

## 7. SUPPORTING STUDIES

- Supporting studies confirmed the safety and support the efficacy established in the pivotal clinical trials.

### Open label long-term extension studies (Studies 040 and 041)

- Long term use of cilomilast (1000 patients up to 3 years) identified no new safety concerns.
- In both long-term extension studies the efficacy (FEV<sub>1</sub> and SGRQ) was maintained beyond 24 weeks.

### Study 168

- A greater magnitude of response in FEV<sub>1</sub> was demonstrated in the more reversible patients.

### Study 111

- In a study that evaluated static lung volumes patients treated with cilomilast demonstrated clinically meaningful improvements in FRC and RV, indicating a reduction in hyperinflation.

### 7.1. Open-label Long-Term Extension Studies

Long-term safety was assessed in Studies 040 and 041. Each study was a multicenter, Phase III, open-label extension study in patients with COPD. Patients completing EU studies 042 or 091 according to the protocol were eligible for entry into Study 040, and patients completing NA Study 039 were eligible for entry into Study 041. Patients in 041 were given 15mg BID and were required to attend the clinic after one, two, and four weeks and then at four-week intervals during the duration of the study. Patients in 040 were given 15mg BID and were required to attend the clinic after one, two, and four weeks intervals until at least week 48 and then at twelve-week intervals for the duration of the study. The baseline characteristics of the patients enrolled into the uncontrolled studies are the baseline characteristics at entry into the respective feeder studies (i.e., Studies 042 and 091 for Study 040, and Study 039 for Study 041).

The primary objective for each study was to evaluate the long-term safety and tolerability of cilomilast administered at a dosage of 15mg BID in patients with COPD. Secondary objectives included further efficacy evaluations of cilomilast in terms of pulmonary function, disease symptoms, and quality of life.

The long-term extension studies were ongoing at the time of the NDA submission and the data presented below are from the interim study reports. Enrollment in the uncontrolled studies was 723 for Study 040 and 355 for Study 041. Concomitant on-demand inhaled

beta<sub>2</sub>-agonists and anticholinergic medication were permitted throughout each study and where possible stable doses were to be administered. All other COPD medications with the exception of theophylline and aminophylline (oral and intravenous) were permitted without restriction during the studies.

### **7.1.1. Study Population**

#### **7.1.1.1. Description of Population**

Patients who fulfilled the following criteria were eligible for inclusion in Studies 040 and 041:

- Males or females with COPD who had completed Study 039, 042, or 091 where patients received cilomilast 15mg twice daily or placebo for 24 weeks without tolerability problems.

Patients who fulfilled any of the following criteria were not eligible for inclusion in Studies 040 and 041:

- Patients who had withdrawn from Study 039, 042, or 091 for any reason.
- Patients who had a positive FOB test between Weeks 20 and 24 in Study 039, 042, or 091.
- Patients who had experienced a serious adverse event, a gastrointestinal adverse event (GIAE), or a clinically significant laboratory abnormality, which in the opinion of the Investigator was attributed to study medication during Study 039, 042, or 091, and which was still present at the end of their study.

#### **7.1.1.2. Population for Analysis**

Safety and Efficacy results are presented for the intent-to-treat (ITT) population. The ITT population consisted of all randomized subjects who had taken at least one dose of study drug.

### **7.1.2. Statistical Methods**

Lung function data, consisting of FEV<sub>1</sub>, health-related quality of life data, consisting of total score of the SGRQ, and COPD exacerbation rates in the open-label long-term extension studies were summarized according to randomized treatment in the double-blind feeder studies. The baseline data for the open-label extension studies represent Baseline (i.e., Visit 3) of the feeder studies (039, 042, and 091). An estimate of an annualized rate for COPD exacerbations for patients treated with cilomilast was determined from a Poisson regression model. Only the data from the open-label extension studies are used in the estimation. The safety data was summarized descriptively.

### **7.1.3. Demographics**

Overall demographic characteristics of patients in the long term extension studies were similar to that observed at entry into the pivotal studies. Patients previously treated with placebo or cilomilast had comparable demographic characteristics.

### **7.1.4. Subject Accountability**

Overall, a total of 440 of 1078 patients (40.8%) were withdrawn from the long term extension studies. The most common reason reported for withdrawal was adverse event, which occurred in 18.3% of all patients.

