment. Although COPD exacerbation rates were higher in the placebo groups for roflumilast trials, the differences were not large enough to counter balance the effects of high AE rate in the roflumilast group. The dropout rates were higher for longer trials.

Among the 6 main Phase III trials (M2-124, M2-125, M2-111, M2-112, M2-127 and M2-128), the dropout rates in the Rof500 treated groups were 28.5-38% for the 52 week trials (M2-124, M2-125, M2-111 and M2-112) and 16.7%-22.9% in the 24 week trials (M2-17 and M2-128). The corresponding dropout rates in the placebo treated groups were 21.7-31.1% for the 52 week trials and 10.5-17.5% for the 24 week trials.

AEs, SAEs and withdrawals due to AEs tended to be higher in patients >65 years and those with very severe COPD with consistent trends for differences between roflumilast and placebo treatment groups. However, the incidence of withdrawals due to AEs in roflumilast group was higher in patients aged >65 years compared to those <65 years (19.1% vs 10.4%). The corresponding incidence of withdrawals due to AEs in placebo group was 13.8% vs 9.7%. Across all AE categories, AE rates in both roflumilast and placebo groups were higher in former compared to current smokers.

### List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

#### Pharmacokinetics

1. Formula B was used in the clinical development program. In study report (FHP016) it is not clear why the wider bioequivalence range was used for  $C_{max}$  than the more typical 80 to 125% bioequivalence range?
2. As the  $t_{1/2}$  and the  $t_{max}$  of the N-oxide metabolite are 25.7 and 8.53 h, respectively, why weren't longer sampling times used in the PET study [FHP011] than 24 and 8 h?
3. Were the PKs of roflumilast examined in subjects of Asian descent?
4. Although the incidence of the dual mutation identified in one subject is unlikely to occur in the Caucasian population, what other mutations can cause poor metabolism of CYP1A2/3A, what is the incidence of these mutations especially in other races such as Japanese and should PK studies address the issue of poor metabolisers further?
5. Are there data on the interaction between roflumilast and oral contraceptives or HRT?
6. Why weren't PK studies, other than simulations, conducted in the target population of patients with COPD?
7. Clarification on why the authors of the *Clinical Overview* believe that significant increases in exposure to roflumilast and its active metabolite that are caused by coadministration of drugs that inhibit CYP 1A2/3A are unlikely to be clinically relevant, especially in "at risk groups" such as females, the elderly, Black / Hispanics and subjects with hepatic impairment?

#### Pharmacodynamics

1. Clarification on why the authors of the *Clinical Overview* believe that significant increases in the tPDE4i activity of roflumilast caused by coadministration of drugs that inhibit CYP 1A2/3A are unlikely to be clinically relevant, especially in the "at risk groups" above?
2. What are the PD effects following roflumilast in the one subject with the rare single mutations that induce the poor metabolism of CYP1A2/3A?

#### Efficacy

1. In the dose ranging studies, only Rof500 was associated with reduction in incidence of COPD exacerbations and 250 µg roflumilast failed to show any improvement over placebo for endpoints such as SGRQ, exacerbations, symptom score and use of rescue



medication. Based on the general lack of separation in efficacy parameters between the 250 and 500 µg doses, dose selection for the roflumilast program appears to have been arrived at by selection of the maximally tolerated dose. There is only 1 tablet strength and proposed dose for roflumilast and possibility of other effective doses or dose adjustments was not adequately evaluated.

2. In the pivotal studies, by limiting the enrolment to patients who had exacerbation in the year prior to the trial but excluding patients who had exacerbation during the run-in period, the trials have selected a special patient population (those at the highest risk of exacerbation) during a specific time frame. Furthermore, these patients took roflumilast as add-on to some form of bronchodilator therapy. However, the proposed indication is more general and is not justified based on submitted data.
3. The study design of the pivotal studies met the current regulatory guidelines for drugs for the treatment of COPD. However, the intervention driven type of definition for 'exacerbations' raises concerns because the decision to intervene may be a subjective decision by a health care provider that can vary depending on local practices. Thus, in order to help standardize the definition of a COPD exacerbation, it is important to link a decision to intervene in the care of the patient with specific criteria which must be met in order to declare an intervention a COPD exacerbation. However, this was not done in the roflumilast clinical program. It is acknowledged that there is no consensus on definitions for exacerbations and the sponsor appears to have taken adequate precautions to gather as much information as possible in the CRF regarding deterioration of symptoms, but analysis and correlation of these symptoms with the above intervention based definition of COPD exacerbations was not clearly established.
4. In no study was the efficacy of roflumilast compared to what has become standard of care treatment for patients with COPD, concomitant use of a LAMA and an inhaled corticosteroid in combination with a LABA. Furthermore, it appears to be implied that roflumilast could be used as a substitute to ICS as these were prohibited in the pivotal studies (M2-124 and M2-125). In the pivotal studies, prevalent use of prohibited COPD drugs (ICS and inhaled combinations of ICS and LABA by almost 10-11% of patients in each treatment group) suggested that patients in these studies were under treated. The other 1 year studies (M2-111 and M2-112) which allowed the use of ICS failed to demonstrate a significant reduction in the rate of moderate or severe exacerbations. Although both studies did show significant improvement in pre-bronchodilator FEV<sub>1</sub>, the effects were not maintained after Week 20 in this patient population.
5. In the pivotal studies, the use of prohibited ICS (alone or in combination with LABA) and non-compliance was higher in the roflumilast group compared with placebo; this may have biased interpretation of results in favour of roflumilast; more efficacy from steroid use and less side effects from non-compliance with roflumilast.
6. The exacerbation analyses for the pivotal studies did not explicitly examine potential attenuations in treatment effect during long term treatment; of the four statistical models presented, the Poisson and the negative binomial models only assessed roflumilast's effect averaged over the entire course of each study, while the proportional hazards and the log rank tests only assessed times to onset of exacerbations in each study, without including all exacerbation recurrences. An analysis to examine mean number of exacerbations per patient year for each time interval, similar to those used for the FEV<sub>1</sub> analyses would help interpretation of results regarding possible attenuation of efficacy. Since the proposed indication is for maintenance treatment of COPD, it is important to unequivocally establish that the

reduction in COPD exacerbations following treatment with Rof500 od is sustained over the 1 year treatment period.

## Safety

1. Limited dose ranging data provided evidence that the incidence of AEs, SAEs, deaths and discontinuations due to AEs in the Rof250 treated patients was similar or less than that in placebo treated patients. However, in patients treated with the proposed dose of 500 µg, AEs/SAEs/discontinuations were higher than in patients treated with 250 µg. The incidence of AEs, SAEs and withdrawals due to AEs tended to be higher in patients >65 years in both roflumilast and placebo groups. However, the incidence of withdrawals due to AEs on roflumilast was higher with age >65 years vs <65 years. The proposed PI states that no dose adjustment is required in elderly patients or those with mild/moderate hepatic impairment; however, the sponsor has not evaluated the safety of 500 µg in patients with hepatic impairment as only the 250 µg dose was used in those studies. The sponsors have not provided adequate information to justify use of only one roflumilast dose (500 µg) in all patients and this issue needs to be addressed before consideration of roflumilast for the proposed indication.
2. While there were no overall differences in mortality between Rof500 and placebo, more roflumilast treated patients, compared to placebo, died of cardiac arrest (7 versus 1), suicide and suicide attempt (3 and 2 versus 0) and acute pancreatitis (2 versus 0). These cases, although small in number may be significant due to the finding that higher numbers of cases of atrial fibrillation, depression and acute pancreatitis were also reported with roflumilast.
3. For nearly all Phase II and III trials included in the COPD development program, the Rof500 groups had higher early termination rate than the placebo groups, largely driven by the higher number of AEs that ultimately led to early withdrawal. This is contrary to the findings from most other COPD drug trials, in which the dropout rates were usually higher for placebo because of lack of effect. Although COPD exacerbation rates were higher in the placebo groups for the roflumilast trials, the differences were not large enough to counter balance the effects of high AE rate in the roflumilast group.

## Product information/consumer medical information

Questions on these issues are beyond the scope of this AusPAR.

## Clinical Summary and Conclusions

### Clinical Aspects

#### *Pharmacokinetics*

Based on the results of 15 single dose studies, comprising 212 subjects, following a single oral dose of 500 mg roflumilast, the median AUC of roflumilast across studies was 40.5 µg.h/L, the  $C_{max}$  was 7.04 µg/L,  $t_{1/2}$  was 18.4 h and  $t_{max}$  was 1 h. By contrast, the median AUC of roflumilast N-oxide was 415 µg.h/L,  $C_{max}$  was 9.49 µg/L,  $t_{1/2}$  was 25.7 h and  $t_{max}$  was 8.53 h. Exposure to the pharmacologically active N-oxide metabolite was approximately tenfold higher than to the parent compound. Based on the results of ten repeat dose studies, comprising 231 subjects, following repeated oral doses of Rof500 od, the median AUC of roflumilast was 35.9 µg.h/L, the median  $C_{max}$  was 7.29 µg/L, the median  $C_{trough}$  was 0.72 µg/L, the median  $t_{1/2}$  was 16.6 h and the median  $t_{max}$  was 1 h. For roflumilast N-oxide the AUC was 436 µg.h/L, the  $C_{max}$  was 24.4 µg/L, the median  $C_{trough}$  was 14.5 µg/L, the median  $t_{1/2}$  was 29.7 h and the median  $t_{max}$  was 3 h. The estimated average time to reach steady state for roflumilast and roflumilast N-oxide was 4 and 6 days, respectively. The

liver is considered to be the major site of roflumilast metabolism (via CYP1A2/2C19/3A4), with a possible contribution of some gastrointestinal CYP 3A4.

Exposure to roflumilast and roflumilast N-oxide was increased in women, the elderly, Blacks/Hispanics, poor metabolisers of CYP1A2/3A, patients with hepatic impairment and following coadministration of drugs that inhibit CYP1A2/3A. Dosage adjustment may be necessary if roflumilast is coadministered with drugs that affect the metabolism of CYP1A2/3A. This increased exposure may be further exacerbated in certain "at risk" groups such as women, the elderly, subjects with hepatic impairment and poor metabolisers of CYP1A2/3A. There is a lack of definitive PK data in the target population of patients with COPD. No interaction studies examined the interaction between roflumilast and oral contraceptives. No studies examined the PKs of roflumilast in pregnant or breast feeding mothers, subjects undergoing hormone replacement therapy or subjects of Chinese descent.

### ***Pharmacodynamics***

Roflumilast is a selective PDE4 inhibitor. PDE4 is the major cAMP-metabolising enzyme found in inflammatory and immune cells, which include mast cells, neutrophils, eosinophils, macrophages and T-lymphocytes. Inhibitors of PDE4 are potential antiinflammatory drugs, which may be useful in the treatment of inflammatory pulmonary diseases such as COPD and asthma.

Pharmacodynamics of roflumilast were not evaluated in "at risk" patients (women, the elderly, Blacks and Hispanics) nor in those with single mutation of CYP1A2/3A genes; furthermore, pharmacodynamic effects of roflumilast were not compared with existing medications used in the treatment of COPD.

Roflumilast has not been studied in patients with severe liver impairment (Child-Pugh C) and is therefore not recommended to be used in these patients. Furthermore, it is important to note that the roflumilast dose (250 mg) used in patients with mild/moderate hepatic impairment was lower than the proposed dose of 500 mg.

### ***Clinical efficacy***

Over 6500 patients with COPD were evaluated in 18 Phase II and III studies; these included six important Phase III studies: 2 pivotal one year studies (M2-124 and M2-125), 2 supportive six month studies (M2-127, M2-128) and 2 one year supportive studies (M2-111 and M2-112). While generally similar in design, there were some notable differences between the Phase III studies. Studies M2-111 and M2-112 evaluated a broad population of patients with severe COPD while M2-124 and M2-125 required patients to have recent histories of chronic bronchitis (cough and sputum production) and COPD exacerbations. Additionally, studies M2-124 and M2-125 allowed concomitant treatment with LABAs (50% of the patients in each study took LABAs) but prohibited the use of inhaled corticosteroids and LAMAs during the treatment period. Conversely, studies M2-111 and M2-112 allowed the use of inhaled corticosteroids however prohibited use of LABAs and LAMAs altogether. The 6 month studies evaluated efficacy of roflumilast 500 µg in patients on background therapy with salmeterol (M2-127) or tiotropium (M2-128). The differences in study design and use of concomitant medications used to treat COPD make inter-study comparisons difficult. The evaluator noted that in no study was the efficacy of roflumilast evaluated compared to what has become standard of care treatment for patients with COPD, concomitant use of a LAMA and an inhaled corticosteroid in combination with a LABA. Furthermore, it appears to be implied that roflumilast could be used as a substitute to ICS as these were prohibited in the pivotal studies (M2-124 and M2-125). In the pivotal studies, prevalent use of prohibited COPD drugs (ICS and inhaled combinations of ICS and

LABA by almost 10-11% of patients in each treatment group) suggested that patients in these studies were under treated.

The study design of the pivotal studies met the current regulatory guidelines for drugs for treatment of COPD. However, the intervention driven type of definition for 'exacerbations' raises concerns because the decision to intervene may be a subjective decision by a health care provider that can vary depending on local practices.

The 1 year studies M2-111 and M2-112 which allowed the use of ICS failed to demonstrate a statistically significant reduction in the rate of moderate or severe exacerbations. Although both studies did show significant improvement in pre-bronchodilator FEV<sub>1</sub>, the effects were not maintained after Week 20 in this patient population. The sponsor noted that this was incorrect: the primary analysis (repeated measures) showed significant results for all visits. *Post hoc* analyses were then used to define a more responsive patient population (those with chronic bronchitis and a history of cough, sputum production and recent exacerbations) which was carried forth in the year long studies designated as pivotal (M2-124 and M2-125).

The pivotal studies used lung function (pre-bronchodilator FEV<sub>1</sub>) and a symptomatic benefit endpoint (rate of COPD exacerbations) as primary endpoints, which complied with regulatory guidance. Both pivotal studies demonstrated superiority of Rof500 treatment over placebo for both primary endpoints. Compared to placebo, roflumilast improved the pre-bronchodilator FEV<sub>1</sub> by about 39 mL in study M2-124 and by 58 mL in study M2-125, representing a mean gain in airflow of about 4 to 6% over baseline. These results were consistent with a mild bronchodilatory effect for roflumilast. Using the Poisson regression model, the reduction in rate of moderate/severe COPD exacerbation was statistically significantly greater (by 15-18%) in the roflumilast group compared with placebo. The results were consistent and robust in study M2-125 but not so in study M2-124 (PP analysis did not show statistically significant reduction in moderate/ severe exacerbations). Analysis according to exacerbation severity in the ITT population indicated that COPD exacerbations of all severity decreased with roflumilast in both trials. However, there were no statistically significant differences between treatments for severe exacerbations in either trial and for mild exacerbations in trial M2-124. The differences in moderate or severe exacerbation rate between roflumilast and placebo were driven by reduction in the rate of moderate exacerbations, which was based on use of systemic steroid prescribed by the investigators according to their clinical judgments.

The effect of roflumilast on improvement in pre- and post-bronchodilator FEV<sub>1</sub> was maintained throughout the 1 year study. However, evidence for long term maintenance of reduction of exacerbations was not unequivocal. The sponsor indicated that this was incorrect. The time to first, second, third, fourth and fifth exacerbations was analysed to examine effects on exacerbations at later times during the trial period. These analyses confirmed the sustained effect of roflumilast during the pivotal trials.

Roflumilast efficacy results in the pivotal studies were observed independent of concomitant treatment with LABA. Results of key secondary endpoints post-bronchodilator FEV<sub>1</sub> and TDI focal score, as well as additional secondary endpoints provided some supportive evidence for efficacy of roflumilast.

