1. INTRODUCTION AND BACKGROUND

- COPD is a progressive disease and is one of the few major diseases with increasing mortality. COPD is characterized by persistent reduction in expiratory flow, lung hyperinflation and a progressive deterioration in lung function despite aggressive treatment.

- The US Centers for Disease Control and Prevention (CDC) estimates that as many as 24 million individuals in the US had evidence of impaired lung function in 2000; only 10 million of those with evidence of impaired lung function (42%) reported a physician diagnosis of COPD.

- In an analysis of a nationally representative US cohort with over 20 years follow-up, the presence of moderate COPD was associated with a 1.6 times greater risk of death; patients with severe COPD experienced 2.7 times greater risk of death compared to the general population.

- A major cause of mortality in patients with COPD is acute exacerbation. Between 10 and 30% of patients with severe COPD will die following admission to a hospital for an exacerbation of COPD. Long-term survival rates after an exacerbation are poor, with mortality reaching 22-40% within one year of hospital admission.

- For many patients, currently available therapy does not meet their needs. New therapies with novel mechanisms of action are needed to treat this debilitating disease.

- Cilomilast, a novel PDE4 inhibitor, targets inflammatory mediators and airway smooth muscle activity associated with COPD. This anti-inflammatory activity has been demonstrated in patients with COPD by a reduction in sub-epithelial CD68+ macrophages and CD8+ lymphocytes.

- Cilomilast is a second generation PDE4 inhibitor which has been designed to retain the therapeutic activity of the first generation compounds but with a reduced propensity to elicit gastrointestinal effects.

- The clinical development program evaluated patients with COPD who were poorly reversible to albuterol. Patients with poor reversibility, when compared to those who are more reversible have been shown to have an increased rate of decline in FEV_1. Lower FEV_1 is associated with trends for increased morbidity and mortality.

- The proposed indication for cilomilast is *"**ARIFLO** is indicated for the maintenance of lung function (FEV_1) in patients with chronic obstructive pulmonary disease (COPD) who are poorly responsive to albuterol (increase in FEV_1 of $\leq$15% or $\leq$200 mL)."*

- Treatment with cilomilast, 15mg taken twice daily as an oral tablet, may simplify treatment and improve adherence for many patients with COPD.

1.1. COPD Overview

COPD is defined by the American Thoracic Society (ATS) as 'a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible'. Evidence–based guidelines [NHLBI/WHO Workshop Report, 2001] prepared as part of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) reiterate the partially reversible, progressive nature of the airflow limitation in COPD. In addition, the GOLD Guidelines recognize the inflammatory aspect of the disease. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

1.1.1. Burden of Disease

The exact prevalence of COPD is not well characterized due to variable disease definitions over time and a high proportion of undiagnosed disease; however, COPD affects millions of individuals in the US and data suggest that the prevalence is rising. The US Centers for Disease Control and Prevention (CDC) estimates that as many as 24 million individuals in the US had evidence of impaired lung function (FEV_1/FVC <70%) in 2000; only 10 million of those with evidence of impaired lung function (42%) reported a physician diagnosis of COPD [Mannino, 2002]. For both mild and moderate COPD, the prevalence was higher among men than women and increased with age. When severity of lung function impairment was determined on the basis of pulmonary function testing and categorized according to ATS Guidelines, 62% of physician-diagnosed patients had mild FEV_1 impairment, 25% had moderate impairment and 13% had severe impairment [Coultas, 2001]. There is also some evidence that COPD patients with poor reversibility to bronchodilators, when compared to those who are more reversible, have an increased rate of decline in FEV_1 [Anthonisen, 1986]. Lower FEV_1, in turn, is associated with trends for increased morbidity and mortality [Hansen, 1999; Postma, 1985; Postma, 1989].

COPD exacts a considerable toll on patients and society. COPD is currently the fourth-leading cause of death in the US [National Center for Health Statistics, 2001] and is projected to be the third-leading cause of death globally by the year 2020 [Murray, 1996]. COPD is a progressive disease and is one of the few major diseases with increasing mortality in the US over the last 20 years. The age-adjusted annual death rate for COPD increased 67%, from 40.7 per 100,000 in 1980 to 66.9 per 100,000 in 2000 [Mannino, 2002]. A major cause of mortality in patients with COPD is acute exacerbation. Between 10 and 30% of patients with severe COPD will die following admission to a hospital for an exacerbation of COPD [Anto, 2001]. Long-term survival rates after an exacerbation are poor, with mortality reaching 22-40% within one year of hospital admission [Almagro, 2002; Fuso, 1995; Wildman, 2002]. Within three years, about two-thirds of patients admitted to the hospital for an exacerbation will die [Almagro, 2002].