Patients previously treated with placebo withdrew more frequently than patients previously treated with cilomilast (46.2% for placebo and 37.8% for cilomilast). Withdrawals due to adverse events accounts for this difference with more patients previously treated with placebo leaving the study (24.3% for placebo and 15.0% for cilomilast). All other reasons for withdrawal were comparable for the previous treatments.

### **7.1.5. Extent of Exposure**

The long term extension studies evaluated over 1000 patients up to 3 years. Patients previously treated with placebo had lower mean days of exposure than patients previously treated with cilomilast (556.4 days for placebo and 638.6 days for cilomilast 15mg BID). At 6 months, 1 year and 2 years, respectively, 288 (75%), 263 (69%) and 188 (49%) patients in the prior placebo group and 603 (87%), 555 (80%) and 406 (58%) patients in prior cilomilast group were exposed to cilomilast during the long term extension studies.

Among patients treated with cilomilast in the feeder studies and in the long term extension studies mean exposure was 812.5 days. This long term exposure to cilomilast allows for an adequate safety assessment of the chronic administration of this compound in the population of interest.

### **7.1.6. Adverse Events in Long Term Extension Studies**

#### **7.1.6.1. Adverse Event Collection and Analysis**

The methods for collection and analysis of adverse events in the long-term, uncontrolled extension studies (i.e., Study 040 and Study 041) were essentially the same as those used for the phase III pivotal studies.

#### **7.1.6.2. All Adverse Events**

The numbers (%) of these patients with the most frequently reported on-therapy AEs, as defined by occurring in  $\geq 5\%$  of patients in either prior treatment group, are summarized in Table 22 below.

**Table 22** Number (%) of patients with the most frequently reported adverse events (greater than or equal to 5.0% of patients in either prior treatment group) – long term extension studies

Adverse Event (Preferred Term)	Cilomilast 15mg BID (prior placebo) (N = 383)		Cilomilast 15mg BID (prior cilomilast) (N = 695)	
	n	(%)	n	(%)
Total	359	(93.7)	650	(93.5)
Chronic Obstructive Airways Disease	206	(53.8)	447	(64.3)
Upper Respiratory Tract Infection	59	(15.4)	128	(18.4)
Diarrhea	85	(22.2)	90	(12.9)
Abdominal Pain	77	(20.1)	96	(13.8)
Injury	44	(11.5)	98	(14.1)
Nausea	71	(18.5)	69	(9.9)
Headache	54	(14.1)	66	(9.5)
Back Pain	32	(8.4)	85	(12.2)
Dyspepsia	50	(13.1)	64	(9.2)
Rhinitis	41	(10.7)	73	(10.5)
Infection Viral	35	(9.1)	61	(8.8)
Coughing	26	(6.8)	57	(8.2)
Pharyngitis	22	(5.7)	60	(8.6)
Arthralgia	30	(7.8)	47	(6.8)
Chest Pain	28	(7.3)	45	(6.5)
Sinusitis	25	(6.5)	48	(6.9)
Insomnia	21	(5.5)	49	(7.1)
Respiratory Disorder	15	(3.9)	55	(7.9)
Urinary Tract Infection	17	(4.4)	50	(7.2)
Vomiting	28	(7.3)	38	(5.5)
Hypertension	18	(4.7)	44	(6.3)
Dyspnea	22	(5.7)	39	(5.6)
Dizziness	20	(5.2)	40	(5.8)
Bronchitis	22	(5.7)	34	(4.9)
Pain	16	(4.2)	37	(5.3)
Pneumonia	20	(5.2)	33	(4.7)
Hyperglycemia	13	(3.4)	37	(5.3)
Anxiety	22	(5.7)	25	(3.6)
Arthritis	19	(5.0)	27	(3.9)
Myalgia	22	(5.7)	23	(3.3)

The overall incidence of AEs, irrespective of relationship to study medication, in the uncontrolled studies was comparable between patients who had previously received cilomilast during the feeder study (93.5%) and patients who had previously received placebo (93.7%). Chronic obstructive airways disease occurred more frequently in patients previously treated with cilomilast. Gastrointestinal intolerance occurred more

frequently in patients previously treated with placebo. In general in the prior placebo group GIAEs occurred early as was seen in the pivotal studies.

