

## Press Release

### **Roflumilast, a novel once-a-day tablet for COPD, reduces exacerbations and improves lung function**

- Roflumilast an investigational drug
- Offers a new treatment principle that addresses the underlying inflammation of chronic obstructive pulmonary disease (COPD)
- Clinically meaningful benefit, also when given in addition to established bronchodilator therapy.

**Results of four placebo controlled phase III trials, presented today in Vienna at the European Respiratory Society Congress 2009, show that roflumilast, a phosphodiesterase 4 (PDE4) inhibitor, produces a statistically significant and clinically relevant reduction in exacerbations in patients with moderate to severe COPD. The studies also demonstrated that roflumilast works independently of current COPD treatments and provides additional benefits, such as reducing exacerbations and improving lung function when added to standard bronchodilator therapy.<sup>1,2,3</sup>**

Roflumilast, a once daily oral tablet, is a novel treatment being developed specifically for treatment of COPD. If approved, it will be a new approach to treat COPD and the underlying chronic inflammation with a fundamentally different mode of action. COPD is an under-diagnosed progressive lung disease that may lead to death. Worldwide, COPD kills one person every 15 seconds<sup>4</sup> and the World Health Organization predicts that it will be the third leading cause of death by 2030.<sup>5</sup>

The four placebo controlled trials demonstrated significant reductions in exacerbations between 15% and 37% and significant improvements in lung function.<sup>1,2,3</sup> Patients taking roflumilast also had a prolonged time to the first exacerbation in both six-month trials when compared with salmeterol or tiotropium alone and in the combined 12-month studies when compared with placebo, as well as a prolonged time to a recurrent exacerbation in the 12-month studies.<sup>1,2</sup> In the six-month studies, roflumilast treatment resulted in a reduction of up to 40% in the number of patients experiencing exacerbations compared with those using standard treatment alone, i.e. salmeterol+roflumilast vs. salmeterol alone (p=0.0015).<sup>2</sup>

In the 12-month studies (pooled data) patients on roflumilast also showed a significant reduction in exacerbations requiring intervention with antibiotics or systemic corticosteroids (excluding severe events). Severe exacerbations requiring hospitalisation were also less common in the roflumilast treated group in the pooled analysis with a reduction of 18% (p=0.1334).<sup>1</sup>

The demonstrated reduction of exacerbations with roflumilast treatment is important, as recurrent exacerbations in COPD have been shown in the literature to be associated with long term decline in lung function, a worse prognosis, including increased mortality and a diminished quality of life, reducing a patient's ability to carry out normal daily activities.<sup>6,7,8</sup> Research also suggests that for patients, an exacerbation can be every bit as terrifying and bewildering as a

heart attack<sup>7,8</sup> and that following an exacerbation, patients admit to giving up hope of ever being able to live a normal life again.<sup>8</sup>

Evidence shows that mortality at 12 months following hospital admission for an exacerbation of COPD is worse than the mortality observed at 12 months following hospital admission with an acute heart attack.<sup>9</sup> The potential to reduce exacerbations addresses a clear unmet need in COPD management.

The number of patients that needed to be treated with roflumilast to prevent one moderate to severe COPD exacerbation per year was small (about five patients).<sup>1</sup> This is much lower than the number of people that need to be treated with cholesterol lowering drugs in order to prevent one heart attack.<sup>10</sup>

In the placebo controlled 12-month trials, roflumilast also provided consistent and statistically significant improvements in lung function measured both as pre- and post- bronchodilator FEV<sub>1</sub> (forced expiratory volume in one second). On average, pre-bronchodilator FEV<sub>1</sub> improved by 48 mL and post-bronchodilator FEV<sub>1</sub> by 55 mL compared with placebo (p<0.001; pooled analysis).<sup>1</sup>

In the six-month trials roflumilast showed incremental benefit when used concomitantly with current standard bronchodilator therapies, i.e. salmeterol or tiotropium. On average the pre-bronchodilator FEV<sub>1</sub> improved by 49 mL in the salmeterol/roflumilast trial and 80 mL in the tiotropium/roflumilast trial compared with salmeterol or tiotropium respectively, plus placebo (p<0.001).<sup>2</sup>

“Roflumilast could be an important new treatment for COPD,” said Professor Fernando Martinez, University of Michigan, and a lead author of the 12-month studies. “We clearly need new options for patients with COPD and the results of the studies confirm that roflumilast is beneficial. It reduced exacerbations and significantly improved lung function, in a patient population whose lung function is very poor.”