The 6 month studies M2-127 and M2-128 demonstrated statistically significant improvements over placebo for the primary efficacy endpoint of pre-bronchodilator FEV<sub>1</sub> following treatment with Rof500 od in patients with moderate to severe COPD on a background therapy of LABA (salmeterol) or tiotropium. Similar to the results of the one year studies described above, modest increases (3-5%) in pre-bronchodilator FEV<sub>1</sub> were observed compared to placebo in both of the studies, 49 and 80 mL for studies M2-127

and M2-128, respectively. However, the 6 month studies failed to show any significant improvement in any symptomatic endpoints of COPD exacerbation rate, SGRQ, SOBQ, TDI or COPD symptom score. The sponsor indicated that this interpretation was incorrect. Roflumilast has shown a statistically significant benefit in the secondary endpoints for dyspnoea as assessed by BDI/TDI and SOBQ. Roflumilast treatment was associated with significant reduction in use of rescue medication only in study M2-128 in patients on background tiotropium treatment. Furthermore, in both studies, roflumilast was associated with an increased risk of withdrawal due to AEs, although the risk of withdrawal due to COPD exacerbation was similar with roflumilast and placebo. Results of these 6 month studies are important because in clinical practice, roflumilast will most probably be given not instead of but in addition to current COPD treatment.

Compared with placebo, the treatment effect of roflumilast was lower in females, patients aged <65 years and Asians. In the pivotal studies pool, the reduction in rate of moderate/severe COPD exacerbations with roflumilast was comparable in the subgroups of patients with severe or very severe COPD; the effect was substantially smaller in patients with moderate severity of COPD. Independent of disease severity, the treatment differences between roflumilast and placebo for pre-bronchodilator FEV<sub>1</sub> were consistently in favour of roflumilast in all integrated analyses. Smoking status and geographic region did not affect efficacy of roflumilast. Independent of concomitant SAMA, LABA or ICS use, the treatment difference between roflumilast and placebo for pre-bronchodilator FEV<sub>1</sub> and reduction of moderate/severe COPD exacerbations favoured roflumilast, although the reduction in exacerbation rate tended to be larger in roflumilast treated patients taking concomitant SAMAs, LABA and ICS.

### ***Clinical safety***

The safety of roflumilast was evaluated in over 6500 COPD patients in 18 Phase II and III COPD trials (5766 of the patients received at least one 500 µg dose, 797 patients received at least one 250 µg dose) and 1232 patients received the proposed dose of 500 µg for ≥1 year, which complied with regulatory guidelines for drugs used for chronic illness.

Limited dose ranging was performed in the clinical trials with only 2 doses, 250 and 500 µg once daily, being evaluated in COPD patients. There appears to be a dose dependent increase in the prevalence of AEs, treatment related AEs, deaths, SAEs and AEs leading to withdrawal (AELW) associated with the 500 µg once daily dose of roflumilast.

Furthermore, AEs, SAEs and AELW were similar or slightly less with Rof250 vs placebo. Approximately two thirds of patients in the COPD safety pool (roflumilast 500 µg: 67.2%, placebo 62.8%) had at least one treatment emergent AE. The AEs reported at a higher frequency in the Rof500 group, in order of descending prevalence, were diarrhoea, weight loss, nausea, headache, back pain, insomnia, dizziness, decreased appetite, depression and anxiety. AEs that occurred at a higher rate in the placebo group included COPD, URTI and hypertension. Nasopharyngitis was common in both groups at equal rates. The majority of AEs were mild to moderate and most occurred after at least 4 weeks on treatment (72-87%) with a higher incidence in the roflumilast group in the first 4 weeks of treatment. Most AEs (>78%) resolved during the course of the study.

Among the almost 12,000 patients included in the COPD safety pool, there were 177 deaths, 84 on roflumilast 500 µg, 86 on placebo and 7 on roflumilast 250 µg. Cardiac disorders and COPD were the most common fatal AEs. While there were no overall differences in mortality between Rof500 and placebo, more roflumilast treated patients, compared to placebo, died of cardiac arrest (7 versus 1), suicide and suicide attempt (3 and 2 versus 0) and acute pancreatitis (2 versus 0).

For the COPD safety pool, the SAE rates were 13.5% and 14.2% for Rof500 and placebo, respectively. However, the Rof500 group reported more severe cases of bronchitis, pneumonia, atrial fibrillation, intractable diarrhoea, acute pancreatitis, prostate cancer and acute renal failure. In contrast, the placebo group had more COPD related events, acute respiratory failure, coronary artery disease and thromboembolic events. The overall dropout rate for patients receiving roflumilast was approximately 28% compared to about 23% for patients who received placebo. For nearly all Phase II and III trials included in the COPD development program, the Rof500 groups had higher early termination rate than the placebo groups, largely driven by the higher number of AEs that ultimately led to early withdrawal. This is in contrast to the findings from most other COPD drug trials, in which the dropout rates were usually higher for the placebo group because of lack of effect from the placebo treatment.

AEs, SAEs and withdrawals due to AEs tended to be higher in patients >65 years and those with very severe COPD, with consistent trends for differences between roflumilast and placebo. However, withdrawals due to AEs with roflumilast were higher in patients aged >65 years compared to those <65 years (19.1% vs 10.4%); corresponding incidence of withdrawals due to AEs in placebo group was 13.8% vs 9.7%. Across all AE categories, AE rates in both roflumilast and placebo groups were higher in former compared to current smokers.

## **Benefit risk assessment**

### ***Benefits***

Compared to bronchodilator containing drugs for which pronounced benefits on lung function in COPD can be readily demonstrated, antiinflammatory therapies such as roflumilast typically achieve more modest effects on FEV<sub>1</sub>. With respect to quality of life, the SGRQ has been used in many clinical trials evaluating new COPD treatments. However, none of the currently approved COPD treatments have been able to consistently demonstrate a clinically meaningful and statistically significant benefit on SGRQ, despite having robust effects on FEV<sub>1</sub>. Consequently, more recent studies with roflumilast (M2-111, M2-112, M2-124, M2-125) examined the effect on exacerbation rate as a primary endpoint.

The endpoint of COPD exacerbations is a clinical diagnosis and the decision to initiate treatment (with corticosteroids) or hospitalization is investigator driven leaving room for variations in the definition of what constitutes an exacerbation and the severity of the exacerbations. However, it was acknowledged that the start of the roflumilast program almost 10 years previously predates much of the more recent discussion regarding how to define COPD exacerbations. Although the sponsor did collect information regarding deterioration of symptoms, analysis and correlation of these symptoms with the above intervention based definition of COPD exacerbations was not clearly established.

Both the dose ranging studies (FK1-101 and M2-107) showed a trend suggesting a higher response for the 500 vs the 250 µg dose for the primary and most secondary lung function endpoints, although results were not as robust in study FK1 101. Statistically significant differences between the two roflumilast doses in favour of the higher dose were seen in Study M2-107 for the secondary endpoints post-bronchodilator FEV<sub>3</sub> and FEV<sub>6</sub> as well as for time to first mild, moderate or severe exacerbation. However, only the 500 µg dose of roflumilast was associated with reduction in the incidence of COPD exacerbations and 250 µg failed to show any improvement over placebo for clinical endpoints such as SGRQ, exacerbations, symptom score and use of rescue medication. Hence, the 500 µg dose was selected as the optimal dose for further clinical development by the sponsor although the minimum effective dose of roflumilast was not adequately established.

The pivotal studies involved a very specific population of patients with severe to very severe COPD with chronic bronchitis and history of exacerbations in the past year (but not in the 4 week run-in period) as add-on to bronchodilator therapy (ICS and combination treatment with ICS and LABAs were not allowed). Results from these studies showed modest improvements in FEV<sub>1</sub> (average of 54 ml or about 3-5% of FEV<sub>1</sub>). The pivotal studies also showed reduction of moderate/severe exacerbation rates (by 15-18%). However, in pivotal study M2-124, the results were not robust and consistent as the PP analysis failed to confirm the significant findings observed in the ITT analysis; many patients were excluded from the PP analysis due to intake of prohibited medications such as ICS and combination therapy with ICS+LABA, which may have confounded the results. In study M2-124, the NNT to avoid one moderate or severe exacerbation per patient per year in the ITT analysis was 5.3, but it was 11.63 for the PP analysis. However, in study M2-125, the NNT to avoid one moderate or severe exacerbation per patient per year was similar in the ITT (3.6) and PP analysis (3.12). With regard to other non-spirometric or exacerbation related endpoints, there were no meaningful differences between roflumilast and placebo for quality of life, dyspnoea, rescue medication use, symptom scores, mortality and time to mortality.

The effect of roflumilast on improvement in pre- and post-bronchodilator FEV<sub>1</sub> was maintained throughout the 1 year pivotal studies. However, similar evidence for long term maintenance of reduction of exacerbations was not unequivocal. The exacerbation analyses provided by the sponsor did not examine potential attenuations in treatment effect during long term treatment with roflumilast. Of the four statistical models presented, the Poisson and the negative binomial models only assessed roflumilast's effect averaged over the entire course of each study, while the proportional hazards and the log rank tests only assessed times to onset of exacerbations in each study, without including all exacerbation recurrences. An analysis to examine mean number of exacerbations per patient year for each time interval, similar to those used for the FEV<sub>1</sub> analyses would help interpretation of results regarding possible attenuation of efficacy following long term roflumilast treatment. The sponsor noted that the time to first, second, third, fourth and fifth exacerbations was analysed to examine effects on exacerbations at later times during the trial period. These analyses confirmed the sustained effect of roflumilast during the pivotal trials.

The Phase III one year studies (M2-111 and M2-112) involved 2686 patients with severe to very severe COPD who were not required to have chronic bronchitis or history of exacerbations as in the pivotal studies (LABAs, combination of short acting anticholinergics with  $\beta$ 2 agonists, inhaled long acting anticholinergic such as tiotropium were not allowed). These studies failed to demonstrate statistically significant reduction in rate of moderate/severe exacerbations. Both these studies showed significant improvements in pre-bronchodilator FEV<sub>1</sub>, but the effects on FEV<sub>1</sub> were not maintained after Week 20 in this patient population. The sponsor noted that this was incorrect: the primary analysis (repeated measures) showed significant results for all visits.

Two 6 month studies (M2-127 and M2-128) in 1676 patients with moderate to severe COPD on background therapy with salmeterol (50  $\mu$ g twice daily) or tiotropium (18  $\mu$ g od) showed modest increases in pre-bronchodilator FEV<sub>1</sub> (by 3-5%); however, both studies failed to show any significant improvement in any symptomatic endpoints of COPD exacerbation rate, SGRQ, SOBQ, TDI or COPD symptom score.

Independent of concomitant SAMA, LABA or ICS use, the treatment difference between roflumilast and placebo for pre-bronchodilator FEV<sub>1</sub> and reduction of moderate/severe COPD exacerbations favoured roflumilast, although the reduction in exacerbation rate tended to be larger in roflumilast treated patients taking concomitant SAMAs, LABA and

ICS. However, the efficacy of roflumilast was not evaluated compared to what has become standard of care treatment for patients with COPD, that is, concomitant use of a LAMA and an inhaled corticosteroid in combination with a LABA

### **Risks**

In the pivotal COPD studies and the overall COPD safety pool, there was a higher incidence of AEs, SAEs and AEs leading to withdrawals with roflumilast vs placebo. The AEs reported at a higher frequency in the Rof500 group, in order of descending prevalence were diarrhoea, weight loss, nausea, headache, back pain, insomnia, dizziness decreased, appetite, depression and anxiety. AEs that occurred at a higher rate in the placebo group included COPD, URTI and hypertension. Most AEs were mild to moderate and most occurred after at least 4 weeks on treatment (72-87%), with a higher incidence in the roflumilast group in the first 4 weeks of treatment. Most AEs (>78%) resolved during the course of the study.

Serious safety issues were noted with roflumilast. This PDE4 inhibitor causes significant and at times severe gastrointestinal adverse events (diarrhoea, nausea and pancreatitis) and weight loss in many patients. The effects are dose related, with greater frequency observed in patients receiving the proposed 500 µg dose. However, the minimum tolerated dose of roflumilast was not clearly identified as the prevalence of AEs, treatment related AEs, deaths, SAEs and withdrawals due to AEs was similar in the Rof250 group and the placebo groups. While the 500 µg dose was what was felt to be the maximally tolerated dose for chronic use in healthy subjects, the high frequency of AEs in patients with COPD suggests the highest tolerable dose for this older population with other comorbidities may be lower than 500 µg once daily.

Among the almost 12,000 patients included in the COPD safety pool, there were 177 deaths, 84 in the Rof500 group, 86 in the placebo group and 7 in the Rof250 group. Cardiac disorders and COPD were the most common fatal AEs. While there were no overall differences in mortality between the Rof500 and the placebo groups, more roflumilast treated patients, compared to placebo, died of cardiac arrest (7 versus 1), suicide and suicide attempt (3 and 2 versus 0) and acute pancreatitis (2 versus 0).

For nearly all Phase II and III trials included in the COPD development program, the Rof500 groups had higher early termination rate than the placebo groups, largely driven by the higher number of AEs that ultimately led to early withdrawal. This is in contrast to the findings from most other COPD drug trials, in which the dropout rates were usually higher for the placebo group because of lack of effect from the placebo treatment.

### **Balance**

Overall, the pivotal and main supportive Phase III studies used acceptable efficacy endpoints which evaluated both lung function parameters as well as symptomatic benefit in terms of COPD exacerbation rates. Over 6500 COPD patients were treated with roflumilast in the 18 Phase II and III studies. However, it needs to be stressed that the pivotal studies involved a very narrow population of 3096 patients with severe or very severe COPD associated with chronic bronchitis (with >2 sputum and cough score) and history of exacerbations in past year (but not in the run-in period of 4 weeks); furthermore, roflumilast was given as add-on to bronchodilator treatment and ICS or combination treatment with ICS + LABA was not allowed in the pivotal studies. This is especially important as a significant limitation of this submission was the lack of evaluation of efficacy of roflumilast compared to what has become standard of care treatment for patients with COPD, that is, concomitant use of a LAMA and ICS in combination with LABA.



While the difference in FEV<sub>1</sub> between roflumilast and placebo was statistically significant in the clinical studies, the differences between the groups in mean change from baseline were quite modest at approximately 50 mL. To provide a sense of the bronchodilator effect of approved medications for COPD, tiotropium demonstrated 87 to 103 mL improvement in end of dosing interval FEV<sub>1</sub> over placebo throughout a 4 year trial.<sup>67</sup> Similarly, salmeterol, a long acting beta agonist, demonstrated an approximately 170 mL improvement in 2 hour post-dose FEV<sub>1</sub> relative to placebo at the end of a 24 week dosing period in COPD patients.<sup>68</sup> It was acknowledged that roflumilast is not a bronchodilator like tiotropium and salmeterol and this may account for the minimal clinically important difference in trough FEV<sub>1</sub> between active treatment with roflumilast and placebo. However, use of roflumilast for maintenance treatment of COPD would then need to be justified based on results on clinical and QoL endpoints.

Improvement in FEV<sub>1</sub> was maintained for the 1 year of treatment but evidence for long term maintenance of effect on reduction of COPD exacerbation rate was not unequivocal. If the reduction of exacerbations is not evident after few months, then a long term maintenance indication for roflumilast may not be justified. The sponsor noted that the time to first, second, third, fourth and fifth exacerbations was analysed to examine effects on exacerbations at later times during the trial period. These analyses confirmed the sustained effect of roflumilast during the pivotal trials.