As in the pivotal studies, the majority of patients treated with cilomilast 15mg BID in the uncontrolled studies reported AEs whose maximum intensity was mild or moderate.

#### 7.1.6.3. Withdrawals Due to Adverse Events

The numbers (%) of patients with adverse events leading to the withdrawal of  $\geq 1.0\%$  of patients from the uncontrolled studies are summarized below in Table 23.

**Table 23 Adverse events leading to withdrawal of greater than or equal to 1.0% of patients – long term extension studies**

Adverse Event (Preferred Term)	Cilomilast 15mg BID (prior placebo) (N = 383) n (%)	Cilomilast 15mg BID (prior cilomilast) (N = 695) n (%)
Total	88 (23.0)	89 (12.8)
Abdominal Pain	23 (6.0)	13 (1.9)
Nausea	22 (5.7)	4 (0.6)
Diarrhea	16 (4.2)	7 (1.0)
Chronic Obstructive Airways Disease	6 (1.6)	11 (1.6)
Vomiting	10 (2.6)	2 (0.3)
Pulmonary Carcinoma	1 (0.3)	8 (1.2)

As shown in Table 23, more patients previously treated with placebo (23.0%) were withdrawn due to AEs than patients previously treated with cilomilast (12.8%).

#### 7.1.6.4. Additional Assessments of Gastrointestinal Safety

As previously discussed in Section 6.5.2.4, 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.

To further evaluate gastrointestinal safety, gastrointestinal adverse events of concern (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, or vomiting that concerned the patient or interfered with his/her daily activities) were closely monitored during the Phase III long term extension studies. Investigators identified gastrointestinal adverse events (GIAEs) of concern based on reports from patients of GI symptoms. Investigators completed a clinical assessment of each such GI symptom within 24 hours of its occurrence including physical examination, FOB (fecal occult blood), complete blood count, and orthostatic vitals. In addition, if the FOB test was positive or if the patient reported melena during the treatment phase, the patient was to be referred to a gastroenterologist for a complete colonoscopy. Assessments of FOB,

complete blood count, and orthostatic changes in blood pressure were continued until the GIAE of concern resolved.

### ***Gastrointestinal Adverse Events (GIAEs) of Concern***

The numbers (%) of patients with the most frequently reported on-therapy GIAEs of concern in the uncontrolled studies, as defined by occurring in  $\geq 0.5\%$  of patients in either prior treatment group, are summarized in Table 24 below.

**Table 24** Number (%) of patients with most frequently reported gastrointestinal adverse events of concern (greater than or equal to 0.5% of patients in either prior treatment group) – long term extension studies

Adverse Event (Preferred Term)	Cilomilast 15mg BID (prior placebo) (N = 383)	Cilomilast 15mg BID (prior cilomilast) (N = 695)
	n (%)	n (%)
<b>Total</b>	69 (18.0)	72 (10.4)
Abdominal Pain	35 (9.1)	30 (4.3)
Diarrhea	30 (7.8)	17 (2.4)
Nausea	21 (5.5)	9 (1.3)
Vomiting	12 (3.1)	6 (0.9)
Dyspepsia	7 (1.8)	3 (0.4)
Melena	3 (0.8)	7 (1.0)
Gastritis	4 (1.0)	2 (0.3)
Constipation	0 (0.0)	4 (0.6)
Gastroesophageal Reflux	2 (0.5)	2 (0.3)
Hemorrhoids	0 (0.0)	4 (0.6)
Gastrointestinal Disorder NOS	2 (0.5)	1 (0.1)
GI Hemorrhage	2 (0.5)	1 (0.1)
Anorexia	2 (0.5)	0 (0.0)

The overall incidence of GIAEs of concern in the long term extension studies was higher in patients who had previously received placebo during the feeder study (18.0%) than in patients who had previously received cilomilast (10.4%). The individual GIAEs of concern of gastrointestinal intolerance (abdominal pain, diarrhea, nausea, vomiting, and dyspepsia) occurred more frequently in patients who had previously received placebo than in patients previously treated with cilomilast.

### ***Fecal Occult Blood Results from Patients with GIAEs of Concern***

Of the 69 patients previously treated with cilomilast in the feeder studies who had FOB tests performed in the long term extension studies, 11.6% (8 patients) had a positive test result which was consistent with that observed in the pivotal studies (7.8% cilomilast; 11.9% placebo). Of the 59 patients previously treated with placebo in the feeder studies who had an accompanying FOB test performed during the long-term extension studies while on cilomilast, 1.7% (1 patient) tested positive for fecal occult blood.

