

EXECUTIVE SUMMARY

INTRODUCTION AND BACKGROUND

Introduction

The purpose of this briefing package is to provide information on **ARIFLO**[†] (cilomilast) tablets and its proposed use in the management of COPD to the Pulmonary and Allergy Drugs Advisory Committee members and consultants. Included are relevant nonclinical, clinical pharmacology, clinical efficacy and clinical safety data for cilomilast. This document also provides recommendations for appropriate use of cilomilast. The terms cilomilast and **ARIFLO** are used synonymously throughout this document. Cilomilast represents a new class of compounds, PDE4 inhibitors, and offers an alternative, novel treatment option for the management of poorly reversible patients with COPD.

Proposed Indication, Dosage and Administration

The proposed indication 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 ≤ 200 mL). The efficacy of **ARIFLO** has not been established in clinical trials beyond 24 weeks.*

The recommended dose of **ARIFLO** is 15mg twice daily taken with food.

Regulatory History

The original Investigational New Drug Application was submitted and later amended for the evaluation of cilomilast in COPD. The key FDA interactions included an End-of-Phase 2 meeting, discussions on the clinical safety database, and Pre-NDA meetings. To date, cilomilast is not approved or marketed in any foreign country.

Overview of COPD and Rationale for use of Ariflo in COPD

- 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

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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 (increase in FEV₁ of $\leq 15\%$ or ≤ 200 mL). Patients with poor reversibility, when compared to those who are more reversible have been shown to have an increased rate of decline in FEV₁. Lower FEV₁ is associated with trends for increased morbidity and mortality.
- Treatment with cilomilast, 15mg taken twice daily as an oral tablet, may simplify treatment and improve adherence for many patients with COPD.

NONCLINICAL

There were no signals in nonclinical studies to indicate that cilomilast would be associated with the convulsions, the severity of gastrointestinal effects, arrhythmias and drug interactions seen with currently available non-selective phosphodiesterase inhibitors. When pharmacologically predictable adverse effects were evaluated in animals, cilomilast was associated with a lower magnitude of effect than the first generation PDE4 inhibitor, rolipram. In toxicity studies in laboratory animals, gastrointestinal, cardiovascular, testicular, and neuroendocrine effects were observed. However, following thorough evaluation in the clinical development program there is no evidence to indicate that cilomilast is associated with toxicity at a dose of 15mg BID in humans.

CLINICAL PHARMACOLOGY

The clinical pharmacology program established the pharmacokinetic and, pharmacodynamic profiles of cilomilast in 1297 human subjects enrolled into 51 studies.

- Cilomilast demonstrated complete oral absorption and negligible first-pass metabolism. It has very high plasma protein binding (99.4%), but with a large binding reserve. The steady-state volume of distribution (typically 10 – 17L) is small.
- Cilomilast exhibited slow metabolic clearance through multiple, parallel pathways to metabolites with lower potency (at least 10-fold) which were rapidly cleared in the urine.
- The elimination half-life was seven hours. The pharmacokinetics of cilomilast were dose- and time-independent and showed low variability. Steady-state plasma concentrations were achieved within two days of BID dosing.
- With the exception of dose limiting nausea and vomiting, the safety and tolerability profile of cilomilast was similar to placebo. The highest dose tolerated by patients was 15mg BID.
- Pharmacodynamic studies designed to follow-up non-clinical safety findings did not demonstrate evidence of gastrointestinal, cardiovascular, male reproductive or neuroendocrine system safety issues in humans.
- Investigations involving the elderly, smokers, Japanese and Chinese subjects did not reveal pharmacokinetic, pharmacodynamic or tolerability differences indicating a requirement for dose adjustment.
- Studies in patients with hepatic and renal impairment demonstrated an increased exposure to unbound cilomilast and the potential for reduced gastrointestinal tolerability.
- In patients with COPD, pharmacokinetic parameter estimates were consistent with those in healthy subjects - therefore routine monitoring of plasma concentrations while treating patients with COPD is not indicated.
- Cilomilast had no pharmacokinetic or pharmacodynamic interactions with a range of drugs likely to be co-administered in patients with COPD with the exception of erythromycin, which was not well tolerated. Metabolism based drug-drug interactions are not anticipated.

OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

The cilomilast clinical development program included 66 studies, 12 of which were conducted in patients with COPD. Two North American (studies 039 and 156) and two European (studies 042 and 091) pivotal, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies evaluated the use of cilomilast 15mg BID for 24-weeks in patients with COPD. Six of the twelve COPD studies were placebo-controlled supporting studies, and two were open-label, long-term extension studies.