Professor Leonardo Fabbri, Professor of Respiratory Medicine, University of Modena and Reggio Emilia, Italy, and lead author of the six-month studies, said: “Roflumilast has a novel mode of action and has the potential to become the first of a new class of drugs as well as the only completely new treatment option for COPD in the next several years. The studies show that in addition to confirming the sustained, statistically significant improvements in lung function, roflumilast also provided additional benefit on symptoms, in particular when given in addition to the long acting inhaled bronchodilator tiotropium. The results of the two six-months trials examining the additive effect of roflumilast on top of salmeterol or tiotropium, support and extend the findings of the 12-month trials, by showing a clinically relevant lung function improvement in patients with impaired lung function on top of maximum bronchodilation.”

Nycomed’s Executive Vice President R&D, Anders Ullman, said: “We are very pleased with the clinical data on roflumilast. In four phase III studies: two 12-month studies and two six-month studies, roflumilast showed clear therapeutic potential, decreasing exacerbations and improving lung function. The uniformity of the results is really encouraging and gives us great hope that our faith in roflumilast has been confirmed. We are now undergoing the regulatory review process with the European and US authorities.”

The two six-month trials and two replicate 12-month trials, involving 4,500 patients, were conducted in 10 countries.<sup>1,2</sup> The 12-month trials compared roflumilast with placebo;<sup>1</sup> the six-month trials compared roflumilast with placebo, each given in combination with either salmeterol or triotropium, current bronchodilator treatments for COPD.<sup>2</sup>

Roflumilast was generally well tolerated. Nausea, diarrhoea and weight loss were the most common adverse events recorded in patients in the four trials. Diarrhoea and nausea were generally mild to moderate in intensity and most evident in the first weeks of treatment and usually disappeared after one or a few weeks of treatment. Most patients who experienced weight loss regained weight after stopping treatment.<sup>1,2</sup>

## About Roflumilast

Roflumilast is an orally administered phosphodiesterase 4 (PDE4) enzyme inhibitor targeting cells and mediators in the body believed to be important in the COPD disease process. Roflumilast is expected to act on the underlying mechanism of COPD and related inflammatory diseases. If approved, roflumilast, a once-a-day oral tablet, will be the first in an entirely new class of treatment for COPD. It will also be the first oral anti-inflammatory treatment for COPD patients. Current treatment for COPD patients includes the use of inhaled bronchodilators and inhaled corticosteroids.

## Roflumilast at ERS 2009

<b>Date, time, venue</b>	<b>Event</b>
Sunday 13, 13.00-14.00, Room C8 & D3	Clinical Trial session: "PDEIV inhibitors in the treatment of COPD - the Roflumilast Trials"
Sunday 13, 15.45-17.00, ERS Media Centre	Nycomed press conference: Roflumilast Breaking News: Phase III trial results
Sunday 13, 17.15-19.00, Room D3	Evening Symposium: Emerging Novel Therapies in COPD
Monday 14, 8.30-10.30, Lehar 3-4	Oral presentation – Phase III studies

## About Nycomed

Nycomed is a privately owned global pharmaceutical company with a differentiated portfolio focused on branded medicines in gastroenterology, respiratory and inflammatory diseases, pain, osteoporosis and tissue management. An extensive range of OTC products completes the portfolio.

Its R&D is structured around partnerships and in-licensing is a cornerstone of the company's growth strategy.

Nycomed employs 12,000 associates worldwide, and its products are available in more than 100 countries. It has strong platforms in Europe and in fast-growing markets such as Russia/CIS and Latin America. While the US and Japan are commercialised through best-in-class partners, Nycomed plans to further strengthen its own position in key Asian markets.

Headquartered in Zurich, Switzerland, the company generated total sales of €3.4 billion in 2008 and an adjusted EBITDA of €1.2 billion.

For more information visit [www.nycomed.com](http://www.nycomed.com)

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