Of the 36 patients previously treated with cilomilast in the feeder study who had FOB tests performed within 14 days of the event, only 19.4% (7 patients) had a positive test result, which was consistent with the percentage of positive tests observed in the pivotal studies (9.8% cilomilast; 17.9% placebo). Of the 32 patients previously treated with placebo in the feeder study who had FOB tests performed within 14 days of the event, 3.1% (1 patient) tested positive for fecal occult blood.

Overall, there were too few patients who had a positive FOB result in the uncontrolled studies to draw any conclusions between patients who previously received cilomilast and placebo in the feeder studies.

#### ***Orthostatic Vital Signs and Colonoscopy Results from Patients with GIAEs of Concern***

A total of 80 patients (37 prior placebo, 43 prior cilomilast) who reported one or more GIAEs of concern also had accompanying orthostatic vital signs. For each of the three vital signs assessments, the overwhelming percentage of patients exhibited normal values: 81.3% (65 of 80 patients) for systolic blood pressure; 91.3% (73 of 80 patients) for diastolic blood pressure; and 96.3% (77 of 80 patients) for heart rate. Studies 040 and 041 were amended to include a requirement for a colonoscopy to be performed on patients who reported at least one GIAE of concern and a positive fecal occult blood test or melena during the study. Fifteen patients with GIAEs of concern underwent colonoscopies. In Study 041 a total of 26 patients who did not report GIAEs of concern had colonoscopies or other GI procedures performed. Of these 26 patients, 11 patients with on-therapy AEs of the gastrointestinal system (not reported as GIAEs of concern) had colonoscopies and other GI procedures performed. Overall the colonoscopies and other GI procedures noted expected findings for the population studied e.g., diverticulitis, polyps and hemorrhoids, and did not identify any cilomilast related safety concerns.

#### **7.1.7. Routine FOBs (including FOBs performed for GIAEs of Concern)-Long Term Extension Studies**

A total of 8 (2.7%) of 291 patients who previously received placebo and 30 (5.1%) of 588 patients who previously received cilomilast and who had negative FOB results at baseline, shifted to positive during treatment in the long term extension studies. FOB results at Endpoint (last on therapy measurement) for the uncontrolled studies revealed that a smaller number patients in both treatment groups shifted from baseline FOB negative to positive at endpoint (prior cilomilast 10 patients, 1.7%; prior placebo 4 patients, 1.4%).

#### **7.1.8. Serious Adverse Events-Long Term Extension Studies**

Two hundred seventy-three patients (25.3% of the 1078 enrolled patients) had one or more SAEs during the studies.

**Table 25** Number (%) of patients with the most frequently reported on-therapy SAEs (greater than or equal to 1.0% of patients in either treatment group) – long term extension studies

Adverse Event (Preferred Term)	Cilomilast 15mg BID (prior placebo) (N = 383)		Cilomilast 15mg BID (prior cilomilast) (N = 695)	
	n	(%)	n	(%)
<b>Total</b>	95	(24.8)	178	(25.6)
Chronic Obstructive Airways Disease	30	(7.8)	55	(7.9)
Pneumonia	13	(3.4)	21	(3.0)
Injury	2	(0.5)	18	(2.6)
Chest Pain	4	(1.0)	9	(1.3)
Angina Pectoris	4	(1.0)	6	(0.9)
Pulmonary Carcinoma	1	(0.3)	9	(1.3)
Myocardial Infarction	6	(1.6)	3	(0.4)
Neoplasm NOS	4	(1.0)	5	(0.7)
Abdominal Pain	4	(1.0)	2	(0.3)

As shown in Table 25, many of the SAEs involved diseases of the pulmonary or cardiac systems and were likely complications of the patient's underlying COPD; nearly all were events that are commonly observed in a population of older patients.

Serious adverse event (including deaths) narratives were searched for any reference to ischemic bowel disease. This search included patients that did not have ischemic bowel disease reported as a serious adverse event. Ischemic bowel disease was reported in two patients during the Phase III open label extension studies. Brief descriptions of the events are provided below.