Two 6 month, dose ranging studies (FK1-101 and M2-107) in 1927 patients with moderate to severe COPD provided some evidence that the 500 µg dose would be more effective than the 250 µg, although the evidence was not conclusive. Hence, the minimum effective dose of roflumilast for maintenance treatment in COPD was not adequately established. Treatment with roflumilast 500 µg was associated with a higher incidence of AEs compared with placebo. In addition to gastrointestinal side effects, patients treated with roflumilast also demonstrated a 2 to 3 times increased occurrence of psychiatric AEs such as anxiety, depression and insomnia. For nearly all Phase II and III trials included in the COPD development program, the roflumilast 500 µg groups had higher early termination rate than the placebo groups largely driven by the higher number of AEs that ultimately led to early withdrawal.

While there were no overall differences in mortality between the Rof500 and the placebo groups, more roflumilast treated patients, compared to placebo, died of cardiac arrest (7 versus 1), suicide and suicide attempt (3 and 2 versus 0) and acute pancreatitis (2 versus 0). These rare fatality cases, although small in number are significant due to the finding that higher number cases of atrial fibrillation, depression and acute pancreatitis were also reported in the roflumilast group.

Overall, there were concerns that the modest improvements in lung function and inconclusive reductions in moderate/severe exacerbations do not justify the considerable safety risks associated with use of roflumilast 500 µg od for maintenance treatment of COPD.

### **Conclusions**

The benefit/risk balance for roflumilast 500 µg tablets for oral administration was negative for the proposed indication of:

*maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations.*

## V. Pharmacovigilance Findings

### Risk Management Plan

#### Safety Specification

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review.

The sponsor did not identify any potential or identified risks with roflumilast. An area of missing/limited information concerns use during pregnancy and lactation.

While there were no identified or potential risks identified, it was the opinion of the OPR reviewer that the following safety related issues warrant further consideration:

- Neuropsychiatric adverse events in particular depression and suicidality
- Nonclinical studies in pregnant mice showed adverse effects on uterine muscle and its relevance to humans remains unknown.
- Safety in patients with mild to moderate hepatic impairment.

Evaluation of the clinical data revealed an overall higher incidence of atrial fibrillation and acute pancreatitis in the COPD safety pool. The sponsor was asked to focus on reports of cardiac arrhythmia and pancreatitis as adverse events of interest in ensuing Periodic Safety Update Reports (PSURs).

#### Pharmacovigilance Plan and Risk Minimisation Activities

Routine pharmacovigilance measures are proposed to monitor the safety of roflumilast.<sup>72</sup> There are no ongoing studies and no additional risk minimisation activities are planned.<sup>73</sup>

#### Pharmacovigilance Summary and Conclusions

The OPR reviewer made a number of recommendations concerning the proposed PI which are beyond the scope of this AusPAR.

In addition, evaluation of the clinical data revealed an overall higher incidence of atrial fibrillation and acute pancreatitis in the COPD safety pool. The sponsor was asked to focus on reports of cardiac arrhythmia and pancreatitis as adverse events of interest in ensuing PSURs.

The sponsor was also asked to comment on the following:

Off label use in asthmatic adult and paediatric patients is considered a reasonable possibility; does the sponsor intend to implement any measures to mitigate this risk?

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<sup>72</sup> Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

<sup>73</sup> Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

## VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

### Quality

The quality evaluator noted that roflumilast, a synthetic pyridine derivative, is not closely related to theophylline (a non-selective PDE inhibitor) or to the leukotriene receptor antagonists, montelukast or zafirlukast. The chemistry and quality control questions were resolved.

With regard to bioavailability, an absolute bioavailability study was submitted but the evaluator had reservations about the conduct of the study, including insufficient sampling to characterise properly the elimination of the principal N-oxide active metabolite. However, it can be said that absorption by the oral route is extensive but not precisely quantified.

The effect of food on bioavailability was studied on a formulation that was used in the clinical trials. Food reduced and delayed  $C_{max}$  and had an imprecisely quantified effect on the extent of absorption, "While fed and fasting dosing is not strictly bioequivalent, the food effect is not dramatic."

The PSC initially considered the application at its 133rd meeting, in July 2010, at which numerous issues were of concern. The application was again referred to the PSC where it was considered at the 139th meeting. The PSC recommended that the issues of concern in relation to the biopharmaceutical data raised at its 133rd meeting have now been resolved and that there should be no objection on pharmaceutical and biopharmaceutical grounds to the approval of this application.

Consequently, there were no objections to registration on pharmaceutical chemistry and quality control grounds.

### Nonclinical

Roflumilast was shown *in vitro* to be a potent and selective PDE4 inhibitor. Moreover, roflumilast did not interact directly with muscarinic, histaminergic, purinergic or adrenergic receptors in isolated tissue preparations. Roflumilast's inhibition of cAMP degradation potentiated the effects of various drugs, most notably those of  $\beta_2$ -adrenoceptor agonists.

PDE4 degrades cAMP in various immune, airway and other cells. Inhibition of inflammatory responses from stimulated human polymorphonuclear leukocytes and eosinophils, monocytes and macrophages and human T cell proliferation and cytokine release were demonstrated. *In vivo*, at exposures similar to that expected clinically, roflumilast inhibited cytokine release, as well as other indicators of a bronchial inflammatory response such as inflammatory cell accumulation, in rodent models of COPD.

Safety pharmacology studies suggested adverse effects at high multiples of the proposed human dose; nervous system effects in mice and rats included hypoactivity, hypothermia and impaired coordination (at  $\geq 4.5$  times the clinical  $C_{max}$ ). Roflumilast had proconvulsant effects in mice. Alterations in heart rate, blood pressure and cardiac contractility suggestive of a vasodilatory effect were restricted to dogs and cats. These occurred at subclinical plasma concentrations. No such effects were seen in other species (at least 9 times the clinical  $C_{max}$ ). An increase in urinary volume with a concomitant increase in osmolality was seen in the rat but was not considered toxicologically significant. Roflumilast was not a respiratory depressant.

Roflumilast is rapidly absorbed in the species that were studied. Plasma protein binding by roflumilast and roflumilast N-oxide was high in animal and human serum and tissue distribution of roflumilast and/or its metabolites in rodents was wide. Roflumilast crosses the blood-brain barrier. Roflumilast is rapidly metabolised to roflumilast N-oxide, an active metabolite, by CYP3A4. Both roflumilast and its principal metabolite are inhibitors of PDE4. Roflumilast N-oxide was equipotent *in vivo*, and is expected to be the main contributor to PDE4 inhibition in patients. Roflumilast and its metabolites (16 were identified in the nonclinical data set) appear in the urine and faeces. Biliary excretion was demonstrated in rats. *In vitro* studies did not suggest much potential for enzyme induction or inhibition.

Roflumilast was not considered to be genotoxic. No treatment related increase in tumour incidence was observed in the mouse study. It was commented that: "An increased incidence of myeloid hyperplasia was seen in male mice at the highest dose level, but in the absence of similar findings in other studies, this is likely to represent an adaptive response to generalised inflammation and congestion and not a pre-neoplastic concern."

Dose dependent toxicities included gastrointestinal tract lesions, nausea/vomiting and reduced weight gain in monkeys. Nasal cavity lesions were seen in rodents, including laceration, squamous metaplasia and tumours in hamsters. Dogs and some mice and monkeys showed cardiac lesions attributed to inotropic effects. Testicular toxicity and decreased fertility in males was seen in rats and mice. Roflumilast crosses the placenta of rats and fetal exposure was associated with skeletal ossification abnormalities. Roflumilast has a tocolytic effect in near term mice. Roflumilast appears in the milk of lactating rats.

Altered oestrous/menstrual cycling, at low relative exposures in females from three species, is potentially of clinical significance.

A number of the abovementioned toxicities might reflect species specific sensitivities. "Emesis, occurring in dogs at subclinical exposures and possibly directly related to PDE4 inhibition, and adverse effects on body weight, seen in monkeys at low multiples of the clinical exposure, are identified as the main toxicological concerns."

Overall, the evaluator concluded that the mechanistic studies support a rational basis for efficacy in humans with COPD.

The Delegate commented on the implications of the nonclinical data for efficacy.

The Delegate noted that the nonclinical data suggest that roflumilast might reasonably be used as an add-on agent to LABAs, inhaled corticosteroids and LAMAs. It would be therefore necessary to demonstrate this role in Phase II studies in humans and in Phase III studies, possibly in a multiple arm study. The postmarketing commitment for the FDA may generate some answers in regard to this.

Inhibition of inflammatory responses from stimulated human polymorphonuclear leukocytes and eosinophils, monocytes and macrophages and human T cell proliferation and cytokine release were demonstrated. This is the basis for an implication that Daxas might be a disease modifying agent or at least complementary to corticosteroids. Both of these possibilities were ignored in the clinical drug development program.

The Delegate also commented on the implications of the nonclinical data for safety.

Inevitably, new classes of drugs with multiple sites of action raise many questions. As noted by the evaluator, "macrophages, eosinophils and neutrophils, the main cell types present in the lungs of COPD patients. PDE4 is also expressed in airway smooth muscle, pulmonary epithelial, pulmonary vascular endothelial and sensory nerve cells". This list is not assumed to be exhaustive.

It is unlikely that emesis is the cause of weight loss in humans but anorexia would need to be captured by a suitably sensitive instrument. Food diaries in future human studies might help.

Preclinical data suggested some capacity for a proconvulsant effect: the clinical safety data base need to be checked periodically for signals with respect to convulsions.

Preclinical signals of immunosuppression might be tested in humans, for example, including response to challenges that are T-cell immune mediated.

Roflumilast's inhibition of cAMP degradation potentiated the effects of various drugs, most notably those of  $\beta_2$ -adrenoceptor agonists. It is therefore notable that, in the Phase III studies, LABAs were used with Daxas and that Daxas was not used alone. This might raise the possibility that Daxas simply increases the activity of the LABAs that are used with it. Against this: "Roflumilast and roflumilast N-oxide consistently demonstrated a dose and time dependent inhibition of 5-HT and histamine induced bronchoconstriction in rats and guinea pigs." The tocolytic action of roflumilast in near term mice also suggests a direct effect in some smooth muscle sites. Further, the bronchodilator effects of roflumilast in conjunction with corticosteroids (with and without beta adrenergic agents) would have been interesting to see.

A diuretic effect is implied in rats. The observed heart lesions in dogs are consistent with chronic administration of a vasodilator affecting cardiac output. This is reminiscent of oxpentifylline. Suggestions of vasodilation were also seen in cats. All of this is reminiscent of the effects of the methylxanthines. One might therefore expect "steal" effects, in those arteries that are distal to partial luminal obstructions, due to vasodilation in other arteries. The potential for "steal" effects has implications for use in persons with known or suspected atherosclerotic disease. Persons with coronary atheroma might also have ischaemic cardiomyopathy.

The evaluator commented: "cAMP is an essential signalling component in the mammalian olfactory system. PDE4A is present in the dendrites, soma and axons of olfactory neurons and treatment of mice with the PDE4 inhibitor, rolipram, altered the odour perception profile of mice. Although not tested in submitted studies, roflumilast may also be expected to have a similar effect. Therefore patients receiving roflumilast may experience alterations in olfactory perception, which may have follow-on taste effects. These effects are not likely to be adverse and would be expected to be reversible." This is perhaps a minor potential adverse effect that may result in food consumption. Dysgeusia should be sought in the adverse events in the postmarketing reports.

Perhaps most importantly of all, the evaluator commented: "Roflumilast exhibited very high specificity for PDE4, and no relevant secondary pharmacological targets were identified. Pharmacodynamic studies show that potentiation of cellular/tissue responses to various drugs can be expected to occur where both agents act to increase intracellular cAMP; this is most relevant to  $\beta_2$ -adrenoceptor agonists." The draft PI includes a claim that applies to rats, "Studies in rats with radiolabelled roflumilast indicate low penetration across the blood-brain barrier." What is missing here are data on the CNS effects in mammalian brains that might lead to reduced food intake, weight loss and depression/anhedonia or suicidality. The endocannabinoid antagonist class (for example rimonabant) was recently abandoned due to depression and suicidality despite suggestions of modest efficacy in achieving weight loss<sup>74</sup>. CB1 antagonism was not examined in this data package.

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<sup>74</sup> "Serious psychiatric side-effects were more frequent with rimonabant than with placebo (2.5% vs 1.3%). Suicide attempts (nine patients on drug vs five on placebo), and completed suicides (four vs

Potential effects on T-cell mediated immunity were not adequately explored. Even if this can be excused, a well designed and sensitive prospective study on tumour incidence is needed [see EU postmarketing study protocol, as mentioned above] given that the treatment population is likely to have been in general exposed to tobacco smoke. In regard to the findings in male mice, it would require replicate studies to provide support for the suggestion that: “this is likely to represent an adaptive response to generalised inflammation and congestion and not a pre-neoplastic concern”. The nonclinical evaluator commented: “Based on a weight of evidence review in accordance with the relevant guideline, the drug’s pharmacology and the suggestion of potential immune effects in the existing studies support the need for specialised immunotoxicity studies.<sup>75</sup> A study to assess T cell dependent antibody responses, in particular, should have been conducted to further investigate whether roflumilast poses an immunotoxic risk. Without this evidence, based on its intended mode of action, effects on T cell dependent immune responses may be expected.” The nonclinical evaluator’s concluding recommendation may not be realised in the absence of specific pharmacodynamic studies on human T-cell mediated immunity. The nonclinical evaluator added: “These effects [on T-cell immunity] would be expected to be reversible upon cessation of treatment.” This may not be invariably correct in the case of tumourogenesis.

## Clinical

### Pharmacokinetics

Studies were conducted in healthy subjects (n=663) as well as children with asthma (n=24) and adults with impaired renal function (n=12) and impaired hepatic function (n=8). Studies were of acceptable design.

As noted by the evaluator, the absolute bioavailability of a 500 mg dose of roflumilast was estimated from study FHP006, conducted 13 male volunteers, to be 79%, the volume of distribution was 2.92 L/kg and clearance was 0.137 L/h/kg. Following oral administration of roflumilast, the AUC of roflumilast N-oxide was about 12.5-fold higher than the AUC of roflumilast, whereas, following IV administration, the AUC of roflumilast N-oxide was about 7.5-fold higher. A population pharmacokinetic study in COPD patients versus healthy volunteers found reduced clearance of roflumilast and somewhat reduced its active metabolite in the COPD patients.

In study FHP036 oral absorption of [<sup>14</sup>C]-Rof500 was 84%, based on dose normalised plasma [<sup>14</sup>C]-radioactivity, and 99%, based on dose normalised amounts excreted in urine. Bioavailability based on the dose corrected AUC ratio for unchanged roflumilast in plasma after oral and intravenous administration of compared with IV infusion of roflumilast 150 µg was 64%. Based on plasma AUC, the sum of roflumilast and roflumilast N-oxide accounted for 57% and 5% of the total radioactivity after IV and oral administration, respectively, suggesting the formation of metabolites other than roflumilast N-oxide. The AUC<sub>∞</sub> of roflumilast N-oxide was approximately ten times higher than that of roflumilast (314 and 28.1 µg.h/L, respectively) and the t<sub>1/2</sub> of the metabolite was longer (17.7 and 13.4 h, respectively). Approximately 70% of both dose forms were excreted in the urine over these time periods and a further 20 % was excreted in the faeces.

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one, respectively) also occurred more frequently in the drug group. The investigators do not report whether the participants who committed suicide had depression at baseline. In view of the known neuropsychiatric side-effects of rimonabant, it is unclear why depression was not an exclusion criterion.” Boekholdt, SM, Peters RJG. Rimonabant: obituary for a wonder drug. *Lancet* 2010; 376: 489-490.

<sup>75</sup> This analysis was not accepted by the sponsor.