Overall, a total of 4093 patients were randomized in the Phase II and III controlled clinical studies, with 2586 receiving cilomilast and 1507 receiving placebo. In the long term extension studies safety was evaluated in over 1000 patients for up to three years.

PIVOTAL STUDIES

Dose Rationale

In the Phase II dose-ranging studies cilomilast 15mg BID was the only dose superior to placebo with regard to significant improvements in pulmonary function and positive trends in symptoms and quality of life in patients with COPD. Therefore, a 15mg BID dose was taken into the Phase III clinical development program.

Study Design

- Two North American (studies 039 and 156) and two European (studies 042 and 091) pivotal, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies evaluated the use of cilomilast 15mg BID for 24-weeks in patients with COPD.
- All studies investigated patients with poor reversibility, defined as $\leq 15\%$ or $\leq 200\text{mL}$ increase in FEV₁ (or both) post-bronchodilator.
- The primary efficacy variables were change from baseline in trough FEV₁ and total score of the SGRQ averaged over 24 weeks. Secondary measures of efficacy were COPD exacerbation rates, FVC, summary symptom score, exercise tolerance, and post-exercise breathlessness.
- The following safety parameters were evaluated: adverse events, assessments of gastrointestinal safety, clinical laboratory values, vital signs, electrocardiograms and 24-hour Holter monitoring.

Demographics and Baseline Characteristics

- The population evaluated in the pivotal programs were characteristic of subjects with moderate-severe COPD.
- As determined by entry criteria, reversibility to albuterol was low with mean reversibility ranging from 4.9% to 8.6% with a mean increase in FEV₁ of 80ml.
- Overall with the exception of history of chronic bronchitis, percent reversibility, percent predicted DLCO and gender, demographic characteristics were similar between NA and EU pivotal studies.

Efficacy Results

- Clinical benefits were achieved in the NA studies with cilomilast 15mg BID for the two co-primary endpoints, trough FEV₁ and patient reported health related quality of life (SGRQ).
- In the poorly reversible COPD population studied, cilomilast treated patients across all four studies demonstrated a maintenance of FEV₁ over time while the placebo treated patients generally showed deterioration in FEV₁ over time.
- Significant improvements in QOL (SGRQ) were demonstrated in both NA studies with one study achieving the clinically meaningful improvement of -4.0 points. Consistent improvements from baseline in SGRQ were observed in patients receiving cilomilast across the NA and EU studies.
- In one NA and one EU study, the relative risk of experiencing at least one level 2/3 COPD exacerbation (requiring physician intervention or hospitalization) was reduced by 40% (Study 039) and 32% (Study 042) in patients treated with cilomilast compared with placebo.

SUPPORTING STUDIES

Efficacy Results

Study 168

Study 168 was 12-weeks in duration and the only study to evaluate patients with COPD without regard to reversibility to albuterol. All other studies in the clinical development program were restricted to patients with poor reversibility to bronchodilators ($\leq 15\%$ or $\leq 200\text{mL}$ improvement in FEV₁ post-bronchodilator). Study 168 was primarily a cardiovascular safety study, but efficacy was also assessed. The key efficacy variable was FEV₁.

- A greater magnitude of response in trough FEV₁ was observed in the reversible (difference from placebo 130ml) as compared to the poorly reversible patients (difference from placebo 30ml).

Study 111

Lung hyperinflation is common in patients with COPD and is associated with functional impairment (decreased exercise tolerance). The measurement of static lung volumes is useful in assessing degree of hyperinflation and provides complementary information to spirometry especially in patients with poor reversibility to bronchodilators. Study 111 was designed to evaluate the effect of cilomilast on static lung volumes. Key findings are summarized as follows:

- At Endpoint, patients treated with cilomilast demonstrated clinically meaningful improvements in functional residual capacity (FRC) of -290ml, residual volume (RV)

of -390ml, slow vital capacity (SVC) of 110ml, and total lung capacity (TLC) of -250ml as compared to placebo treated patients. These substantial improvements in lung volumes were observed in the absence of significant changes in FEV₁.

- The improvements in lung volumes indicate a reduction in hyperinflation.