Patient 091.164.09439 in Study 040 (after 6 months of treatment with cilomilast in the double blind study and approximately 2 months of treatment with cilomilast in study 040) underwent a left femoral and right ileo femoral bypass and Fogarty balloon angioplasty that was complicated by renal failure and a right popliteal thrombosis. The patient's thrombosis worsened, affecting the mesenteric vessel, resulting in mesenteric infarction. The patient later died due to cardiorespiratory failure.

Patient 091.010.09989 in Study 040 (after 6 months of treatment with cilomilast in the double blind study and approximately 18 months of treatment with cilomilast in study 040) had a complicated medical history including rheumatoid arthritis, weight loss, laxative abuse and anorexia and was hospitalized due to a deterioration in health status. During the hospitalization, the patient underwent a x-ray of the colon that was reported to show no visible stenosis, but "sequelae of ischemic colitis". However, ischemic colitis was not reported anywhere else in the patient's medical history nor was it reported as an adverse event.

Patient 041.070.06135 in Study 041 (after 6 months of treatment with placebo in the double blind study and approximately 2.5 years of treatment with cilomilast in Study 041) was admitted to the hospital with severe exacerbation of COPD. During the hospitalization, the subject became constipated and complained of abdominal pain. The abdomen was found to be increasingly distended with reduced bowel sounds and abdominal films revealed bowel perforation. The subject was taken to the operating room for emergency exploratory laparotomy. The entire transverse colon was removed due to ischemic necrosis and a permanent colostomy was performed. The patient experienced acute respiratory distress and required mechanical ventilation with marginal blood pressure requiring increasing pressors. The subject was noted to be bradycardic and went into asystole and was pronounced dead, fourteen days after admission. The final autopsy report stated the major findings in this subject included chronic ischemic heart disease with associated severe chronic obstructive pulmonary disease. It was noted that the immediate cause of death was probably related to the ischemic necrosis of transverse colon with perforation and associated severe ischemic heart disease with chronic obstructive pulmonary disease.

#### **7.1.9. Deaths-Long Term Extension Studies**

Twenty-four patients died during the long-term extension studies. Eight patients died during treatment with cilomilast and 16 died after discontinuing treatment. Eight patients died from respiratory complications, thirteen died from cardiac complications, two died from neoplasms and one suicide. The investigators judged all of the fatal SAEs not related or unlikely related to study medication.

#### **7.1.10. Cardiovascular Safety (ECGs)**

Extensive cardiovascular monitoring during the development program included frequent ECGs (>70,000 ECGs with over 6,000 obtained at Cmax). In the long-term extension, a 12-lead ECG was performed at each visit. The ECGs were transmitted electronically via modem to a centralized facility for interpretation by a Board-certified cardiologist and data processing. ECGs values (atrial rate, ventricular rate, QRS duration, PR duration, QT interval, QTc interval, QRS axis) were summarized by mean values and by sponsor defined threshold values (transitions from normal to low, low concern, high and high concern). ECG values of concern are defined in Table 16. Transitions in ECG values are summarized in Table 26.

