# 8. DISCUSSION OF BENEFIT/RISK

## 8.1. Introduction

The increasing morbidity and mortality from COPD in the US suggests that, for many patients, currently available therapy does not meet their needs. Bronchodilators provide symptomatic benefit and are the only approved drugs to treat COPD. The complexity of COPD pathophysiology suggests that many patients will require more than one class of medication to optimally control their disease.

COPD is a heterogeneous disease characterized by a chronic and sustained inflammatory response, associated with many inflammatory cells and mediators. The rationale for the use of PDE4 inhibitors in the treatment of COPD is based upon the predominance of the PDE4 isozyme in inflammatory cells and its role as a major regulator of cyclic adenosine monophosphate (cyclic AMP) in airway smooth muscle [Torphy, 1991; Torphy, 1993]. Treatment with cilomilast, a second generation oral PDE4 inhibitor, would provide an important new treatment option for patients with COPD.

The clinical utility of first generation PDE4 inhibitors was limited by class-associated gastrointestinal side effects such as nausea and vomiting. Cilomilast was designed to improve the therapeutic activity of the first generation compounds but with a reduced propensity to elicit gastrointestinal effects.

The following sections will discuss evidence supporting the use of cilomilast for the maintenance of lung function in patients with COPD.

## 8.2. Benefits

### 8.2.1. Lung Function

Clinical development programs for drugs used to treat COPD and asthma, have relied on $FEV_1$ as the gold standard for the assessment of efficacy. Due to the irreversible lung damage associated with COPD, a smaller magnitude of effect is expected in patients with COPD as compared to asthma. The cilomilast pivotal development program was restricted to include only patients with COPD who were poorly reversible to bronchodilators (less than 15% or 200mL improvement over baseline in $FEV_1$) with an 80ml (6.6%) increase in $FEV_1$ observed post-albuterol at baseline. Poorly reversible patients with COPD are known to have a decreased magnitude of $FEV_1$ response to COPD medications as compared to a more reversible COPD population [Mahler, 1999; Rennard, 2001].

Overall in the phase III pivotal studies, $FEV_1$ was maintained in patients treated with cilomilast, whereas lung function declined in placebo treated patients. The magnitude of effect across all pivotal studies was similar. In both NA studies the difference from placebo was statistically significant and this is the patient population for which we are seeking approval. In patients with COPD the progressive loss of lung function is associated with increasing morbidity and mortality. The results of the four 24-week

studies suggest that treatment with cilomilast could lead to clinically relevant benefits associated with the long-term maintenance of lung function in poorly reversible patients with COPD; however, placebo controlled data are not available beyond 6 months. The pathophysiological mechanisms underlying these benefits are not fully understood, however, in poorly reversible patients, the maintenance of lung function may be related to anti-inflammatory activity.

Open-label long-term extension studies conducted for up to three years allowed for an evaluation of cilomilast in over 1000 patients with COPD. With all the caveats inherent to uncontrolled studies, the prior cilomilast group, maintained $FEV_1$ at a value similar to baseline at 60 weeks, in an otherwise progressively deteriorating condition. Patients not previously treated with cilomilast showed an early improvement in $FEV_1$, followed by a gradual deterioration similar to the deterioration seen in the group of patients previously treated with cilomilast. Patients newly exposed to cilomilast in the long-term studies (prior placebo group) generally did not achieve the same mean changes from Baseline in $FEV_1$ as the group started earlier on cilomilast (prior cilomilast group). This observation implies that the 6-month delay in initiation of therapy resulted in a small loss of pulmonary function, which was not regained throughout the long-term extension studies.

Study 168 permitted the evaluation of cilomilast in the broader population of patients with COPD. A greater magnitude of response was observed in the reversible (difference from placebo 130ml) as compared to the poorly reversible patients (difference from placebo 30ml). This result is not unexpected as $beta_2$ agonists relax smooth muscle via the activation of adenyl cylase, which elevates intracellular cyclic AMP, with the functional response measured by $FEV_1$. Hence, the expected response to PDE4 inhibitors, which also elevate cyclic AMP, should be proportional to bronchodilator reversibility. This suggests that in the broader population of patients with COPD, a larger magnitude of response would be observed with cilomilast.

Although the measurement of $FEV_1$ is of unquestionable diagnostic utility, and has been an accepted measure of disease severity in COPD, there is evidence to indicate that $FEV_1$ alone may have limitations as a clinical outcome measure for the evaluation of efficacy in COPD [Belman, 1996; O'Donnell, 1998; O'Donnell, 1999; O'Donnell, 2000]. Patients treated with cilomilast demonstrated substantial and clinically relevant improvements in lung volumes, with modest improvements in $FEV_1$ when compared to placebo. These findings are consistent with previous studies of albuterol in patients with COPD [Newton, 2002; O'Donnell, 2001], and the changes seen in lung volumes and $FEV_1$ in these studies were similar to the changes seen with cilomilast in Study 111. The benefits observed on lung hyperinflation are of importance because they are more predictive than $FEV_1$ for functional impairment in patients with COPD [O'Donnell, 2001].