Compared to the general population, patients with COPD also experience greater all-cause mortality. In an analysis of a nationally representative US cohort with over 20 years follow-up, the presence of moderate COPD was associated with a 1.6 times greater

risk of death; patients with severe COPD experienced 2.7 times greater risk of death [Mannino, 2003]. An analysis of UK cohort similarly found all-cause mortality rates elevated in patients with COPD compared to the general population [Soriano, 2000]. After five years of follow-up, 80% of men without COPD were living—compared to 72% of men with mild COPD and 65% of men with moderate COPD. Survival in women with mild and moderate COPD was also lower (78% and 71%, respectively), compared to women without COPD (86%). For both men and women, significantly greater mortality was observed with increasing COPD severity. Only 24% of male patients and 30% of female patients with severe COPD survived after five years. Patients with severe COPD died an average of four years before the age and sex-matched reference population [Soriano, 2000].

COPD is also associated with considerable morbidity. COPD-related morbidity can be quantified using hospitalization rates, as well as the total costs attributed to caring for patients with the disease. Since 1990, hospitalizations for COPD have increased among all age groups, with a 62% increase among 65-74 year olds. An estimated 726,000 hospital discharges were reported in 2000, a discharge rate of 40.8 per 10,000 population [Mannino, 2002]. According to recent estimates, in 2002 the annual cost to the US for COPD was $32.1 billion [NHLBI Chartbook, 2002]. This included $18.0 billion in direct healthcare expenditures, $6.8 billion in indirect morbidity costs and $7.3 in indirect mortality costs. Analysis of patients covered by a US managed care organization showed that annual inpatient and outpatient expenditure per patient with COPD was significantly higher than expenditure per age-matched patient without COPD ($11,680 vs. $5815, $p<0.001$) [Mapel, 2000]. As the disease progresses, so does its economic cost. A five-year study of 413 patients with COPD in the US demonstrated that healthcare costs rise significantly with the severity of disease [Hilleman, 2000]. The median healthcare cost per patient-year for patients in the milder COPD category (FEV_1 >50% predicted) was $1681, compared to $10,812 per patient-year for those in the most severe COPD category (FEV_1 <35% predicted).

COPD related morbidity is also captured by quality of life measurements. The terms quality of life and more specifically health-related quality of life (HRQOL) refer to the physical, psychological and social domains of health, seen as distinct areas that are influenced by a person's experiences, beliefs, expectations and perceptions [Brook, 1979; Patrick, 1973; Brook, 1983]. Correlations between changes in spirometry and changes in patients' perceptions of their general HRQOL have traditionally been very low, suggesting improvements in this physiologic measure of disease severity is not necessarily associated with improvements in patients perceptions of general health [Jones, 1991].

1.1.1.1. Co-morbid Conditions

The extrapulmonary effects of COPD include systemic inflammation, skeletal muscle dysfunction, bone demineralization, nutritional abnormalities and weight loss [Agusti, 2003]. While the exact mechanisms by which lung disease causes early non-respiratory morbidity and mortality are unknown, it is certain that co-morbid diseases related to chronic exposure to tobacco smoke occur more frequently in patients with COPD relative to patients without COPD. In a study to determine the prevalence of common diseases in

patients with COPD, 73% of patients were shown to suffer from at least one other disease in addition to COPD [van Manen , 2001]. 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 is also more common among patients with COPD, as compared to those without the disease. A study of patients treated in the Veterans Administration Medical System found that cardiovascular complications, including arrhythmias, myocardial infarction and congestive heart failure were more common among patients with COPD, as compared to age-matched patients without COPD [Mapel, 2002; GSK Report WE156, 2002]. Seventy-one percent of COPD patients had prevalent heart disease compared with 50% of age-matched patients without COPD.