The effect of food upon the absorption of roflumilast was examined in study FHP010 in 12 healthy volunteers. Food decreased  $C_{max}$  but had little effect on the bioavailability of roflumilast and its active metabolite.

Dose dependency of absorption was examined in study FHP040 in which single oral administrations of 125 µg, 250 µg or 500 µg roflumilast under fasting conditions were given in an open label, randomised, three period, crossover study, conducted in 12 healthy subjects (8 female), aged between 27 and 45 years. Dose proportionality was not shown for roflumilast ( $C_{max}$  was relatively higher at the lowest dose; the extent of absorption increased proportionately with dose) whereas the principal metabolite did not depart from dose proportionality. Time of administration (morning or evening) had little effect on the extent of absorption of roflumilast.

There is a high degree of concentration independent binding of roflumilast and roflumilast N-oxide to human plasma proteins (99% and 97%, respectively), chiefly to albumin but also to  $\alpha$ 1-acid glycoprotein.

Also in regard to distribution, study FHP011 is of interest because it was a study of [ $^{18}$ F]-roflumilast in six healthy adult volunteers: there was a rapid uptake of the tracer from the gastrointestinal tract with significant non-vascular localisation in lung, muscle (arms) and brain tissue. In the brain, the non-vascular concentration was about 8% of that of plasma, in muscle 15% and in lung 45% in this single dose study. The sampling times were not considered to be adequate to characterise the distribution of the active metabolite.

Metabolism is extensive. As noted by the evaluator, CYP 3A4 was the major contributor (93.1%) to the conversion of roflumilast to descyclopropyl roflumilast (via dealkylation) with a minor contribution from CYP 2C19 (6.9%) and extra-hepatic CYP 1A1. In parallel, dealkylation of roflumilast N-oxide was completely catalysed by CYP 3A4 with a contribution of extra-hepatic CYP 1A1. Descyclopropyl roflumilast N-oxide was exclusively formed by CYP 2C19 from descyclopropyl roflumilast.

In a substudy of study FHP036, roflumilast was not detected in urine, whereas, roflumilast N-oxide was a trace metabolite (less than 1%).

In special populations, Study CP-050 compared the pharmacokinetics of roflumilast and its active metabolite in three age groups: 20 healthy "young" (18 to 45 years) and 22 healthy "middle aged" (46 to 64 years) and in 22 healthy elderly ( $\geq$  65 years) subjects. The study used a daily dose of 500 µg for 15 days. Blood was taken pre-dose and at intervals on Day 15 up to 144 h later. The results suggest relatively reduced clearance in the elderly and, incidentally, in females versus males.

In renal impairment, a single dose (Rof500) in 12 healthy adults versus 12 severe renally impaired ( $10 \leq CL_{Cr} \leq 30$  mL/min/1.73 m<sup>2</sup> body surface area) adult subjects suggested somewhat reduced absorption of roflumilast and reduced exposure to the active metabolite.

A small study in healthy or impaired hepatic function subjects (Child-Pugh A or B) suggested increased exposure to roflumilast and its active metabolite with the degree of impairment. The  $C_{max}$  of roflumilast was 2% higher in Child-Pugh A and 26% higher in Child-Pugh B patients and that of roflumilast N-oxide were 25% higher in Child-Pugh A and 40% higher in Child-Pugh B patients. Clearance was not reported.

Other inferred population pharmacokinetic results were noted, particularly that cigarette smoking increases clearance of roflumilast and its active metabolite.

Drug interaction studies confirmed interactions with inhibitors and inducers of CYP3A4. Of note, repeated doses of rifampicin decreased the  $AUC_{\infty}$  of roflumilast by 80% (from 38.4 to 7.8  $\mu\text{g}\cdot\text{h}/\text{L}$ ) and that of roflumilast N-oxide by 56% (from 414 to 180  $\mu\text{g}\cdot\text{h}/\text{L}$ ). Rifampicin decreased the  $C_{\text{max}}$  of roflumilast by 68% (6.8 to 2.16  $\mu\text{g}/\text{L}$ ) but increased that of roflumilast N-oxide by 30% (9.45 to 12.2  $\mu\text{g}/\text{L}$ ).

With regard to CYP1A2 inhibitors, fluvoxamine had a significant interacting effect: repeated doses of fluvoxamine increased the  $AUC_{\infty}$  of roflumilast by 156% (from 55.2  $\text{ng}\cdot\text{h}/\text{L}$  to 141  $\text{ng}\cdot\text{h}/\text{L}$ ) and that of roflumilast N-oxide by 52% (from 780  $\text{ng}\cdot\text{h}/\text{L}$  to 1190  $\text{ng}\cdot\text{h}/\text{L}$ ). Cigarette smoking induces CYP1A2. An interaction with digoxin was not shown. Interactions were not seen with salbutamol or formoterol. Budesonide did not interact with roflumilast but when roflumilast was given in combination with budesonide the  $AUC_{0-12}$  and  $C_{\text{max}}$  of budesonide was reduced by 16% and 14%, respectively.

### Pharmacodynamics

Ten studies, involving 145 healthy subjects (aged 19 to 78 years) and 57 subjects with COPD (aged 20 to 75 years) examined the pharmacodynamics of roflumilast (these exclude those involved in the population studies).

A food study examined a pharmacodynamic endpoint: the increase in systemic exposure to roflumilast in fed subjects was not clinically relevant as there was little difference in tPDE4i activity between fed and fasted subjects.

The effects of Rof500 on inflammatory cells and mediators in BALF after segmental pulmonary LPS challenge was examined in study [M2-117] in 43 healthy volunteers, aged 20 to 43 years. Following endotoxin challenge, influx of total cells (difference from baseline) in BALF of roflumilast treated subjects was 35% lower than with placebo ( $p=0.02$ )

In COPD patients, there is a suggestion from study FHP030 that roflumilast may reduce sputum neutrophils.

Secondary pharmacology studies included effects on blood pressure and heart rate after IV infusion of up to 150  $\mu\text{g}$  roflumilast, cardiovascular safety in an interaction study with formoterol – both studies showed minor effects.

Study CP-070 examined the cardiovascular safety of combined exposure to roflumilast and sildenafil. The evaluator concluded that the additive effects were modest.

Study FHP030 enrolled 41 patients with COPD. It identified a statistically significant improvement of  $FEV_1$  (post- and pre-bronchodilator) after 4 weeks of treatment with Rof500 in COPD patients with an increase of 64 mL (post-bronchodilator  $FEV_1$ ) and 71 mL (pre-bronchodilator  $FEV_1$ ) under roflumilast when compared with placebo. Other lung function variables, for example, forced vital capacity, forced expiratory flow 25 to 75%, and peak expiratory flow, did not show any statistically significant improvement.

In the light of data on patients with hepatic impairment, the evaluators concluded: “The proposed dose of 500  $\text{mg}$  od was not evaluated as patients with hepatic impairment only received 250  $\text{mg}$  od - hence dose was already decreased in these patients but still led to significant increase in tPDE4i activity. Hence, due caution should be exercised when giving roflumilast to patients with mild/moderate hepatic impairment and safety of proposed dose of 500  $\text{mg}$  was not established.”

In regard to dose finding, Study FK1 101 was a Phase II/III randomized, double blind, placebo controlled, 26 week, dose ranging and proof of concept study with administration of placebo and two doses of roflumilast (250  $\mu\text{g}$  and 500  $\mu\text{g}$  od) in 516 patients with moderate to severe COPD. The evaluators concluded: “This study failed to demonstrate



statistically significant improvements with roflumilast (250 µg and 500 µg) over placebo for both primary efficacy endpoints of pre-bronchodilator FEV<sub>1</sub> and SGRQ total score.” ... “The number of COPD exacerbations was lesser in the 500 µg roflumilast group, but it was similar in the 250 µg and placebo groups. Other symptomatic endpoints such as symptom score and use of rescue medication also failed to show statistically significant differences between roflumilast and placebo groups. Overall, results of this study did not show any significant benefit of the 250 µg dose over placebo and the 500 µg dose also appeared to show modest efficacy.”

Study M2-107 was another dose finding study with multiple endpoints. It was a multicentre Phase III, randomized, double blind, 24 week study, comparing roflumilast 250 µg and 500 µg od with placebo in 1,411 patients with moderate to severe COPD of which 1,157 patients completed the treatment period. There was a 2 week single blind baseline period followed by 24 weeks of double blind treatment period. The study treatment was administered orally once daily in the morning after breakfast and treatment compliance was high with a mean between 95% and 99% in each treatment group. The primary endpoints were change from baseline to end of treatment in FEV<sub>1</sub> (post-bronchodilator) and in the SGRQ total score.

Secondary endpoints included further lung function endpoints, SGRQ component scores, diary morning PEF, symptom score, use of rescue medication and exacerbations (number and time to event).

A sample size of 400 patients in each roflumilast group and 200 patients in the placebo group had power of 90% for demonstrating superiority of 500 µg roflumilast over placebo based on a two sample t test under the following assumptions (p= 0.025, one-sided; effect size =0.281, for example, difference between group means= 70 mL, common standard deviation = 250 mL). When including the total score of SGRQ in the confirmatory strategy, the power to conclude superiority with regard to the primary and co-primary variable was lower than as specified when planning the study on FEV<sub>1</sub> alone (81% and 64% for FEV<sub>1</sub> and SGRQ total score, respectively). The ITT analyses demonstrated significant improvements in post-bronchodilator FEV<sub>1</sub> vs placebo with both roflumilast doses (between treatment difference: 97 mL for Rof500, 74 mL for Rof250, for both p=0.0001, 2-sided). The FEV<sub>1</sub> improvements were observed in patients with a mean post-bronchodilator baseline FEV<sub>1</sub> of 1.5 to 1.6 L, representing an approximate 5% gain. The difference between the two roflumilast doses for post-bronchodilator FEV<sub>1</sub> was 23 mL (p = 0.1166, 2-sided) favouring the 500 µg dose. The SGRQ total score improved with all treatments but not to statistical significance; the pre-bronchodilator FEV<sub>1</sub> showed statistically significant greater improvements over placebo with both Rof250 and Rof500 (difference from placebo was 64 mL and 88 mL with 250 µg and 500 µg, p<0.006); and the proportion of patients experiencing moderate or severe COPD exacerbations was lower in the Rof500 group (28.3%) compared to the placebo (34.6%) and 250 µg (35.9%) groups – statistical significance was claimed for this trend.

## **Efficacy**

Initial studies focused on FEV<sub>1</sub> and quality of life (SGRQ) as efficacy endpoints. As the SGRQ turned out to be an insensitive endpoint to assess the treatment effect of an antiinflammatory agent such as roflumilast, the rate of mild, moderate<sup>76</sup> or severe COPD exacerbations was used as primary symptomatic benefit endpoint in the 1 year studies. Later studies (studies M2-111, M2-124, M2-125, M2-127, and M2-128) and study FK1 101

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<sup>76</sup> As described in the sponsor’s efficacy summary: “Moderate exacerbations were defined as those requiring oral or parenteral glucocorticosteroid therapy, severe exacerbations as those requiring hospitalization and/or leading to death.”

used pre-bronchodilator FEV<sub>1</sub> as primary endpoint. Post-bronchodilator FEV<sub>1</sub> was assessed as the primary endpoint in earlier studies (FK1 103, M2-107, M2-110, M2-112, and M2-121) and was also used as key secondary endpoint in studies M2-111, M2-124, M2-125, and M2-128. The pivotal studies M2-124 and M2-125 were performed in patients with severe to very severe COPD and a background of chronic bronchitis, as these were the patients who were expected to benefit most from roflumilast treatment. The primary endpoints included both COPD exacerbation rate and lung function (as measured by pre-bronchodilator trough FEV<sub>1</sub>). The supportive studies were either performed in a different patient population than the pivotal studies or used different endpoints. Among the supportive studies, special focus is on the 1 year studies (M2-111 and M2-112) and the 6 month studies M2-127 and M2-128, the latter two evaluating roflumilast in patients on maintenance treatment with long-acting bronchodilators. M2-127 used concomitant LABA and M2-128 used concomitant LAMA.

The evaluators commented: “No study was conducted to evaluate efficacy of roflumilast compared to what has become standard of care treatment for patients with COPD, i.e., concomitant use of a LAMA and an inhaled corticosteroid in combination with a LABA.”

As noted by the evaluators, eighteen Phase II and III studies examined the efficacy and safety of roflumilast in patients with moderate to very severe COPD (classified according to the ATS/ERS COPD guidelines or the GOLD guidelines. All of these efficacy studies were placebo-controlled and complied with CHMP guidelines for investigation of medicinal products in the chronic treatment of patients with COPD patients.

Of note, ICS were generally not used, the exceptions were three supportive studies: “In Studies M2-111, M2-112, and M2-121 patients were permitted to take ICS up to 2000 µg BDP or equivalent, when used prior to study enrolment.”

All of the large studies were multicentre studies that were conducted in numerous countries.

### ***Pivotal Studies***

Two studies were considered to be pivotal by the sponsor.

Two 6 month studies investigated the effects of Rof500 od treatment in patients with moderate to severe COPD receiving long acting bronchodilator maintenance treatment (salmeterol in Study M2-127 or tiotropium in Study M2-128). Of note, the sole primary outcome was pre-bronchodilator FEV<sub>1</sub>. There were numerous secondary endpoints including exacerbations, breathlessness, other lung function parameters, use of rescue medication etc. As described by the evaluators: “Studies M2-127 and M2-128 were randomized, double blind, 24 week studies, comparing the benefit of roflumilast (500 µg od) in 1676 patients with moderate to severe COPD when added to maintenance treatment with long acting bronchodilators, either salmeterol (50 µg twice daily in M2-127) or tiotropium (18 µg od in M2-128). On this background of long acting bronchodilator therapy, patients were randomized to receive roflumilast or placebo. The duration of the double blind treatment period was 24 weeks after a single blind run-in phase of 4 weeks in duration.

The main focus of these studies was to evaluate if roflumilast adds additional benefit on lung function beyond the effects of long acting bronchodilators. These studies included patients with moderate as well as severe COPD (FEV<sub>1</sub> of 40-70% predicted) and were not required to have a history of chronic bronchitis with sputum production and/or COPD exacerbations. Patients were required to be current or former smokers with a smoking history of at least 10 pack years, have a post-bronchodilator FEV<sub>1</sub>% predicted between 40 and 70%, and an FEV<sub>1</sub>/FVC ratio of <70%. In Study M2-128 patients were additionally

required to present with chronic bronchitis at study enrolment. To be eligible for randomization, patients were required to use >28 puffs rescue medication during the week preceding randomization in Study M2-128. Rescue medication (salbutamol) was allowed on an as needed basis during the entire run-in and treatment period. Other COPD treatment with the exception of the underlying long-acting bronchodilators had to be withdrawn prior to study start. Concomitant systemic glucocorticosteroids were only allowed for the treatment of exacerbations; ICS were not allowed during the treatment period.”

A total of 1,679 patients were included in the supportive 6 month Studies M2-127 and M2-128 and treatment discontinuation was higher in Study M2-127 (18% to 23%) as compared to Study M2-128 (11% to 17%) with higher incidence in the roflumilast than in the placebo group. In study M2-127, the evaluators found:

“Roflumilast given to patients on salmeterol maintenance treatment significantly increased the pre-bronchodilator FEV<sub>1</sub> (primary endpoint) by 49 mL as compared to placebo (95% CI: 27, 71 mL, 2-sided p-value = <0.0001). The difference in FEV<sub>1</sub> between treatments was statistically significantly in favour of roflumilast over placebo at each of the study visits during the 24 week treatment period.