### 8.2.2. SGRQ

Quality of life is recognized as an important factor to consider when evaluating the treatment of patients with COPD. The quality of life in patients with COPD decreases significantly as the disease progresses. Because patients often modify their lifestyles to compensate for dyspnea and activity limitation, it is important that treatment also result in improvements in the patient's quality of life. In both NA studies, statistically significant

differences from placebo were observed for the SGRQ total score. In Study 039 patients treated with cilomilast demonstrated a clinically meaningful improvement of -4.1 points in total score of the SGRQ relative to placebo. In Study 156, an improvement from baseline in SGRQ total score of -3.2 points was observed; however, placebo also showed some improvement and the resulting difference from placebo was -1.9 points.

The EU studies did not demonstrate a significant difference between patients receiving cilomilast and placebo. This was due to a larger placebo response, which may be related to differences in baseline SGRQ scores across the EU countries. However, consistent improvements from baseline in SGRQ were observed in patients receiving cilomilast across the NA and EU studies.

Patients who completed NA Study 039 were eligible to enter the NA open-label extension Study 041. In those patients treated with cilomilast in Study 039, a clinically meaningful benefit was observed and this was maintained throughout the open label extension Study 041. Those patients initially treated with placebo in Study 039, showed no benefit in SGRQ, however, when cilomilast was administered to this group of patients a clinically meaningful benefit was obtained at most timepoints. These findings are in contrast to prior observations of a progressive decline in total score of the SGRQ in patients with COPD [Spencer, 2001].

The efficacy seen in the cilomilast treatment group during the pivotal studies was maintained beyond 24 weeks in the open label extension studies. Those patients initially treated with placebo in the pivotal studies also demonstrated improvements in SGRQ when treated with cilomilast in the open label extension studies.

### 8.2.3. COPD Exacerbations

Two of the four pivotal studies showed significant reductions in the relative risk of experiencing at least one level 2 or 3 COPD exacerbation. However, the analysis of time to first level 2 or 3 COPD exacerbation did not take into account the frequency and duration of COPD exacerbations. Consequently, a post-hoc analysis was performed to compare the percent of patients experiencing an exacerbation on any given day throughout the pivotal studies. Using the pooled data from all pivotal trials, cilomilast significantly reduced the percent of patients experiencing a level 2/3 COPD exacerbation on any given day by 24% as compared with placebo.

In the long-term extension studies, the rate of exacerbations was low and was less than expected compared to published literature where the average ranges between 1-3 exacerbations/patient-year [Anthonisen, 1987; Seemungal, 1998; Seemungal, 2000; Seemungal, 2001].

## 8.3. Risks

Co-morbid conditions occur frequently in patients with COPD. Locomotive diseases, sinusitis, migraine, depression, stomach or duodenal ulcers, colon ischemia and cancer are among the diseases significantly more common in patients with COPD than in age matched cohorts without COPD [van Manen , 2001; GSK Report EPI 40259, 2003].

Since patients with COPD are usually elderly and most have a history of extensive tobacco smoking, cardiovascular disease prevalence is higher among patients with COPD, as compared to patient cohorts without COPD [Mapel, 2002; GSK Report WE156, 2002].

Currently available non-selective phosphodiesterase inhibitors (e.g. theophylline) have been associated with arrhythmias, seizures, gastrointestinal effects and drug interactions. These concerns were extensively evaluated during the cilomilast clinical development program.

During the non-clinical development of cilomilast, the following potential safety concerns were identified: gastrointestinal, cardiovascular, testicular, and neuroendocrine effects. In addition, clinical pharmacology studies evaluated drug-drug interactions and investigated the impact of cilomilast administration to patients with renal and hepatic impairment.

### 8.3.1. Gastrointestinal Effects of Cilomilast

The FDA requested that extensive gastrointestinal monitoring be performed in the clinical development program based on the class effects of PDE inhibitors and non-clinical findings in rodents. No cilomilast-induced increased risk of GI pathology was observed as evidenced by laboratory evaluations, orthostatic vital signs, FOBs, and colonoscopies.