1.1.2. Pathophysiology of COPD

COPD is a disease state characterized by the presence of airflow obstruction due to emphysema or chronic bronchitis. Emphysema and chronic bronchitis are complex pathophysiological conditions and frequently co-exist in the same patient. Emphysema is associated with the destruction of the walls of the alveoli with abnormal permanent enlargement of the airspaces distal to the terminal bronchioles and loss of alveolar attachments. As a result, elasticity of the lung tissue is lost, causing airways to collapse and obstruction of airflow. Chronic bronchitis is associated with inflammation of the respiratory bronchioles, enlargement of bronchial mucous glands accompanied by dilation of gland ducts. Goblet cell size and number are increased, and there may be both metaplasia and hypertrophy of airway smooth muscle. As a result, there is plugging of the respiratory bronchioles with mucus, and distortion due to fibrosis (ATS, 1995).

COPD is a heterogeneous disease characterized by bronchoconstriction, chronic and sustained inflammatory response, tissue remodeling with inappropriate matrix protein deposition and lung tissue destruction [Rutgers, 2001; Nagai, 1991] which is thought to be secondary to the release of proteases such as elastase from various inflammatory cells. These pathological features are thought to be responsible for airflow obstruction and the accelerated rate of decline of FEV_1 in patients with COPD.

Neutrophils are the most common inflammatory cell associated with COPD [Thompson, 1989; Lacoste, 1993; Pesci, 1998]; however, it is clear that many other inflammatory cells are also elevated and activated in the lungs of patients with COPD. These cells include lymphocytes ($CD8^+$) [Saetta, 1993; Saetta, 1999], macrophages [Saetta, 1993; Grashoff, 1997] and eosinophils during exacerbations [Lacoste, 1993; Pesci, 1998; Zhu, 2001; Retamales, 2001]. Influx of inflammatory cells into the lung tissue is dependent on generation of inflammatory mediators as well as upregulation of cell adhesion molecules on the vascular endothelium. Clinical studies have identified a wide range of mediators, which are elevated in the lungs in COPD and could explain many of the cellular and structural changes that are observed. Inflammatory mediators described in the sputum or bronchoalveolar lavage fluid of patients with COPD include tumor necrosis factor α (TNFα), interleukin 8 (IL-8), Eotaxin, RANTES, transforming growth factor β (TGFβ) and endothelin 1 (ET1). There is also upregulation of relevant cell adhesion

molecules, which allows for the diapedesis and accumulation of inflammatory cells in the lung tissue and airway lumen [DiStefano, 1994; Gonzalez, 1996].

One of the most debilitating aspects of COPD is lung hyperinflation. Hyperinflation has a significant impact on normal daily activity as it increases the work of breathing and can severely limit exercise tolerance. Hyperinflation results from reductions in elastic recoil of the lungs and expiratory muscle strength as well as the airway obstruction associated with COPD. Airway obstruction can lead to the start of inspiration before complete expiration of the previous breath. Thus, with each breath more air is inspired than expired resulting in hyperinflation. The effects of resting hyperinflation are amplified during exercise when increased ventilatory demands results in further air trapping [Crapo, 1998].

Persistent reduction in expiratory flow and a progressive deterioration in lung function despite aggressive treatment characterize COPD. Inflammation, fibrosis, goblet cell metaplasia, and smooth muscle hypertrophy in terminal bronchioles, as well as loss of alveolar attachments to bronchioles due to alveolar destruction are important causes of airflow obstruction. Although expiratory airflow may improve significantly with treatment, by definition, expiratory airflow will never normalize and will progressively worsen with time. Patients with COPD have shortness of breath, initially appearing as dyspnea on exertion and then progressing insidiously. Progressively increasing productive cough and sputum production are also symptomatic manifestations of COPD. Patients most often modify their lifestyles to compensate for the dyspnea and activity limitation associated with reduced expiratory airflow [Petty, 2000]. In addition to these symptoms, periods of acute deterioration due to viral or bacterial exacerbations lead to considerable morbidity and mortality from the disease.