Open Label Long Term Extension Studies

Long-term safety was assessed in Studies 040 (EU) and 041 (NA). Each study was a multicenter, Phase III, open-label extension study in patients with COPD. Patients completing study 042 or 091 according to the protocol were eligible for entry into Study 040, and patients completing Study 039 were eligible for entry into Study 041. Patients were given cilomilast 15mg BID:

With all the caveats inherent in uncontrolled studies:

- In both long-term extension studies the efficacy (FEV₁ and SGRQ) was maintained beyond 24 weeks.
- Patients newly exposed to cilomilast in the long-term studies (prior placebo group) generally did not achieve the same mean changes from Baseline in FEV₁ 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.

Safety Results

The safety results from the cilomilast clinical development program can be summarized as follows:

- The safety of cilomilast was extensively evaluated with up to three years of exposure, which translates to nearly 3,000 patient years of exposure.
- Extensive cardiac monitoring (>70,000 ECGs in the clinical development program and >1,000 holters in the phase III program) showed no evidence of an increased risk of cardiovascular events associated with cilomilast therapy.
- The most frequent GIAEs were nausea, diarrhea and abdominal pain, which occurred predominantly in the early weeks of therapy and were mild to moderate in intensity.
- The incidence of SAEs reported by placebo and cilomilast treated patients was low and similar, except that complications of chronic lung disease occurred more frequently in the placebo group.
- While a number of 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.

- Laboratory values, vital signs and other safety monitoring did not reveal any other concerns.
- Long term administration of cilomilast identified no new safety concerns.

Summary of Benefit-Risk

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 FEV₁ 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 FEV₁ 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.

PROPOSED INDICATION AND DOSAGE AND ADMINISTRATION

The results from this clinical program support the following indication and recommendations for dosage and administration:

- **ARIFLO** is indicated for the maintenance of lung function (FEV₁) in patients with chronic obstructive pulmonary disease (COPD) who are poorly responsive to albuterol (increase in FEV₁ of $\leq 15\%$ or ≤ 200 mL). The efficacy of **ARIFLO** has not been established in clinical trials beyond 24 weeks.
- The recommended dose of **ARIFLO** is 15 mg twice daily. It is recommended that **ARIFLO** be taken with food. No dosage adjustments are required for elderly subjects or for smokers. Therapy with **ARIFLO** should be continued during acute exacerbations of COPD. Inhaled albuterol should be used for relief of acute breathlessness.

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Abbreviations Used in this Document

AE	adverse event
ANOVA	analysis of variance
ACTH	Adrenal corticotropin hormone
ANOVA	Analysis of variance
ATS	American Thoracic Society
AUC	Area under the curve
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
Bpm	Beats per minute
CDC	Centers for Disease Control
Cyclic AMP	Cyclic adenosine monophosphate
CI	Confidence interval
CLcr	Creatine clearance
COAD	Chronic obstructive airway disease
COPD	Chronic obstructive pulmonary disease
C _{max}	Maximum concentration
CYP	Cytochrome P450
DLCO	Carbon monoxide diffusing capacity
ECG	Electrocardiogram
ET1	Endothelin 1
EU	European
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV ₁	Forced expiratory volume in one second
FOBs	Fecal occult blood tests
FRC	Functional Residual Capacity
FVC	Forced vital capacity
GI	Gastrointestinal
GIAE	Gastrointestinal adverse event
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
HPA	Hypothalamo-pituitary adrenal
HRQOL	Health Related Quality of Life
IAC	Inhaled Anticholinergic
ICS	Inhaled corticosteroid
IL8	Interleukin 8
IR	Immediate release
ITT	Intent-to-treat
LPS	Lipopolysaccharide
Mcg	Microgram
MDI	Metered dose inhaler
Meq	Milliequivalent
Mg	Milligram
Min	Minimum
ML	Milliliter

MmHg	Millimeters of mercury
Msec	Millisecond
NA	North American
NDA	New Drug Application
NOAEL	No affect dose level
CL/F	Oral clearance
PDE	Phosphodiesterase
PDE4	Phosphodiesterase 4
PFT	Pulmonary function test
PK	Pharmacokinetic
PRN	pro re nata (as needed)
QID	Four times daily
R&D	Research and development
RV	Residual Volume
SAE	Serious Adverse Event
SB	SmithKline Beecham
SD	Standard deviation
SEM	Standard error of the mean
SGRQ	St. George's Respiratory Questionnaire
SNOMED	Systematized Nomenclature of Human (and Veterinary) Medicine
TGF β	Transforming growth factor β
TID	Three times daily
TLC	Total Lung Capacity
Tmax	Time to maximum concentration
TNF α	Tumor necrosis factor α
Vss	Volume of distribution at steady state
Vss/F	Volume of distribution at steady state/ bioavailability
Y/yrs	Years