**Table 26 Transitions from normal range at baseline for trough ECG parameters – long term extension studies**

Parameter	N <sup>b</sup>	On-Therapy <sup>a</sup>				
		Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
<b>Atrial rate (bpm)</b>						
Placebo <sup>c</sup>	331	12 (3.6)	43 (13.0)	201 (60.7)	69 (20.8)	13 (3.9)
Cilomilast 15mg BID	609	21 (3.4)	80 (13.1)	373 (61.2)	123 (20.2)	19 (3.1)
<b>Ventricular rate (bpm)</b>						
Placebo <sup>c</sup>	331	14 (4.2)	42 (12.7)	200 (60.4)	71 (21.5)	11 (3.3)
Cilomilast 15mg BID	611	21 (3.4)	81 (13.3)	376 (61.5)	125 (20.5)	15 (2.5)
<b>QRS interval (msec)</b>						
Placebo <sup>c</sup>	335	0 (0.0)	0 (0.0)	311 (92.8)	24 (7.2)	0 (0.0)
Cilomilast 15mg BID	643	0 (0.0)	0 (0.0)	592 (92.1)	51 (7.9)	0 (0.0)
<b>PR interval (msec)</b>						
Placebo <sup>c</sup>	333	0 (0.0)	0 (0.0)	302 (90.7)	31 (9.3)	0 (0.0)
Cilomilast 15mg BID	615	0 (0.0)	0 (0.0)	541 (88.0)	72 (11.7)	2 (0.3)
<b>QT, uncorrected (msec)</b>						
Placebo <sup>c</sup>	362	NA	NA	357 (98.6)	NA	5 (1.4)
Cilomilast 15mg BID	676	NA	NA	666 (98.5)	NA	10 (1.5)
<b>QTc (absolute values) (msec)<sup>d</sup></b>						
Placebo <sup>c</sup>	262	0 (0.0)	0 (0.0)	120 (45.8)	93 (35.5)	49 (18.7)
Cilomilast 15mg BID	483	0 (0.0)	0 (0.0)	220 (45.5)	169 (35.0)	94 (19.5)
<b>QTc (change from baseline) (msec)<sup>e</sup></b>						
Placebo <sup>c</sup>	262	0 (0.0)	0 (0.0)	173 (66.0)	77 (29.4)	12 (4.6)
Cilomilast 15mg BID	483	0 (0.0)	0 (0.0)	326 (67.5)	130 (26.9)	27 (5.6)

NA = Not applicable.

- Patients are assigned to categories based on their highest and/or lowest on-therapy value. Patients with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable.
- Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range at baseline.
- Indicates patients assigned to placebo in the respective controlled study.
- QT corrected by Bazett's formula.
- Number of patients with at least one on-therapy, change from baseline QTc measurement. Percentages for QTc change from baseline are based on this number.

Overall the percentages of patients that transitioned from a normal baseline value was higher than that observed across the pivotal studies, which may be explained by the frequent testing over the longer period of observation.

The incidence of the most frequent (defined as occurring in greater than or equal to 5% of patients in any treatment group) on-therapy ECG abnormalities that were not present on ECGs recorded pre-therapy at Screening or Baseline and did not occur during the controlled studies is presented in Table 27.

**Table 27** Number (%) of patients with the most frequently reported new-onset ECG abnormalities greater than or equal to 5% of patients in any prior treatment group) – long term extension studies

Adverse Event (Preferred Term)	Cilomilast 15mg BID (prior placebo) (N = 383)	Cilomilast 15mg BID (prior cilomilast) (N = 695)
	n (%)	n (%)
Poor R-wave Progression	60 (18.6)	114 (19.4)
Premature Atrial Contractions NOS	52 (16.4)	96 (16.3)
Premature Ventricular Contractions NOS	40 (11.2)	81 (13.4)
Q-T Interval Increased	40 (15.6)	75 (15.7)
T Wave Abnormal, NOS	38 (12.3)	76 (13.0)
Sinus Tachycardia	44 (13.0)	66 (11.0)
S-T Changes Nonspecific	36 (12.2)	68 (12.5)
Sinus Bradycardia	22 (8.7)	55 (12.1)
Atrial Hypertrophy NOS	29 (8.7)	41 (6.7)
Decreased Voltage EKG	20 (5.5)	47 (7.1)
Left Axis Deviation EKG	19 (5.4)	46 (7.2)
Intraventricular Block NOS	23 (7.4)	41 (7.2)
Left Atrial Hypertrophy (P Mitrale)	21 (6.4)	42 (6.8)
Indeterminate Axis EKG	19 (5.0)	40 (5.9)
PVCs Unifocal	20 (5.6)	37 (5.7)
Sinus Arrhythmia	19 (5.4)	37 (5.7)
Myocardial Infarction Septal Old	19 (5.7)	35 (6.0)
Right Axis Deviation EKG	14 (4.0)	37 (5.7)
Incomplete Bundle Branch Block	17 (4.9)	33 (5.3)
Ectopic Atrial Beats NOS	21 (5.8)	27 (4.1)
Myocardial Infarction Inferior Old	14 (4.0)	32 (5.0)
Left Anterior Hemiblock	18 (5.2)	24 (4.0)
Low Ventricular Voltage NOS	6 (1.6)	35 (5.2)

a. Percentages are based on the number of patients without the specific abnormality pre-therapy.

In general, the treatment emergent ECG abnormalities observed during the open-label extension studies were more frequent than in the respective controlled studies. The increased frequency may be attributable to the longer period of observation as well as progression of the underlying cardiopulmonary disease.