1.1.3. Current Management of COPD and Limitations with Available Therapy

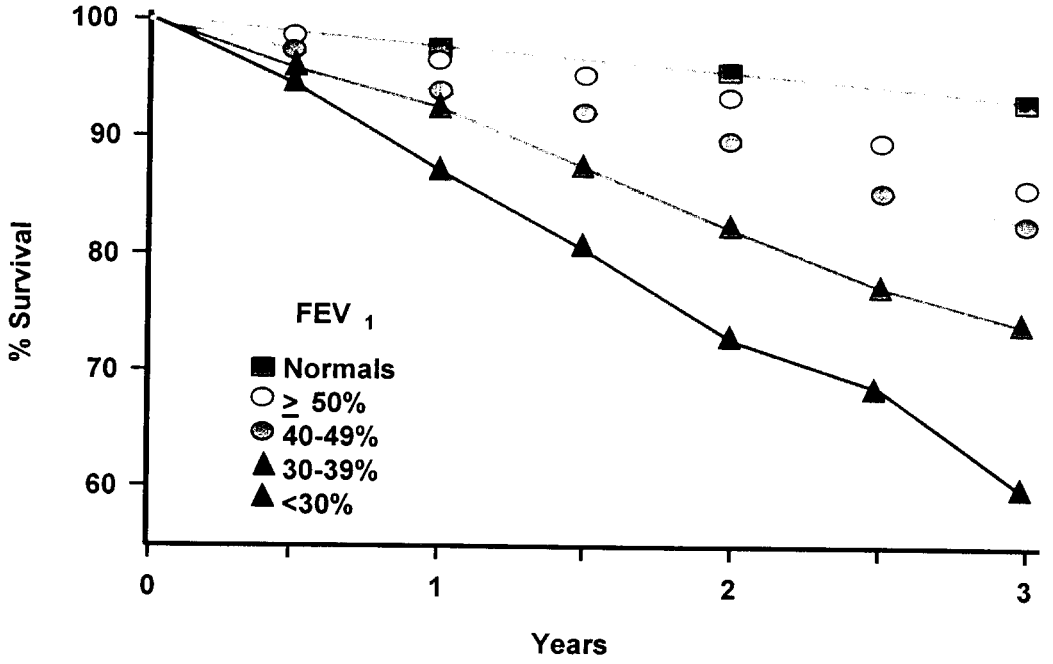
Cigarette smoking is the primary contributing factor in the etiology of COPD. Smoking cessation, which has been shown to slow the rate of decline in lung function by 30ml/yr over an 11 year period, remains a primary objective of treatment [Anthonisen, 2002]. However, even with the best current therapy, smoking cessation is only successful in less than half the smokers who attempt to stop. Additionally, for patients with more advanced COPD, prolonged smoking results in sustained damage to the lungs with persistence of clinical pathology and symptoms despite smoking cessation. Thus, for many patients, pharmacological treatment for the clinical manifestations of COPD is necessary even if they no longer smoke. Since no medication has been shown to modify progression of COPD, pharmacological therapy has focused on the treatment of airway obstruction, symptoms and exacerbations associated with COPD.

Given the complexity of the disease, including inflammation, bronchoconstriction and tissue destruction, many patients require multiple medications to control the various pathophysiological processes responsible for the clinical manifestations of COPD. Despite the availability of medications and guidelines advocating their appropriate use in the management of COPD, the control of COPD in the US remains sub-optimal and

many patients continue to have progressive decline in FEV_1 and worsening symptoms, indicating the need for new therapeutic options.

The increasing morbidity and mortality from COPD in the US suggests that, for many patients, currently available therapy does not meet their needs. Patients with poor reversibility, when compared to those who are more reversible have been shown to have an increased rate of decline in FEV_1 [Anthonisen, 1986]. Lower FEV_1 is associated with trends for increased morbidity and mortality (see Figure 1) [Anthonisen, 1986, Hansen 1999, Postma, 1985, Postma, 1989]. Bronchodilators alone may not be optimal treatment for patients whose disease state is not characterized by reversible bronchoconstriction. This poorly reversible population of patients with COPD was evaluated in the cilomilast clinical development program.

Figure 1 Prognosis in Chronic Obstructive Pulmonary Disease



With nearly 8 million physician visits in the year 2000, COPD is a major burden on the US health care system [Mannino, 2002]. The treatment of patients with COPD is challenging due to the complexity of the disease and the large number of comorbidities with their accompanying medications. Bronchodilators are currently the only class of medications approved in the US for the treatment of COPD. Therapy for patients with COPD may include burdensome dosing regimens (TID, QID dosing), complicated dosing administration procedures (nebulization, MDI), blood level monitoring, and extensive drug-drug interactions (xanthines). Cilomilast a novel COPD medication in tablet form, with convenient BID dosing does not require blood level monitoring and has no known pharmacokinetic drug-drug interactions of clinical significance. Therefore, cilomilast should provide a simpler treatment option for both physicians and patients.