The rate of COPD exacerbations (mild, moderate, or severe) was lower for roflumilast (1.9) than placebo (2.4) with a reduction of 20.7% for roflumilast in the ITT analysis. However, the ratio of the exacerbation rates was not statistically significant (Roflumilast/placebo rate ratio: 0.79, 95% CI: 0.58, 1.08; p = 0.1408, 2-sided). ”

In study M2-128 the evaluators found: “Compared with placebo, roflumilast given to patients on a background of tiotropium maintenance treatment significantly increased pre-bronchodilator FEV<sub>1</sub> by 80 mL (primary endpoint, p=0.0001, 2-sided) in the ITT and 76 mL in the PP analysis.” Some secondary endpoints were in favour of roflumilast.

The sponsor’s summary of efficacy outcomes is shown in Table 11.

**Table 11: Pre- and post-bronchodilator FEV<sub>1</sub> – studies M2-127 and M2-128**

Study or pool	LABD+Placebo		LABD+Rof500		Difference Rof500 vs placebo	
	n	LSMean (95% CI)	n	LSMean (95% CI)	LSMean (95% CI)	p-value <sup>a</sup>
<b>Pre-bronchodilator FEV<sub>1</sub> (primary endpoint)</b>						
M2-127	463	-0.010 (-0.027, 0.007)	456	0.039 (0.021, 0.056)	0.049 (0.027, 0.071)	<0.0001
M2-128	364	-0.016 (-0.038, 0.007)	365	0.065 (0.041, 0.088)	0.080 (0.051, 0.110)	<0.0001
<b>Post-bronchodilator FEV<sub>1</sub></b>						
M2-127	460	0.008 (-0.009, 0.026)	452	0.068 (0.051, 0.086)	0.060 (0.038, 0.082)	<0.0001
M2-128	363	-0.007 (-0.029, 0.016)	364	0.074 (0.051, 0.097)	0.081 (0.051, 0.110)	<0.0001

<sup>a</sup> 2-sided.

B = baseline, CI = confidence interval, COPD = chronic obstructive pulmonary disease, FEV<sub>1</sub> = forced expiratory volume in 1 second, ITT = intention-to-treat, n = number of patients included in the analysis, LABD = long-acting bronchodilator, LS = least squares, post = pre-bronchodilator, post = pre-bronchodilator, rep. = repeated, Rof500 = 500 µg roflumilast once daily, vs = versus.

### Twelve Month Studies

Two pivotal, 52 week studies of identical design (randomised, parallel group, double blind, 52 weeks after a 4 week run-in period) compared the efficacy of Rof500 od vs placebo on exacerbation rate and lung function in 3096 patients with severe to very severe COPD associated with chronic bronchitis and a history of exacerbations (Studies M2-124 and M2-125). Patients could take LABAs or short acting antimuscarinics or tiotropium.

In regard to power calculations and expected outcomes, the evaluators remarked: “The difference of approximately 46 mL in pre-bronchodilator FEV<sub>1</sub> expected in this roflumilast study would provide some indication of mild bronchodilatory effect, which is what would be expected of a drug not known to have significant bronchodilatory effects. Reduction in exacerbation rate of 20% is clinically acceptable. ”

The primary end points were:

- pre-bronchodilator FEV<sub>1</sub>
- Rate of moderate or severe exacerbations

The evaluators were of the view that the studies selected patients at high risk of an exacerbation. In regard to study M2-M125, the evaluators noted: “Patients had severe (60%) or very severe (33%) COPD; for 67% of the patients the history of COPD was combined emphysema and chronic bronchitis; for 33% it was predominately chronic bronchitis. About 50% of the patients were concomitantly treated with LABA and about 40% were pre-treated with ICS. The treatment groups were comparable with respect to baseline demographics and disease characteristics. The incidence of concomitant COPD medications before or during the treatment period was similar in both groups.”

With regard to the primary efficacy outcome, the evaluators found that: “Pre-bronchodilator FEV<sub>1</sub> increased for patients in the Rof500 group (LSMean: 33 mL; confidence interval (CI): 19, 48 mL; ITT), but decreased in the placebo group (LSMean: -25 mL; CI -39, -11 mL; ITT). A significant between treatment difference demonstrated superiority of roflumilast in improving pre-bronchodilator FEV<sub>1</sub> (LSMean: 58 mL; p-value: <0.0001; ITT).”

“Of the patients included in the FAS, 48.3% in the roflumilast 500 µg od group and 54.3% in the placebo group experienced at least one moderate or severe COPD exacerbation. The frequency of patients experiencing at least 2 (and up to 9) moderate or severe COPD exacerbations was higher in the placebo group as well.”

As tabulated by the sponsor the efficacy data for these studies is shown in Tables 12 and 13.

**Table 12: rate of moderate or severe exacerbation – studies M2-124, M2-125 and pivotal COPD studies pool**

Exacerbation Study or pool	Placebo		Rof500		Rof500 vs placebo			
	N	Rate	N	Rate	%Change	Rate ratio	95% CI	p-value <sup>a</sup>
M2-124	758	1.266	765	1.077	-14.9	0.851	0.737, 0.982	0.0278
M2-125	796	1.485	772	1.210	-18.5	0.815	0.710, 0.935	0.0035
124+125 pool	1554	1.374	1537	1.142	-16.9	0.831	0.752, 0.918	0.0003

<sup>a</sup> 2-sided.

CI = confidence interval, COPD = chronic obstructive pulmonary disease, ITT = intention-to-treat, N = number of patients, Rof500 = 500 µg roflumilast once daily, vs = versus.

Of note, the time to first exacerbation was 80 days in the active treatment groups in the pooled analysis versus 71 days in the placebo group.

**Table 13: Number of patients with exacerbations and time to exacerbation: risk and hazard ratios – studies M2-124, M2-125 and pivotal COPD studies pool**

	Risk ratio <sup>a</sup> Rof500/placebo (p-value <sup>b</sup> )					
	M2-124		M2-125		124+125 pool	
N of pts with moderate or severe exac.	0.89	(0.0196)	0.89	(0.0183)	0.89	(0.0006)
N of pts with moderate exacerbation	0.88	(0.0343)	0.88	(0.0188)	0.88	(0.0011)
N of pts with severe exacerbation	0.85	(0.2978)	0.83	(0.1479)	0.84	(0.0715)
	Hazards ratio <sup>c</sup> Rof500/placebo (p-value <sup>b</sup> )					
Time to 1 <sup>st</sup> moderate or severe exac.	0.88	(0.0859)	0.89	(0.1132)	0.89	(0.0185)
Time to 2 <sup>nd</sup> moderate or severe exac	0.79	(0.0290)	0.79	(0.0214)	n.a.	n.a.

<sup>a</sup> Based on Log binominal regression. <sup>b</sup> 2-sided. <sup>c</sup> Based on Cox- proportional hazards regression.  
COPD = chronic obstructive pulmonary disease, exac. = exacerbation, ITT = intention-to-treat, N = number, pts = patients, n.a. = not available, Rof500 = roflumilast 500 µg once daily.

The NNT to avoid one moderate or severe exacerbation in one year were calculated as 5.3 in M2-124 and 3.6 in M2-125.

Lung function changes are shown in Table 14.

**Table 14: Pre- and post-bronchodilator FEV<sub>1</sub> – studies M2-124, M2-125 and pivotal COPD studies pool**

Study or pool	Placebo		Rof500		Difference Rof500 vs placebo	
	n	LSMean (95% CI)	n	LSMean (95% CI)	LSMean (95% CI)	p-value <sup>a</sup>
<b>Pre-bronchodilator FEV<sub>1</sub> (primary endpoint)</b>						
M2-124	745	0.008 (-0.008, 0.023)	745	0.046 (0.030, 0.062)	0.039 (0.018, 0.060)	0.0003
M2-125	766	-0.025 (-0.039, -0.011)	730	0.033 (0.019, 0.048)	0.058 (0.041, 0.075)	<0.0001
124+125 pool	1511	-0.009 (-0.019, 0.002)	1475	0.040 (0.029, 0.050)	0.048 (0.035, 0.062)	<0.0001
<b>Post-bronchodilator FEV<sub>1</sub> (key-secondary endpoint)</b>						
M2-124	736	0.008 (-0.009, 0.025)	729	0.057 (0.040, 0.073)	0.049 (0.026, 0.071)	<0.0001
M2-125	764	-0.017 (-0.031, -0.003)	724	0.044 (0.030, 0.059)	0.061 (0.044, 0.079)	<0.0001
124+125 pool	1500	-0.004 (-0.015, 0.006)	1453	0.050 (0.039, 0.061)	0.055 (0.041, 0.069)	<0.0001

<sup>a</sup> 2-sided.

B = baseline, CI = confidence interval, COPD = chronic obstructive pulmonary disease, FEV<sub>1</sub> = forced expiratory volume in 1 second, ITT = intention-to-treat, n = number of patients included in the analysis, LS = least squares, post = post-bronchodilator, pre = pre-bronchodilator, rep. = repeated, Rof500 = 500 µg roflumilast once daily, vs = versus.

### Supportive studies

Of note, study FK1 103 was a randomized, double blind, 24 week study, comparing Rof500 od with placebo in 581 patients with COPD. The study evaluated the effects of roflumilast withdrawal, that is, patients received roflumilast for 12 weeks followed by treatment with placebo for an additional 12 weeks (Roflumilast-placebo). Hence, there were 3 treatment groups: Rof500 (n=200); Rof500/ placebo (n =195) and placebo (n=186). Primary endpoints were the changes from baseline to end of treatment in post-bronchodilator FEV<sub>1</sub> and SGRQ total score. Compared to placebo, 24 weeks treatment with roflumilast 500 µg od increased post-bronchodilator FEV<sub>1</sub> non-significantly by 39 mL but no treatment effect was seen with respect to the SGRQ. On withdrawal effects, the evaluators found: “withdrawal of roflumilast after 12 weeks of treatment led to a statistically significant decline in post-bronchodilator FEV<sub>1</sub> over a period of approximately 4 to 8 weeks (mean decline observed was 49 mL at 12 weeks); a decline was not observed in patients on

continuous treatment with roflumilast. Despite withdrawal of drug, the post-bronchodilator FEV<sub>1</sub> levels in the withdrawal arm remained above placebo levels.” It can be said that a rebound effect was not shown.

Study M2-121 was a Phase IIIb, randomized, double blind, 24 week study (conducted in 2004-2005), including patients with moderate to very severe COPD comparing Rof500 od with placebo focussing primarily on parameters indicative for hyperinflation (functional residual capacity [FRC]) and lung function). Roflumilast treatment significantly increased the primary endpoint post-bronchodilator FEV<sub>1</sub> with a between treatment difference of 36 mL, favouring roflumilast (p = 0.0061). This was noted in patients with a mean post-bronchodilator FEV<sub>1</sub> at baseline of 1.3 L. A non-significant between-treatment difference of 37 mL in favour of placebo was seen for the second primary endpoint, FRC. For the key secondary endpoints there were either no (TDI) or small, non-significant improvements (RV) in favour of roflumilast (between treatment differences: TDI: -0.01, RV: -25 mL).

Several other studies were considered supportive for this submission by the sponsor.

These include the 1 year studies (M2-111 and M2-112) and the 6 month studies M2-127 and M2-128, the latter two examining roflumilast in patients on maintenance treatment with long acting bronchodilators.

M2-111 used pre-bronchodilator FEV<sub>1</sub> as primary endpoint. M2-112 used post-bronchodilator FEV<sub>1</sub> as primary endpoint and also the SGRQ. As noted by the evaluators: “Patients in Studies M2-111 and M2-112 were not required to have a history of exacerbations and chronic bronchitis as in the pivotal studies. The definitions of moderate and severe exacerbations as well as the primary endpoint, rate of exacerbations differed from that of the pivotal studies; exacerbations were captured differently in study M2-111 and study M2 112 as compared to the pivotal studies, M2-124 and M2-125. An exacerbation free period of at least 10 days was required for separate exacerbations in Study M2-111, while at least one exacerbation free day was required to separate exacerbations in Study M2-112.”

M2-111 was a Phase III, double blind, randomized, parallel group, 52 week study (with a 4 week single blind placebo baseline period). ICS were permitted. The co-primary endpoints were the change from baseline in pre-bronchodilator FEV<sub>1</sub> and number of moderate (treated with oral or parenteral glucocorticosteroids) or severe (leading to hospitalization and/or death) COPD exacerbations per patient per year. A statistically significant greater improvement in pre-bronchodilator FEV<sub>1</sub> was seen in the roflumilast treatment group compared with placebo (difference in LSMeans: 36 mL, 95% CI: 6 to 57 mL; p = 0.0160, 2-sided, ITT, confirmed by PP analysis). Exacerbations were somewhat reduced. The evaluators described the benefits to FEV<sub>1</sub> as modest: “Modest improvements in LS Means of pre-bronchodilator FEV<sub>1</sub> ranging from 21 to 45 mL in favour of Rof500 compared with placebo were seen at all visits, although treatment differences were not statistically significant after Week 20...” The sponsor noted that this was incorrect: the primary analysis (repeated measures) showed significant results for all visits.

M2-112 was a Phase III, double blind, randomized, parallel group, 52 week study (with a 4-week single-blind placebo baseline period) conducted at 159 centres. The co-primary endpoints were the change from baseline in post-bronchodilator FEV<sub>1</sub> and number of moderate (treated with oral glucocorticosteroid and/or antibiotics) or severe (leading to hospitalization) COPD exacerbations per patient per year. The key secondary endpoint was the change in total score of SGRQ. As reported by the evaluators, the ITT last value analysis showed that the increase in post-bronchodilator FEV<sub>1</sub> was statistically significantly greater in the roflumilast group compared with the placebo group (difference

in LSMeans: 39 mL, 95% CI: 16 to 62 mL,  $p=0.0005$  ITT). The mean number of observed moderate/severe exacerbations and of moderate/mild exacerbations was lower in the roflumilast group, but the mean number of observed severe exacerbations was comparable between the treatment groups. No differences were seen with respect to the SGRQ. The evaluators concluded: "Overall, this study showed very little evidence of symptomatic improvement; the pre- and post-bronchodilator FEV<sub>1</sub> did show significant improvements with roflumilast over placebo, although these appeared to be driven by reductions in placebo group rather than any significant increase in the roflumilast group."

Studies M2-127 and M2-128 examined roflumilast in patients on maintenance treatment with long acting bronchodilators. These studies prohibited use of ICS. They were randomized, double blind, 24 week studies (after a 4 week run-in), comparing the benefit of roflumilast (500 µg od) in 1676 patients with moderate to severe COPD when added to maintenance treatment with long acting bronchodilators, either salmeterol (50 µg twice daily in M2-127) or tiotropium (18 µg od in M2-128). These studies included patients with moderate as well as severe COPD (FEV<sub>1</sub> of 40-70% predicted) and were not required to have a history of chronic bronchitis with sputum production and/or COPD exacerbations.

In these studies, a treatment effect was seen for roflumilast that was greater for co-treatment with tiotropium than for LABA (Table 15).

**Table 15: Change from baseline to end of treatment in pre- FEV<sub>1</sub>: supportive 6 month studies and their integrated analysis**

Study or Treatment pool	n	Baseline Mean	Change from baseline		Difference vs placebo			
			LSMean	95% CI	LSMean	95% CI	p-value <sup>a</sup>	
<b>Moderate to severe COPD, in patients on LABD</b>								
M2-127	Sal+Pbo	463	1.415	-0.010	-0.027, 0.007			
	Sal+Rof	456	1.436	0.039	0.021, 0.056	0.049	0.027, 0.071	<0.0001
M2-128	Tio+Pbo	364	1.492	-0.016	-0.038, 0.007			
	Tio+Rof	365	1.478	0.065	0.041, 0.088	0.080	0.051, 0.110	<0.0001

In M2-127, the rate of COPD exacerbations (mild, moderate, or severe) was lower for roflumilast (1.9) than placebo (2.4) with a reduction of 20.7% for roflumilast in the ITT analysis. However, the ratio of the exacerbation rates was not statistically significant (Roflumilast/ placebo rate ratio: 0.79, 95% CI: 0.58, 1.08;  $p = 0.1408$ , 2-sided).