#### 7.1.11. Laboratory Data and Vital Signs

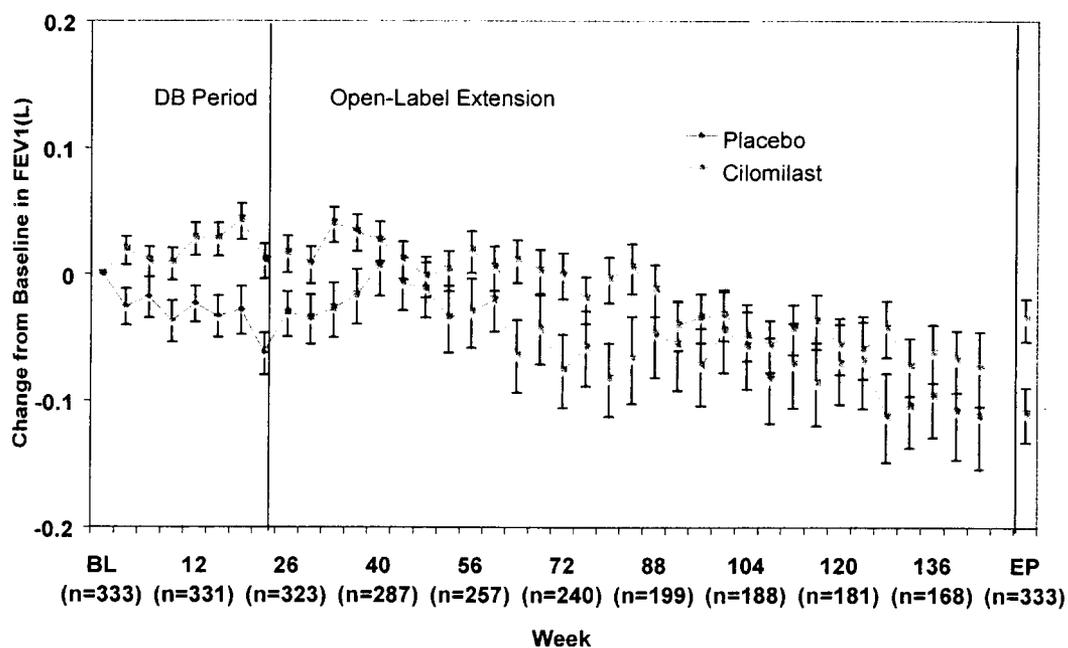
During exposures lasting as long as 30+ months to cilomilast, there was no pattern of changes in hematology or clinical chemistry laboratory values. A small number of patients from both treatment groups in the feeder studies had vital sign transitions to low or high concern. Orthostatic changes were similar at Baseline and Endpoint for blood pressure and heart rate regardless of treatment assignment in the respective feeder study. No significant vital sign changes are associated with prolonged exposure to cilomilast.