1.2. Rationale for use of Ariflo in COPD

1.2.1. PDE4 Inhibitors treat multiple components of COPD

Considering the complexity of COPD, new treatments should target a broad range of pathophysiological processes that are relevant to the disease. It is well-established that elevation of cyclic adenosine monophosphate (cyclic AMP):

- effects the activity of many inflammatory cells germain to the pathophysiology of COPD
- induces airway smooth muscle relaxation
- suppresses smooth muscle mitogenesis
- modulates the activity of pulmonary nerves [Barnette, 1999].

The actions of cyclic AMP are terminated by its metabolism to 5'AMP. This is accomplished by a family of enzymes known as the phosphodiesterases (PDEs). This family is comprised of 11 members of genetically distinct proteins with differential tissue distributions, sensitivity to inhibitors, regulatory properties and biological role. Of these 11 members, PDE4 was found to be the predominant cyclic AMP metabolizing isozyme in immune and inflammatory cells. Together, this information led to the hypothesis that selective inhibitors of PDE4 would be useful in the treatment of chronic inflammatory disease of the lung, such as COPD. Furthermore, because PDE4 inhibitors target only one of the 11 isozymes, it was proposed that these agents would produce fewer side effects than non-selective PDE inhibitors, such as theophylline, that inhibit most forms of PDEs [Torphy, 1991; Torphy, 1998]. Indeed, many if not all of the side effects of theophylline appear to be caused by non-selective inhibition of cyclic AMP breakdown in non-target tissues, whereas mechanisms other than PDE inhibition appear to be responsible for its therapeutic effects [Church, 1986].

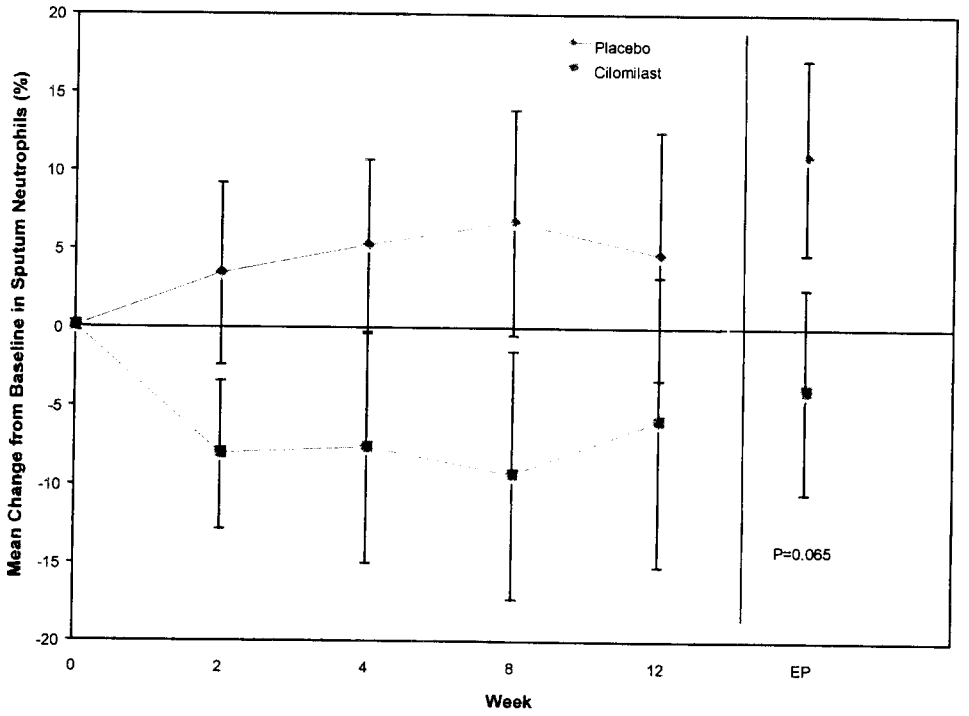
Non-clinical studies with first generation PDE4 inhibitors, such as rolipram, Ro 20-1724, tibenilast and denbufylline, supported the hypothesis that selective PDE4 inhibitors would have therapeutic benefit in the treatment of chronic lung disorders. These agents had activity across a wide range of animal models of inflammation, particularly models of pulmonary inflammation [Barnette, 1999; Torphy, 1991]. The clinical utility of these first generation PDE4 inhibitors was limited by class-associated gastrointestinal side effects such as nausea and vomiting. Cilomilast is a second generation PDE4 inhibitor which has been designed to retain the therapeutic activity of the first generation compounds but with a reduced propensity to elicit these gastrointestinal effects.