In M2-127, although the rate of moderate or severe exacerbations (key secondary endpoint) was reduced by 23.2% with roflumilast compared to placebo, the difference was not statistically significant ( $p = 0.1957$ , 2-sided).

## Safety

As noted by the evaluators, over 6500 COPD patients were exposed to roflumilast in 18 Phase II and III COPD trials, 5766 of the patients received at least one 500 µg dose, 797 patients received at least one 250 µg dose. Most supportive and pivotal studies were of 24 or 52 weeks' duration. 5,766 of the patients received at least one 500 µg dose, 797 patients received at least one 250 µg dose. There is thus sufficient experience to characterise common and uncommon adverse reactions.

Approximately two thirds of patients in the COPD safety pool (roflumilast 500 µg: 67.2%, placebo 62.8%) had at least one treatment emergent AE. The AEs reported at a higher frequency in the Rof500 group, in order of descending prevalence were diarrhoea, weight loss, nausea, headache, back pain, insomnia, dizziness decreased appetite, depression and

anxiety. AEs that occurred at a higher rate in the placebo group included COPD, URTI and hypertension. Nasopharyngitis was common in both groups at equal rates.

Compared to placebo, patients treated with Rof500 od showed higher incidence of weight decreased, diarrhoea, nausea, headache, decreased appetite, back pain, dizziness and insomnia. In contrast, the incidence of COPD (exacerbation), hypertension, bronchitis and URTI was higher in the placebo compared with the Rof500 group in both COPD pools. In the pivotal COPD studies pool, the incidence of pneumonia was slightly more frequent for patients in the Rof500 treatment group than in the placebo group; however, the incidence of pneumonia was balanced between the two treatment groups in the larger COPD safety pool. The incidences of the most frequent AEs in the COPD study duration pools (1 year, 6 months and 3 months) generally followed similar patterns of distribution as those observed for the aforementioned COPD pools

The evaluators were of the view that adverse events were dose dependent: “there appears to be a dose dependent increase in GI, weight loss, and psychiatric AEs associated with 500 µg. The prevalence of AEs, treatment related AEs, deaths, SAEs and discontinuations due to AEs was similar or slightly less in the Rof250 group compared with the placebo group.”

Deaths were of note: “Among the almost 12,000 patients included in the COPD safety pool, there were 177 deaths, 84 in the Rof500 group, 86 in the placebo group, and 7 in the Rof250 group. Cardiac disorder and COPD were the most common fatal AEs. While there were no overall differences in mortality between the Rof500 and the placebo groups, more roflumilast treated patients, compared to placebo, died of cardiac arrest (7 versus 1), suicide and suicide attempt (3 and 2 versus 0) and acute pancreatitis (2 versus 0).”

“Nearly half of the deaths in the COPD studies (84 of 177) occurred in the 52 week pivotal trials M2-124 and M2-125 and mortality rate was similar in the roflumilast (2.6%) and placebo groups (2.7%).”

In regard to events of special interest, the evaluators reported: “Psychiatric AEs were not specifically elicited nor actively sought. Stable patients with psychiatric illness were not excluded from the Phase III studies. However, patients who were not able to follow study procedures (for example, language problems, psychological disorders) were excluded from the studies.

AEs related to the *Psychiatric Disorders* SOC were more common in patients who received Rof500 compared to those who received the 250 µg dose or placebo. There were a total of 403 (6%) psychiatric AEs reported in patients who received Rof500 od compared to 190 (3%) events in the placebo group. The incidence of insomnia, anxiety and depression related AEs in the Rof500 group were 2 to 3 times greater compared to those in placebo.”

Weight loss was a significant adverse reaction. In the pivotal COPD studies pool, 62% of roflumilast treated patients lost weight during the 1 year treatment period, compared to 38% in the placebo group with similar results in the 1 year and 6 month pooled data (Table 16).



**Table 16: Percentage of patients with weight change from baseline by weight decrease category and clinical relevance: pivotal COPD studies pool**

Number of patients	Rof500 (N = 1547) (n = 1498)		Placebo (N = 1545) (n = 1510)	
	n'	(%)	n'	(%)
with weight decrease	935	(62.4) <sup>b</sup>	569	(37.7) <sup>b</sup>
by weight decrease category				
mild (>0% to ≤5%)	527	(35.2) <sup>b</sup>	415	(27.5) <sup>b</sup>
moderate (>5% to ≤10%)	301	(20.1) <sup>b</sup>	125	(8.3) <sup>b</sup>
severe (>10%)	107	(7.1) <sup>b</sup>	29	(1.9) <sup>b</sup>
with weight decrease considered clinically relevant <sup>a</sup>	189	(12.2) <sup>c</sup>	65	(4.2) <sup>c</sup>

Note: Weight decrease analysis in this table was based on baseline and last post-randomization measurements.

<sup>a</sup> clinically relevant = decrease >5% during first month or >10% at any visit after first month of treatment

<sup>b</sup> percentages based on n

<sup>c</sup> percentages based on N

N = number of patients in treatment group, n = number of patients with data available, n' = number of patients in the category, Rof500 = Roflumilast 500 µg once daily.

The evaluators concluded that: "Overall, 62% of COPD patients treated with roflumilast had weight loss compared to only 38% of placebo treated patients. The risk of weight loss following roflumilast treatment did not appear to be increased in underweight patients or those with 'very severe' COPD. A variety of BMI phenotypes are represented and weight decrease associated with roflumilast therapy was observed in all BMI subgroups. After discontinuation of roflumilast, about 80% of patients who took part in a 3 month follow up investigation regained body weight, suggesting that weight decrease is reversible upon treatment cessation. An association between weight loss and the incidence of depression or anhedonia was not specifically evaluated."

### Evaluator's Comments

In regard to the Phase III studies, the evaluator observed:

1. "While generally similar in design, there were some notable differences between the Phase III studies. Studies M2-111 and M2-112 evaluated a broad population of patients with severe COPD while M2-124 and M2-125 required patients to have recent histories of chronic bronchitis (cough and sputum production) and COPD exacerbations. Additionally, studies M2-124 and M2-125 allowed concomitant treatment with LABAs (50% of the patients in each study took LABAs) but prohibited the use of inhaled corticosteroids and LAMAs during the treatment period. Conversely, studies M2-111 and M2-112 allowed the use of inhaled corticosteroids however prohibited use of LABAs and LAMAs altogether. The 6 month studies evaluated efficacy of Rof500 in patients on background therapy with salmeterol (M2-127) or tiotropium (M2-128). The differences in study design and use of concomitant medications used to treat COPD make inter-study comparisons difficult."
2. "It should be noted that in no study was the efficacy of roflumilast evaluated compared to what has become standard of care treatment for patients with COPD, concomitant use of a LAMA and an inhaled corticosteroid in combination with a LABA. In the pivotal studies, prevalent use of prohibited COPD drugs (ICS and inhaled combinations of ICS and LABA by almost 10-11% of patients in each treatment group) suggested that patients in these studies were under treated."

3. There was also a lack of standardised definition of an exacerbation in use across the Phase III studies.

4. Compared to placebo, patients treated with Rof500 od showed higher incidence of weight decreased, diarrhoea, nausea, headache, decreased appetite, back pain, dizziness and insomnia.

The evaluators' recommendation was that: "The benefit/ risk balance for roflumilast 500 ug tablets for oral administration is negative for the proposed indication of "maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations."

The Delegate indicated that the indication has since been modified by the sponsor.

Despite the narrowing of the indication, the sponsor's original summary stated:

The positive treatment effects of roflumilast on lung function were also independent of disease severity. For exacerbations, the treatment effects of roflumilast were highly comparable in the subgroups of patients with severe or very severe COPD. The effect was less pronounced in patients who generally experience exacerbations less frequently (ie patients with moderate airway obstruction). In the latter patient population significant effects would not be expected due to the overall low exacerbation rate which makes treatment effects difficult to discern.

Beneficial effects of roflumilast were observed independent of underlying bronchodilator or ICS therapy, which is of clinical importance as current medical practice recommends and uses these medications in the treatment of COPD.

It is therefore unclear to the Delegate why a more severely affected population would benefit more.

### **Response by the sponsor to the Clinical Evaluation Report**

The sponsor provided a response the evaluation report.

### **Final Comments by the evaluator**

The evaluator examined the additional data provided by the sponsor in regard to suicides. This was a safety review that employed the Columbia Classification Algorithm of Suicide Assessment (C-CASA) for all COPD studies as well as other indications (asthma and COPD were the indications in most of the studies). Forty five studies were searched, including 21,843 patients of which 11,488 received roflumilast, 8,458 placebo and 1,317 and active control plus 220 patients in placebo crossover studies. The texts were searched for terms related to suicidal actions (accident, jump, shooting, monoxide etc.). Mean duration of roflumilast therapy was longer in the COPD studies than in the overall pool (198 vs 159 days) as it was for placebo (226 vs 190 days) and for active control it was 100 days.

The sponsor conducted a review of "possibly suicide related adverse events" using the above C-CASA methodology. No new cases had been found. The cases of "possibly suicide related adverse events" are shown in Table 17.

**Table 17: Number and percentage of patients with possibly suicide related AEs during the double blind treatment period: COPD and Overall Pools**

C-CASA Codes	<i>Pbo</i>	<i>Rof</i>	<i>Pbo</i>	<i>Rof</i>	<i>Active</i>
	(N=5682)	(N=6972)	(N=3458)	(N=11,848)	(N=1317)
	n (%)	n (%)	n (%)	n (%)	n (%)
1 (Completed suicide)	0	1 (0.01)	0	1 (0.01)	0
2 (Suicide attempt)	0	2 (0.03)	0	2 (0.02)	0
3 (Preparatory acts toward imminent suicidal behavior)	0	0	0	0	0
4 (Suicidal ideation)	1 (0.02)	0	1 (0.01)	0	0
5 (Self injurious behavior, intent unknown)	0	0	0	0	0
6 (Not enough information, fatal)	0	0	0	0	0
7 (Self-injurious behavior, no suicidal intent)	0	0	0	0	0
8 (Other, accident, psychiatric, medical)	783 (13.8)	877 (12.6)	860 (10.2)	1024 (8.6)	23 (1.7)
9 (Not enough information, non-fatal)	0	1 (0.01)	0	1 (0.01)	0
<b>Total of all categories</b>	<b>784</b> <b>(13.8)</b>	<b>881</b> <b>(12.6)</b>	<b>861</b> <b>(10.2)</b>	<b>1028</b> <b>(8.7)</b>	<b>23</b> <b>(1.7)</b>

COPD Pool studies (16 studies) are FK1 101, FK1 103, IN-108, JP-706/708, M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-124, M2-125, M2-127 and M2-128.

OVERALL Pool studies (36 studies) include the 16 COPD studies plus the following studies: FHP 031, FKE 001, FKE 002, FK1 003, FK1 004, FK1 005, FK1 008, FK1 009, FK1 011, FK1 020, FK1 021, JP-705/707, M2-012, M2-013, M2-014, M2-017, M2-023, M2-026, and M2-401.

Note: If multiple events were reported in a patient, warranting assignment of more than 1 code (eg. suicidal ideation and other) the most severe event was listed and the patient was counted only once

Active = active control medication (beclomethasone dipropionate or montelukast); C-CASA = Columbia Classification Algorithm of Suicide Assessment; COPD = chronic obstructive pulmonary disease; Pbo = placebo; rof = roflumilast.

Two patients in the COPD studies committed suicide 21 days after ceasing roflumilast. On pharmacokinetic grounds, the evaluator believed that causality “cannot reasonably be assumed”.

The Delegate did not accept this reasoning. Antidepressants have a latency period to onset that is measured in weeks. It cannot be assumed that the time to offset of an agent that is linked to depression will be several elimination half-lives. Equally, the Delegate did not accept the evaluator’s reasoning that previous history or the use of venlafaxine in one case is indicative of anything more than a depressive diathesis and is not exculpatory of roflumilast.

The increase of suicides was not statistically significant. The evaluator concluded overall that evidence for a direct causal association between roflumilast and suicidality had not been unequivocally shown but that a cautionary statement in the PI would be helpful.

### **Risk Management Plan**

The May 2010 document may need revision in the light of responses by the sponsor. However, the evaluator noted that cilomilast was a recent and selective PDE4 inhibitor that was evaluated by the FDA in 2003 and but was not recommended for marketing approval. The evaluator commented: “The sponsor has not identified any potential or

identified risks with roflumilast. An area of missing/limited information concerns use during pregnancy and lactation.” Areas of interest to the evaluator included:

1. Neuropsychiatric adverse events in particular anxiety, depression and suicidality. The evaluator suggests that the PI should be updated to describe better neuropsychiatric adverse events occurring in clinical trials. These adverse effects should receive close attention during ensuing PSURs.

The Delegate noted that this assumes that disclosure alone will mitigate risk. In regard better epidemiological data, a specific study is now in preparation for the EU (see below).

2. Nonclinical studies in pregnant mice showed adverse effects on uterine muscle and its relevance to humans remains unknown. The evaluator suggests studies in human pregnancy.

The Delegate noted that the problem is that roflumilast is a tocolytic agent. It would be difficult to conduct an ethical study, even in women who needed short term tocolysis. Perhaps add-on to salbutamol could be contemplated.

3. Safety in patients with mild to moderate hepatic impairment. To address this, the Australian PI might advise dosage reduction to 250 µg daily in patients with mild to moderate hepatic impairment or limit prescribing to those with mild impairment only (consistent with the proposed US labelling).

The Delegate noted that a problem with this suggestion is the lack of a 250 µg tablet and the need for a rational basis for this dose by reference to pharmacokinetic data. However, the product information document can address this through contraindicating use in moderate and severe hepatic impairment.

4. Events of cardiac arrhythmia and pancreatitis in COPD clinical trials. No specific measures were suggested.
5. As outlined in the RMP, roflumilast is to be claimed to be an alternative anti-inflammatory to ICS; however there will be a natural desire of prescribers to prescribe ICS together with roflumilast in the absence of evidence to support such use. The evaluator recommended that the PI be updated to state that roflumilast is to be used instead of ICS as add on to bronchodilator activity.

### **Response to Risk Management Plan Report**

The sponsor provided a draft protocol which is the safety study that is planned for the EU and a draft effectiveness testing strategy of the educational materials for doctors and patients.

### **Final Comments by RMP Evaluator**

The above protocol was considered to be an acceptable study.

Some further recommendations have been made regarding the effectiveness testing strategy of the educational materials for doctors and patients.

### **Risk-Benefit Analysis**

#### **Delegate Considerations**

#### ***Delegate's Comments upon Clinical Evaluator's Findings***

1. Initial studies focused on lung function (FEV<sub>1</sub>) and quality of life (SGRQ) as efficacy endpoints. As the SGRQ turned out to be an insensitive endpoint to assess the treatment effect of an antiinflammatory agent such as roflumilast, the rate of certain types (moderate or severe) of COPD exacerbations was used as primary symptomatic benefit endpoint in

the 1 year studies. We need to know much more about the concept of quality of life benefit that is not related to respiratory scales. That is, anhedonia and mild depression may cancel out gains from reduced respiratory distress or may inhibit exercise tolerance.