In the pivotal studies, the rate of GIAEs was higher in cilomilast treated patients. The most frequent GIAEs were related to intolerance to cilomilast. These included nausea, diarrhea and abdominal pain, which occurred predominantly in the early weeks of therapy and were mild to moderate in intensity. By 6 weeks of double-blind treatment patients treated with cilomilast were no more likely to experience a first episode of any of these AEs than patients treated with placebo. Serious adverse events in the GI body system occurred at a comparable rate in the cilomilast (0.6%, 10 patients) and placebo (1.1%, 12 patients) treatment groups, suggesting that GI intolerance was not associated with serious adverse events. With the exception of GI intolerance, exposure up to 3 years in long-term extension studies, did not identify GI safety concerns.

While a number of patients may experience gastrointestinal intolerance upon initiation of cilomilast treatment, there is no evidence to suggest that cilomilast is associated with an increased risk of serious GI sequelae.

### 8.3.2. Risk of Cardiovascular Toxicity

Since patients with COPD often have co-existing cardiovascular disease, it is important to establish the cardiovascular safety of any medication that would be prescribed to this patient population. Extensive cardiovascular monitoring during the clinical development program included frequent ECGs (>70,000 ECGs obtained with over 6,000 obtained at $C_{max}$). Additionally, 24-hour Holter monitor examinations were obtained in over 400 patients (approximately 300 treated with cilomilast 15mg BID). The ECGs and Holter monitoring revealed no clinically relevant adverse cardiovascular effects. In

addition, the cardiovascular adverse event profile including vital signs was comparable between cilomilast and placebo treated patients. These data demonstrate that there is no increased risk of cardiovascular events associated with cilomilast therapy.

### 8.3.3. Risks in Patients with Hepatic or Renal Dysfunction

Cilomilast undergoes hepatic metabolism with subsequent conjugation of the metabolites prior to excretion.

Studies in patients with hepatic and renal impairment demonstrated an increased exposure to unbound cilomilast and the potential for reduced gastrointestinal tolerability. Cilomilast is therefore contraindicated in patients with severe hepatic impairment and should be used with caution in patients with mild or moderate impairment. Cilomilast should therefore be used with caution in patients with severe renal impairment (CLcr < 30 mL/min).

### 8.3.4. Risks Associated with Concurrent Use of Other Medications

Because many patients with COPD are on multiple medications, studies were conducted to evaluate the effect of cilomilast on drug-drug interactions. Drug interaction studies in healthy volunteers demonstrated no interactions between cilomilast and albuterol, prednisolone, warfarin, digoxin, magnesium-aluminum-dimethicone antacid, theophylline, ipratropium and cigarette smoking.

Although the combination of erythromycin and cilomilast did not result in pharmacokinetic interaction, there was an increase in the number of gastrointestinal adverse events. These were reduced when erythromycin dosing was initiated once cilomilast was at steady-state. Nonetheless, the concomitant use of cilomilast and erythromycin should therefore be undertaken with caution.

### 8.3.5. Risks to Testicular Function

Due to non-clinical findings in rats and rabbits, a study was designed to evaluate the effects of cilomilast on semen quality in man. This study did not identify any clinically significant changes in sperm quantity, motility, or morphology following chronic dosing with cilomilast.

### 8.3.6. Risk of Adrenal Gland Toxicity

Adrenocortical hypertrophy is a well-recognized response of the rat to PDE4 inhibitors. In the mouse, findings indicative of hyperprolactinemia following administration of cilomilast were observed. Therefore, a clinical pharmacology study was conducted in humans to explore the effects of cilomilast on the HPA axis and prolactin secretion. Serum ACTH, cortisol and prolactin and urinary cortisol levels were not significantly different following repeat dosing of cilomilast and placebo. Additional assessments of HPA axis function were made in six other clinical pharmacology studies and demonstrated similar findings. The results indicated that levels of prolactin, ACTH,

serum cortisol and urinary cortisol were similar following repeat dosing with cilomilast and placebo.

## 8.4. CONCLUSION

Cilomilast provided safe and effective treatment for patients with COPD, thus supporting the proposed indication for the maintenance of lung function in patients with moderate to severe COPD who are poorly responsive to bronchodilators. When administered at a dose of 15mg twice daily, cilomilast demonstrated maintenance of lung function in an otherwise progressively deteriorating disease process. This maintenance of $FEV_1$ was accompanied by improvement in health status, allowing patients to better participate in normal daily activities. When all pivotal studies were considered, there was a decrease in exacerbations in patients receiving cilomilast, suggesting a further clinical benefit in patients with COPD.

Additionally, supporting studies demonstrated a greater magnitude of $FEV_1$ response in the reversible patients as compared to poorly reversible patients and clinically meaningful improvements in hyperinflation.

While some patients may experience gastrointestinal intolerance upon initiation of cilomilast treatment with some resulting in withdrawal, there is no evidence to suggest that cilomilast is associated with an increased risk of serious GI sequelae. Extensive safety monitoring yielded no further issues of concern.

Overall the benefit-risk profile supports approval of cilomilast for the proposed indication.