The primary pharmacological actions of cilomilast have been assessed in a range of in vitro and in vivo studies. In vitro, cilomilast is a potent and selective inhibitor of PDE4 with little affinity for other PDE isozymes as well as a variety of enzymes and receptors [DeWolf, 1998]. In *in vitro* studies, cilomilast suppressed the activation of a wide variety of immune and inflammatory cells including human monocytes, CD4+ and CD8+ T lymphocytes, and neutrophils [Barnette, 1998]. In addition, cilomilast attentuated the proliferative response of airway smooth muscle cells as well as the ability

of lung fibroblasts to migrate [Kohyama, 2002]. Since there is no single animal model that mimics all aspects of COPD, the effects of cilomilast were investigated in a number of animal models that imitate certain characteristics of the pathophysiology of COPD (e.g., airway obstruction, inflammation and neuromodulation). Administration of cilomilast to laboratory animals reduced the bronchoconstriction seen upon antigen challenge [Underwood, 1998], inhibited the recruitment of immune and inflammatory cells to the lung in response to lipopolysacharide (LPS) (neutrophils), antigen (eosinophils) and staphylococcal enterotoxin B (CD8+ T cells) and prevented the increased vascular leakage seen with LPS challenge. Finally, cilomilast potentiated the non-adrenergic, non-cholinergic induced relaxation of human bronchial smooth muscle.

Two exploratory studies (110, 076) of 12-weeks duration were conducted to evaluate the mechanism of action of cilomilast in the treatment of patients with COPD. Study 110 examined the effect of cilomilast on induced sputum and study 076 examined the effect of cilomilast on induced sputum and brochoscopic bronchial biospsy. These studies did not meet statistical significance for the primary endpoint (reduction in sputum neutrophils). However, in Study 110 the reduction in sputum neutrophils was in favor of cilomilast as compared to placebo (see Figure 2).

Figure 2 **Mean (SEM) Percent Change from Baseline in Sputum Neutrophils-Study 110**



In Study 076, there was a mean decrease from Baseline of -42.8 (approximately 42% decrease from Baseline) in sub-epithelial macrophages (CD68+) per area tissue at Endpoint in the cilomilast (15mg BID) treatment group compared to an increase from Baseline of 33.2 (approximately a 56% increase from Baseline) in the placebo treatment

group (difference of -76.0; p = 0.005) (see Figure 3). Also, a mean decrease from Baseline of -132.4 (approximately a 40% reduction from Baseline) in sub-epithelial CD8+ lymphocytes per area tissue at Endpoint was observed in the cilomilast treatment group (15mg BID) compared to an increase of 24.4 (approximately 8% increase from Baseline) in the placebo treatment group (difference of. -156.8, p = 0.055) (see Figure 4).

Figure 3 **Mean Change from Baseline in Sub-epithelial Macrophages (CD68+) - Study 076**