2. Dose finding may not have been exhaustive enough:

[Study FK1 101] “This study failed to demonstrate statistically significant improvements with roflumilast (250 µg and 500 µg) over placebo for both primary efficacy endpoints of pre-bronchodilator FEV<sub>1</sub> and SGRQ total score. Although other lung function parameters such as post-bronchodilator FEV<sub>1</sub>, FVC, etc showed numerically better improvements with roflumilast, the difference from placebo was not statistically significant.” [Study M2-107] “bronchodilator lung function parameters (FEV<sub>1</sub>, FEV<sub>3</sub>, FEV<sub>6</sub>, AEX, FEF200-1200, FEF25-75, FVC, as well as morning PEF). Treatment with roflumilast 500 µg od also improved quality of life and lowered the incidence of COPD exacerbations. Furthermore, it is important to note that the primary lung function parameter in this study was post-bronchodilator FEV<sub>1</sub>, while the primary endpoint in previous dose ranging study FK1 101 and the pivotal studies was pre-bronchodilator FEV<sub>1</sub>. However, Rof250 and Rof500 also showed statistically significant improvements over placebo in pre-bronchodilator FEV<sub>1</sub> in this study.” ... “only the 500 µg dose of roflumilast was associated with reduction in incidence of COPD exacerbations and 250 µg roflumilast failed to show any improvement over placebo for clinical endpoints such as SGRQ, exacerbations, symptom score and use of rescue medication” ... “Based on the general lack of separation in efficacy parameters between the 250 and 500 µg doses, dose selection for the roflumilast program appears to have been arrived at by selection of the maximally tolerated dose.” It was noted that M2-107 used post-bronchodilator FEV<sub>1</sub> assessed as the primary endpoint.

3. The clinical significance of the modest gain in FEV<sub>1</sub> is doubtful, being less than that commonly seen with add-on inhaled corticosteroids (trough FEV<sub>1</sub>), [Study M2-124 12/12] “It is important to note that the study had 90% power to detect a difference of 46 mL in pre-bronchodilator FEV<sub>1</sub> and 80% power to detect 20% reduction in moderate/severe exacerbation between Rof500 and placebo treatment groups. The sponsor noted that this interpretation was incorrect; the sample size was calculated to have 90% power for both primary endpoints FEV<sub>1</sub> and exacerbations.

The results indicate a much smaller effect for roflumilast suggesting reduced power for the study.”<sup>77</sup>

“Although use of ICS and inhaled combinations of ICS and LABAs were prohibited according to study protocol, almost 10-11% of patients in each treatment group still used these drugs. The prevalent use of prohibited COPD drugs suggested that patients in the trials were under treated. This is especially important in light of the study design which seems to imply that roflumilast could be used instead of ICS in patients with severe or very severe COPD.”

The common adverse events are reminiscent of those found for methylxanthines (for example, Nuelin, Trental) but depressed mood is not. The nonclinical data support the crossing of the blood: brain barrier, so depression and anhedonia are plausible adverse effects even if the mechanistic basis is not clear.

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<sup>77</sup> The sample size calculations for M2-124 and M2-125 were actually calculated to have a power of 90% to detect a significant difference (two-sided alpha = 0.05) under the assumptions of a rate of 1.25 exacerbations requiring oral or parenteral glucocorticoids or hospitalisation or leading to death per patient per year (placebo group) and a reduction of 20% with roflumilast 500 µg (resulting in a rate of 1.00 exacerbations per year). The same power would result if the placebo rate were 0.8 and the reduction with roflumilast were 25%.

4. The CHPM's *Points to Consider* document is out of date and is under review.<sup>78</sup>

The replacement guideline will stress a number of secondary endpoints to include muscle strength, dyspnoea, imaging of the lung parenchyma and mortality. Whilst these aspects of the guideline does not apply retrospectively, the principles are sound and take into account the inflammatory nature of COPD and acknowledge that ICS are used in moderate to severe disease. However, this usage is acknowledged in the 1998 *Points to Consider* document.<sup>52</sup>

It is remarked, in the draft replacement guideline: "Weight loss, nutritional abnormalities, skeletal muscle dysfunction, cardiovascular effects, anaemia, systemic inflammation, mental dysfunction are well recognised extrapulmonary effects of COPD." ... "Although much of the damage is irreversible at the time of clinical presentation, early diagnosis and appropriate management can prevent and improve symptoms (particularly dyspnoea), reduce the frequency and severity of exacerbations, improve health status, improve exercise capacity and prolong survival. At present no treatment is shown to modify the rate of decline in lung function." ... "The mainstays of drug therapy for symptomatic relief in stable COPD are bronchodilators (primarily  $\beta_2$  agonists, anticholinergics and less often theophylline) and in more severe disease, inhaled glucocorticoids used in combination with long acting  $\beta_2$  agonists (LABA)." ... "To date no treatment has been shown to modify the long term decline in lung function. A possible effect of any treatment in the prevention of disease progression may be assessed by means of serial measurements of FEV<sub>1</sub> over time, comparing the difference in the decline in FEV<sub>1</sub> as measured by the slope of the FEV<sub>1</sub> curve between treatment groups. Because of the variability shown in longitudinal studies, confident assessment of the rate of decline in an individual patient requires a sufficient period of time, of at least several years." ... "Other measures of lung function which should also be recorded to characterise the effect of a new active substance include inspiratory capacity, FRC, RV/TLC, vital capacity, DLCO. These measures of pulmonary function may correlate better with improvements in symptoms and exercise tolerance than does FEV<sub>1</sub> and should be considered as possibly appropriate alternatives." ... "An evaluation of the frequency of exacerbations should normally be made over a period of at least one year due to seasonal variation in exacerbation rates. In any case, the timing of the study treatment may prove important (for example, capturing the winter cold season in the majority of patients)." ... "Chronic treatment of COPD with bronchodilators as monotherapy is usually restricted to symptomatic patients with moderate disease, since the combination of bronchodilators has shown a good benefit/risk balance. The addition of regular treatment with inhaled corticosteroids (ICS) to bronchodilator treatment is appropriate for symptomatic patients with a FEV<sub>1</sub> < 50% predicted (Stage III and IV COPD) and repeated exacerbations who have significant symptoms despite regular therapy with long acting bronchodilators."; and most significantly,

"New drugs intended to replace well known and well accepted therapies – bronchodilators or inhaled glucocorticosteroids. All patients entered into clinical studies should receive adequate background/maintenance therapy according to the severity of their disease. The appropriate study design would be either a three arm study where patients receive the new drug (the test product) in one arm, an established comparator in the second arm and placebo in the third (preferred option), or a two arm study comparing the new drug with the established active comparator. The three arm study would aim to demonstrate that the test product is superior to placebo and at least non-inferior to the active comparator; the two arm study would aim to demonstrate that the test product is at least non-inferior to

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<sup>78</sup>. CHMP Draft Guideline on clinical investigation of medicinal products in the treatment of COPD CPMP/EWP/562/98 Rev.1. Available at [www.eme.europa.eu/ema/pages/includes/document/open\\_document.jsp?webContentid=WC5000003550](http://www.eme.europa.eu/ema/pages/includes/document/open_document.jsp?webContentid=WC5000003550).

the active comparator. If only a comparison with placebo is available, the effect of the new drug must demonstrate clear statistically significant and clinically significant benefit over placebo and the safety profile must be carefully examined and described to ensure that the benefit/risk ratio is acceptable." ... "Most patients with moderate to severe COPD are treated with bronchodilators alone or bronchodilators plus ICSs. For drugs to be used as add-on therapy, a placebo comparison is acceptable, providing that all patients receive optimised background therapy (LABA in moderate disease or LABA plus ICSs in severe disease)." In regard to safety, "A particular safety concern for any immunomodulatory compound is the long term effect on host defence, cancer defence, wound healing or response to vaccination. Any dossier submitted should address such concerns. The incidence of upper respiratory tract infections, sinusitis, bronchitis, pneumonia and tuberculosis in controlled trials are of particular interest."

5. The clinical evaluator noted that the pivotal studies have taken some account of the newer guidance, "The guidance given to assess lung function and a symptomatic benefit endpoint as primary endpoints has been followed from study M2-107 onwards."

6. The C-CASA analysis of the pooled studies was not able to detect additional cases of suicide or suicidality. There is a problem in terms of sensitivity and it is not now possible to look in retrospect for depressed mood or anhedonia. A postmarketing study is planned for the EU.

### **Conclusion**

Although COPD is an inflammatory disease, the efficacy of inhaled glucocorticosteroids in altering the natural history of the disease has not been shown. The basis of inflammatory processes in COPD is complex and it is not likely that ICS would be effective. The rational basis for the use of ICS in COPD has recently been strongly questioned. An agent like roflumilast that might also, by reason of its primary pharmacology, affect inflammatory responses and also T-cell mediated immunity will arouse interest because of its long term therapeutic potential, particularly in mild to moderate disease. This potential effect on the natural history of the disease should not be attenuated by ICS whereas the symptomatic benefit of the combination with ICS has been left unexplored. This is a curious omission for developing a new drug that might be of benefit in to patients with a disease like COPD in whom there is no obvious reason to contraindicate the combination. It is unsurprising that the FDA has required a new efficacy study.

Roflumilast has not been developed as a second line agent.

If registered, the EU and USA postmarketing studies should be submitted.

Despite the vast development program for roflumilast, many questions remain about the role of this agent in COPD. Its absolute efficacy in the specific niche (add-on to LABAs) is modest and less than would be expected from inhaled corticosteroids. No useful information can be provided to prescribers in respect of use with inhaled corticosteroids. After several years, answers may be obtainable from the FDA's efficacy study.

Safety, especially with respect to depression of various degrees of severity and suicidality has been incompletely defined. The incidence could range from rare to uncommon but this cannot be quantified without studies that used specific and sensitive diagnostic instruments.

The Delegate directed the following questions to the ACPM:

1. Is there any basis for suggesting that roflumilast has a better risk: benefit ratio in severe COPD than in moderate COPD?

2. Given that most patients with severe COPD would be expected to receive inhaled corticosteroids, and that only oral corticosteroids were allowed in the trials, is there a definable patient population based on the submitted pivotal trials?
3. Does the committee agree that the optimal dose has been found?
4. Is the improvement in pre-bronchodilator FEV1 (around 40 mL) clinically significant?
5. Is the change in the rate of severe or moderate exacerbations of COPD (in studies M2-124 and M2-125), that is, about -17% over ... clinically significant?
6. Given the special concerns regarding weight loss, depression and suicidality, is it agreed that the CMI should be quite explicit? Should family members and carers be involved?

The Delegate proposed that the application should be rejected due to a lack of clinically meaningful efficacy and added benefit over risk.

If registered, the product information documents should be amended to reflect the suggestions of the evaluators and of the delegate. In particular the lack of evidence for long term morbidity and mortality benefits should be made clear, as should the lack of any experience of combined use of inhaled corticosteroids.

### **Response from Sponsor**

The sponsor responded to the reasons for the proposed rejection and the queries posed by the TGA Delegate and in respect to the submission and the proposed product information (PI).

The Delegate has stated that the application should be rejected due to:

- A lack of clinical meaningful efficacy: that is, many questions remain about the role of roflumilast in COPD, absolute efficacy is modest and less than would be expected from inhaled corticosteroids, use with inhaled corticosteroids is unknown until more data is available; and
- A lack of benefit over risk: that is, safety with respect to depression of various degrees and suicidality has been incompletely defined.

The sponsor addressed those reasons as follows:

### ***Unmet Clinical Need***

COPD is a major cause of disability, hospital admission and premature death. There is a clinical unmet need for new antiinflammatory treatment options in COPD, such as roflumilast, demonstrated by the inclusion of roflumilast in the GOLD and Australian COPDX guidelines. The pathophysiology is complex and patients with more severe disease remain symptomatic and poorly controlled despite available treatment. The proposed indication reflects this need. However, it is now proposed that the indication be further amended as described above to critically address the population most at risk. This statement is supported by the Chair, Australian Lung Foundation COPD Coordinating Committee, in a supporting letter that states: "...since roflumilast reduces risk of both moderate and severe exacerbations (the latter being characterized by hospitalizations and high cost), its role in event reduction warrants availability of the drug. [...] In summary, there is an unmet clinical need for a new class of drug that has strong evidence for improving symptom control and reducing events such as exacerbations (hospitalizations), with minimal and manageable adverse effects."



## ***Efficacy***

The data submitted clearly demonstrate that the statutory test for efficacy has been clearly met. The patient population roflumilast is proposed for, that is, patients with severe COPD and at risk of frequent exacerbations, is very ill and still inadequately treated. Therefore, any incremental benefit is important in this specific group of COPD patients. Exacerbations not only have a dramatic impact on patients' quality of life but also contribute to long term decline in lung function [Donaldson 2002].<sup>79</sup> Each reduction in occurrence of exacerbations helps to reduce severity and burden of COPD. Consequently, reduction in frequency, severity, or duration, or the prevention of COPD exacerbations is seen as a key goal in COPD management. Regulatory guidelines recommend investigating exacerbations as a primary endpoint during development of new drugs for COPD (CHMP draft COPD guideline, 2 July 2010; FDA draft COPD guidance, Nov 2007).<sup>78,80</sup>

Data from the roflumilast pivotal 1 year studies M2-124 and M2-125, as well as the supportive 6 month studies M-127 and M2-128 and the supportive 1 year studies M2-111 and M2-112 show that roflumilast consistently and clinically reduced the rate of moderate or severe exacerbations.

The proposed indication is based on the two pivotal studies specifically designed to reflect the targeted patient population. In each of these studies, roflumilast significantly improved both primary endpoints, that is, the rate of moderate or severe exacerbations and pre-bronchodilator FEV<sub>1</sub>, over placebo [Calverley 2009].<sup>81</sup> Roflumilast was effective and safe in the subgroups of patients by concomitant LABA treatment, by previously received ICS, and in patients with a history of one, as well as at least two exacerbations in the year prior to the study [Calverley 2009, Bateman 2011].<sup>81,82</sup> Data on roflumilast in patients treated with ICS is available from the earlier large 1 year studies M2-111 and M2-112, demonstrating that roflumilast use is safe and effective in patients treated with ICS. In the supporting 6 month studies M2-127 and M2-128, roflumilast significantly improved lung function and reduced exacerbations in patients already taking the LABA salmeterol or the LAMA tiotropium, respectively. It was considered important to note that the TGA-adopted EU guideline does not require ICS as a comparator in clinical trials.<sup>52</sup> As roflumilast is a new chemical entity and will be used last line as shown by the summary of the ALF "Stepwise Management of Stable COPD", trials were conducted against placebo.

In summary, ICS had not been allowed in the pivotal studies since clinical data for roflumilast and ICS were already available from the earlier 1 year studies M2-111 and M2-112, in which about 60% of patients concomitantly received ICS. Roflumilast was effective with and without concomitant ICS treatment. When the analysis was restricted to patients with chronic bronchitis (with or without emphysema) and severe to very severe COPD, in line with the pivotal studies and the proposed indication, the reduction in moderate or severe exacerbations was 27.6% in patients with ICS and 21.6% in patients without ICS

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<sup>79</sup> Donaldson GC, Seemungal TAR, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57: 847-852.

<sup>80</sup> FDA Draft guidance for Industry, COPD: Developing Drugs for treatment, November 2007.

<sup>81</sup> Calverley PM, Rabe KF, Goehring UM, Kristiansen S et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet* 2009; 374: 685-694.

<sup>82</sup> Bateman ED, Rabe KF, Calverley PM, Goehring UM et al. Roflumilast with long-acting  $\beta$ 2-agonists for COPD: influence of exacerbation history. *Eur Respir J* 2011; 38:553-560.

[Rennard 2011].<sup>83</sup> The NNT to prevent one moderate or severe exacerbation was 5.3 and 3.6 in M-124 and M-125, respectively.

### **Safety**

The sponsor noted that any risks associated with weight loss, depression and suicidality will be highlighted in the PI and CMI similar to the EU version. A suggestion was submitted for the involvement of family members and carers in the aforementioned documents. The sponsor also noted that in the USA a Risk Evaluation and Mitigation Strategy (REMS) was considered as not required by FDA for roflumilast tablets.

PSUR No. 2 dated 18 August 2011 did not identify any new safety signals. Reports of weight loss, depression and suicidality were much lower than observed in clinical trials and as expected, even when accounting for 95% underreporting. This low reporting rate, in spite of the fact of mandatory distribution of educational materials to prescribers and patients highlighting these risks, and despite a manifold higher prevalence of these risks in this population, particularly of depression and suicidality, should reasonably assuage these special concerns. Overall, PSUR No. 2 did not identify any new safety signals. In addition, since the data lock point, no new information was received that would give rise to a late breaking update of this PSUR, were much lower than observed in clinical trials than expected. Risk will also be managed through the proposed RMP.

Nevertheless, the sponsor agreed that the risks of weight loss, depression and suicidality should be highlighted in the PI and CMI. For this purpose, the PI and CMI were to a large extent aligned with the approved EU Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL), with particular focus on the sections on Contraindications, Precautions and Adverse Effects.

#### ***Question 1: Is there any basis for suggesting that roflumilast has a better risk: benefit ratio in severe COPD than in moderate COPD?***

Two subgroup analyses of the clinical database provide the basis for concluding a better risk:benefit ratio of roflumilast in severe than in moderate COPD. Firstly, with respect to COPD severity purely based on lung function, the numbers of patients with mild (<1%) or moderate (7% to 11%) COPD by FEV<sub>1</sub> % predicted values that were randomized into the pivotal trials were limited. The treatment effect of roflumilast was substantially larger in the subgroups with severe or very severe COPD than in moderate COPD.

Secondly, when symptoms and previous exacerbations were taken in determination of disease severity, the reduction in exacerbations achieved with roflumilast versus placebo was 22.3% in patients with at least 2 exacerbations in the year before study start [Bateman 2011].<sup>82</sup> Consistent with the high medical need in these patients, severe COPD patients are considered to benefit the most from roflumilast treatment, which is reflected in the proposed indication.

#### ***Question 2: Given that most patients with severe COPD would be expected to receive inhaled corticosteroids, and that only oral corticosteroids were allowed in the trials, is there a definable patient population based on the submitted pivotal trials?***

The sponsor stated that the definable target population was:

*Adult patients with severe chronic obstructive pulmonary disease (COPD) with chronic bronchitis and recent history of frequent exacerbations as add-on to bronchodilator treatment.*

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<sup>83</sup> Rennard SI, Calverley PM, Goehring UM, Bredenbröker D. Reduction of exacerbations by the PDE4 inhibitor roflumilast – the importance of defining different subsets of patients with COPD. *Respiratory Research* 2011; 12: 18.

The proposed indication reflects the patient population who benefits most from roflumilast as a new treatment option added on to long acting beta-2 agonists and anticholinergic agents. Roflumilast has been shown to be effective and safe in patients on ICS.

The pivotal trials M2-124 and M2-125 were designed and powered based on the findings from the early 1 year studies M2-111 and M2-112. The early studies were conducted in a COPD population only distinguished by severe lung function impairment, but pooled *post hoc* subgroup analyses suggested pronounced treatment effects in patients further characterized by chronic bronchitis and a history of prior exacerbations [Rennard 2011].<sup>83</sup> Therefore the pivotal trials were conducted in a targeted patient population with symptomatic COPD, severely impaired lung function, chronic bronchitis, and a history of exacerbations. Each of the two pivotal trials demonstrated a significant and clinically relevant reduction in the rate of moderate or severe exacerbations, and a significant small improvement of prebronchodilator FEV<sub>1</sub>, over placebo [Calverley 2009].<sup>81</sup> Efficacy was also demonstrated for subgroups by concomitant LABA treatment, by previously received ICS, and in patients with a history of one exacerbation, as well as an even higher effect on exacerbations in patients with at least two exacerbations in the year prior to the study [Bateman 2011].<sup>82</sup>

As explained under the heading Efficacy, ICS were not allowed in the pivotal trials, but in earlier trials.

About 50% of patients in the two pivotal studies were concomitantly treated with LABA, demonstrating that treatment effects of roflumilast on exacerbations and lung function were independent of concomitant LABA therapy [Bateman 2011].<sup>82</sup> Two 6 month studies, M2-127 (maintenance treatment with LABA salmeterol) and M2-128 (add-on to LAMA tiotropium), confirmed that roflumilast adds benefits for patients on concomitant bronchodilator therapy and is safe in these patients. Both studies showed significant improvements in lung function with roflumilast versus placebo. The reduction of moderate or severe exacerbations with roflumilast was in the order of magnitude as that seen in the two pivotal studies or even larger (36.8% in salmeterol-treated [p = 0.0315, 2-sided, *post hoc* analysis] and 23.2% in tiotropium treated patients [p = 0.1957, 2-sided] [Fabbri 2009].<sup>84</sup>

In conclusion, the effects of roflumilast as add-on to currently available COPD medication are important for this patient population considering that these patients are very ill with each exacerbation greatly impacting their daily quality of life. Two large placebo controlled studies are underway to confirm the efficacy of roflumilast as add-on to LABA and ICS.

### ***Question 3: Does the committee agree that the optimal dose has been found?***

The maximal tolerated dose (MTD) of roflumilast was determined as a dose of roflumilast 1000 µg per day, associated with a higher number and more pronounced adverse events as compared with the 500 µg dose.

The selection of the optimal therapeutic dose is primarily based on study FK1 101 and study M2-107. Roflumilast was used at doses of 250 µg and 500 µg in these studies as both doses were shown to be safe and well tolerated in Phase I studies. Both studies showed a consistent dose ordering with a higher response for the 500 µg dose, as compared to the 250 µg dose, for the primary and most secondary lung function endpoints. Statistically

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<sup>84</sup> Fabbri LM, Calverley PM, Izquierdo-Alonso JL, Bundschuh DS. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with long acting bronchodilators: two randomised clinical trials. *Lancet* 2009; 374: 695-703.

significant differences between the two roflumilast doses in favour of the higher dose were seen in study M2-107 for the secondary endpoints post-bronchodilator FEV<sub>3</sub> and FEV<sub>6</sub> as well as for time to first mild, moderate or severe exacerbation. The 250 µg dose was slightly better tolerated than the 500 µg dose, yet both doses were reasonably tolerated.

Overall, based on the broad clinical experience from all roflumilast COPD studies, the 500 µg dose was identified as the optimal dose in the proposed indication, since it provided better treatment effects on lung function compared to the 250 µg dose, a significant effect on COPD exacerbations in the pivotal studies, and was safe and well tolerated.

***Question 4: Is the improvement in pre-bronchodilator FEV<sub>1</sub> (about 40mL) clinically significant?***

Roflumilast consistently demonstrated statistically significant improvements in lung function throughout clinical development. For the intended patient population the lung function improvement is considered clinically relevant. The 48 mL gain in pre-bronchodilator FEV<sub>1</sub> with roflumilast in the pivotal studies was achieved in patients with a mean baseline prebronchodilator FEV<sub>1</sub> of only 1 L. In addition, lung function effects of roflumilast were seen in patients at maximum bronchodilation (post-bronchodilator measurements), and in patients being treated with effective long acting beta-2 agonists or anticholinergic agents, clearly indicating that roflumilast improves lung function over and above what can be achieved with other COPD treatments alone. The sponsor agreed, however, that for an anti-inflammatory compound without direct bronchodilatory activity, FEV<sub>1</sub> measurement can only serve as required evidence for pharmacodynamic effectiveness, but not as a measure for comparison with direct bronchodilators. For clinical efficacy in the intended population, the pivotal trials and the more recent clinical development focused therefore on the reduction of exacerbations as the symptomatic and clinically relevant outcome as reflected in the CHMP and FDA COPD guidelines.<sup>52,80</sup>

***Question 5: Is the change in the rate of severe or moderate exacerbations of COPD (in studies M2-124 and M2-125) that is, about -17% over...clinically significant?***

The sponsor noted that the 17% reduction in exacerbations is over and above the reduction these patients already receive from their bronchodilator medication. Acute exacerbations are significant events for patients with severe COPD, with negative impact on their quality of life and prognosis. Severe or frequent exacerbations are associated with accelerated decline in lung function and health status, increased mortality and escalating healthcare costs. The prevention and reduction of exacerbations remain the focus of management strategies and research.

In the proposed population, the observed reduction of moderate or severe exacerbations represents a clinically relevant effect.

In the pivotal studies, a history of at least one exacerbation was required for inclusion. When the subgroup of patients with at least 2 exacerbations in the year prior to study start was analysed, in analogy to the recently described frequent exacerbator phenotype [Hurst 2010, Soler-Cataluna 2010], the reduction achieved with roflumilast versus placebo amounted to 22.3% [Bateman 2011].<sup>82,85,86</sup> The treatment effects of roflumilast in the two pivotal studies (15% and 19% reduction) were achieved on a background of treatment with long acting beta-2 agonists (50% of patients). In the subset of patients concomitantly

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<sup>85</sup> Hurst JR, Vestbo J, Anzeuto A, Locantore N. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Eng J Med* 2010; 363:1128-1138.

<sup>86</sup> Soler-Cataluna and Rodriguez-Roisin. Frequent chronic obstructive pulmonary disease exacerbators: how much real, how much fictitious? *J Chron Obstruct Pulmon Dis* 2010; 7: 276-284.

receiving LABA, a reduction in moderate or severe exacerbations of 21% was observed with roflumilast plus LABA compared to placebo plus LABA.

These results may be compared to published data from the 1 year TRISTAN study, which also included COPD patients with chronic bronchitis and at least one exacerbation in the year before trial entry [Calverley 2003, Calverley 2006].<sup>87,88</sup> In the subgroup of TRISTAN patients with severe and very severe COPD, the reduction of exacerbations defined by a medical intervention or hospitalization with combined ICS and LABA (fluticasone and salmeterol) over LABA (salmeterol) was 9% [Calverley 2006].<sup>88</sup> In the TRISTAN study [Calverley 2006], the NNT of combined fluticasone and salmeterol was 2.4 per year of therapy compared to the placebo group, and 10 per year comparing combination therapy with salmeterol.<sup>87</sup> In the TORCH study [Calverley Lancet 2007, Halpin 2008], the NNT for salmeterol/formoterol was 3.6 versus placebo and 8.3 versus salmeterol.<sup>89,90</sup> In two studies with budesonide and formoterol [Szafranski 2003, Calverley ERJ 2003], the NNT of combination therapy compared with formoterol alone or with placebo was 2.1 to 2.4.<sup>91,92</sup>

***Question 6: Given the special concerns regarding weight loss, depression and suicidality, is it agreed that the CMI should be quite explicit? Should family members and carers be involved?***

This question was addressed above.

**Advisory Committee Considerations**

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised that the submission has not satisfactorily demonstrated adequate safety and efficacy in the proposed indication for the following reasons:

***Efficacy***

It was noted that all outstanding chemistry and quality control aspects have been addressed.

In general, roflumilast had a modest effect on lung function but no effect on FRC and a modest effect upon the number of exacerbations in COPD trial patients. Any benefit tended to be seen early, with the early benefit maintained or the actively treated group trending towards the placebo group towards the end of studies. The improvement demonstrated in the pre-bronchodilator FEV<sub>1</sub> was not considered clinically significant; however, the committee was of the opinion that the change in the rate of severe or moderate exacerbations of COPD in studies M2-124 and M2-125 was reasonably significant, but the number needed to treat was variable in different studies. There was no evidence available to suggest that an approximate 17% reduction in exacerbations would occur in the context

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<sup>87</sup> Calverley PM, Pauwels RA, Vestbo J, Jones P et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease : a randomised controlled trial. *Lancet* 2003; 361:449-456.

<sup>88</sup> Calverley PM, Pauwels RA, Jones PW, Anderson JA et al. The severity of airways obstruction as a determinant of treatment response in COPD. *International Journal of COPD* 2006; 1: 209-218.

<sup>89</sup> Calverley PM, Anderson JA, Bartolome Celli M, Ferguson GT et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Eng J Med* 2007; 356: 775-789.

<sup>90</sup> Halpin D. Mortality in COPD: Inevitable or preventable? Insights from the cardiovascular arena. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2008; 5: 187-200.

<sup>91</sup> Szafranski W, Cukier A, Ramirez A, Menga G et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2003; 21: 74-81.

<sup>92</sup> Calverley PM, Boonsawat W, Cseke Z, Zhong N et al. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J* 2003; 22: 912-919.

of best standard of care (including, for example, inhaled corticosteroids). The committee noted the narrow patient population in the pivotal trials.

The committee expressed concern that no study was conducted to evaluate efficacy of roflumilast compared to standard treatment care for patients with COPD - concomitant use of a LAMA with and inhaled corticosteroid (ICS) in combination with a LABA. The studies submitted did not investigate roflumilast either as an alternative to, nor was it compared with, these drugs. The committee considered that there was insufficient evidence submitted to suggest that roflumilast has a better risk benefit ratio in severe COPD than in moderate COPD. The dose ranging studies did not provide clear substantiation of an optimal dose.

### **Safety**

The incidence of adverse events and discontinuations was significantly greater in the roflumilast 500 µg group compared to the placebo subjects. The committee noted the higher incidence of weight loss compared to placebo in a patient group who may well already be underweight.

Of particular concern to the committee was the increase in psychiatric adverse events in the roflumilast group compared to placebo, and in none of the three completed suicide cases did the patient have a prior history of depression. The committee noted that additional findings from a different sponsor in Japan showed an approximate twofold increase in psychiatric adverse events in patients receiving 500 µg of roflumilast once daily, persistent across studies in different patient populations and which appears to be dose related. It was also noted that dosing experience in hepatic impairment is limited to 250 µg per day. The optimal dose has not been found although it is unlikely to be higher than that proposed.

With regard to nonclinical safety data the sponsor was encouraged to undertake neuropharmacological studies to ascertain roflumilast's CNS effects, particularly in regard to depression. Due to some concern regarding tumourigenicity, further nonclinical studies examining potential immunosuppression are warranted. As presented, the nonclinical data package appears to be inadequate given some emergent clinical safety signals.

Most patients with severe COPD would be expected to receive inhaled corticosteroids but only oral corticosteroids were allowed in most of the trials, including the designated pivotal ones. There is no definable patient population based on the submitted pivotal trials: the combined use of inhaled corticosteroids, long acting beta adrenergic agonists and long acting muscarinic antagonists is very common. The ACPM noted that drug interactions were confirmed in pharmacokinetic studies. It is doubtful that roflumilast can be used with other agents with effects upon phosphodiesterase, for example, theophylline.

The ACPM was of opinion that the risk benefit profile of roflumilast in this COPD is negative due to a lack of clinically meaningful efficacy compared to added risks. However, the large ongoing studies that are in the planning stage (one principally designed for more realistic efficacy outcomes, the other for safety outcomes) will contribute more relevant information than has been presented in this submission, and the applicant is encouraged to submit these studies when they become available. The efficacy study would be of sufficient duration to suggest information about durability of efficacy, and perhaps effects on the natural history of the disease, both of which are currently unclear.

### **Outcome**

The sponsor elected to withdraw the submission due to commercial reasons before a decision was made.

The sponsor noted that roflumilast tablets have been approved in many countries worldwide, including the EU (05 July 2010), and the USA (28 February 2011) where post-authorisation studies are performed to confirm the place of roflumilast in the COPD armamentarium. The sponsor expected that the outcome of these studies will answer the outstanding questions raised by the Delegate and ACPM.

## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia

Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6232 8605

[www.tga.gov.au](http://www.tga.gov.au)