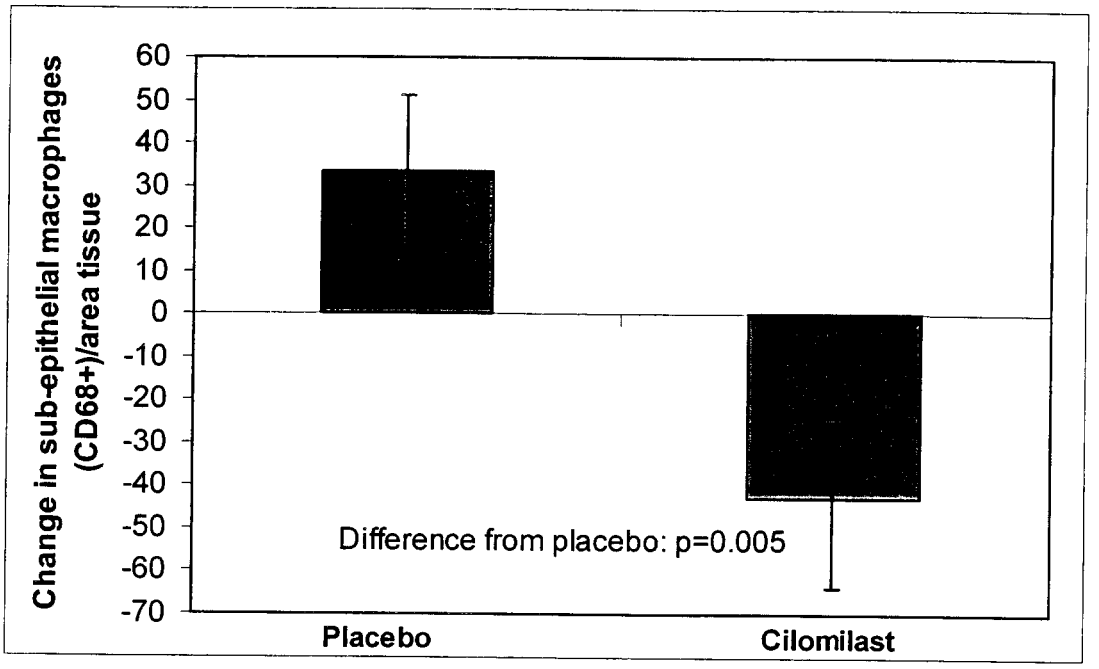
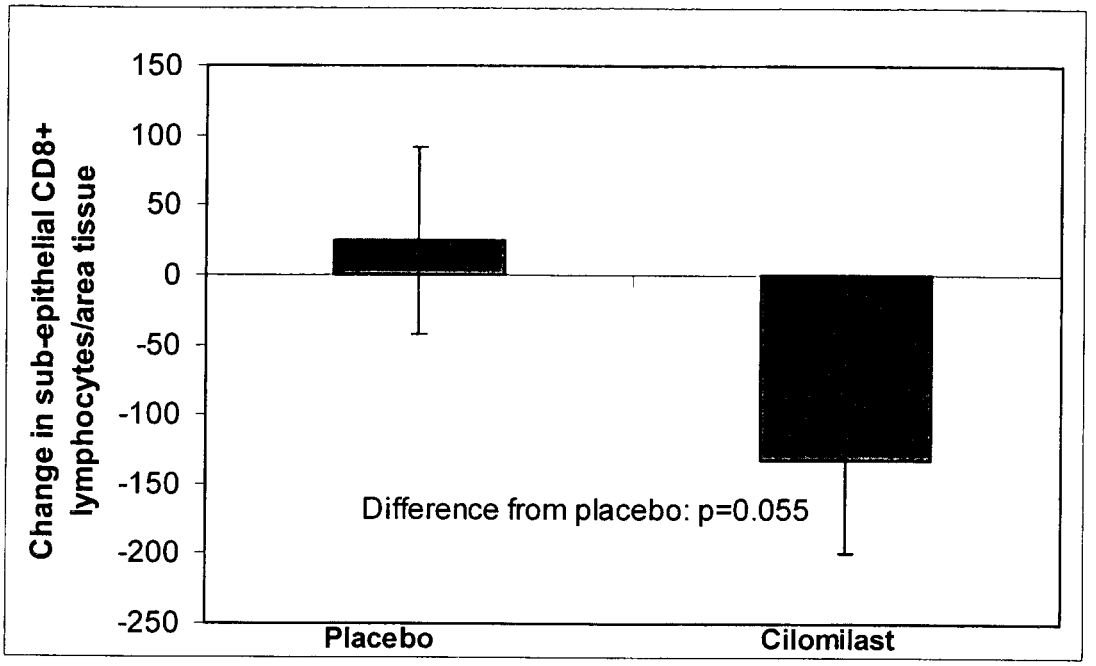


Figure 4 **Mean Change from Baseline in Sub-epithelial Lymphocytes (CD8+)- Study 076**



Treatment with cilomilast, an oral, selective PDE4 inhibitor has effects on both inflammatory mediators and smooth muscle. Cilomilast treats multiple components of BGCOPD in a tablet formulation. Furthermore, approval of cilomilast in the US may help to address some of the limitations with current therapy.