7.1.12. Efficacy Results

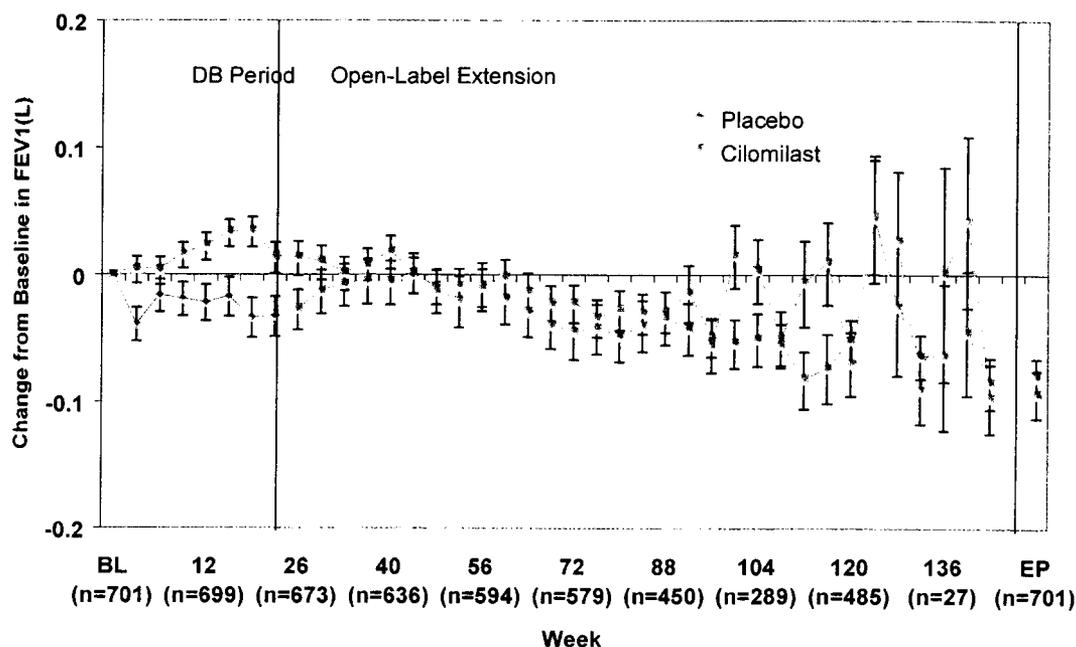
7.1.12.1. FEV<sub>1</sub>

The mean change from Baseline in FEV<sub>1</sub> in the open-label extension studies 041 and 040 and the corresponding double-blind feeder studies by time is presented graphically in Figure 19 and Figure 20.

**Figure 19 Mean (SEM) change from Baseline in FEV<sub>1</sub> (L) by time in the open-label extension study 041 and the corresponding double-blind feeder study 039**



**Figure 20 Mean (SEM) change from Baseline in FEV<sub>1</sub> (L) by time in the open-label extension study 040 and the corresponding double-blind feeder studies 042 and 091**

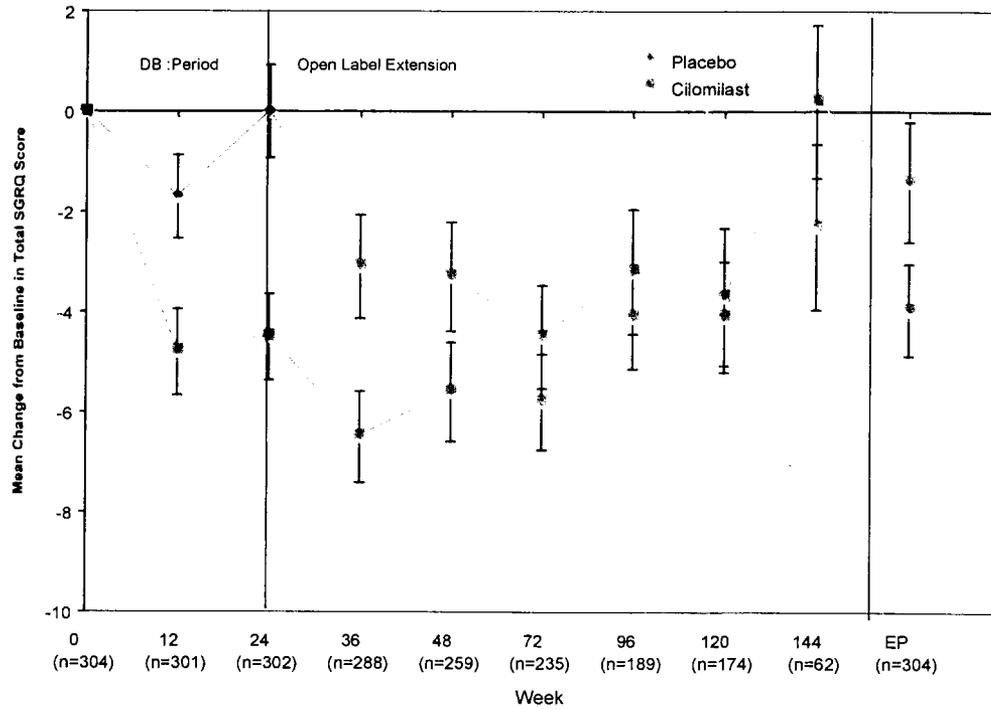


In the long-term extension studies, FEV<sub>1</sub> was maintained up to 60 weeks in the patients previously treated with cilomilast. In contrast, patients not previously treated with cilomilast (prior placebo group) showed an early improvement in FEV<sub>1</sub>, followed by a gradual deterioration 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<sub>1</sub> 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.

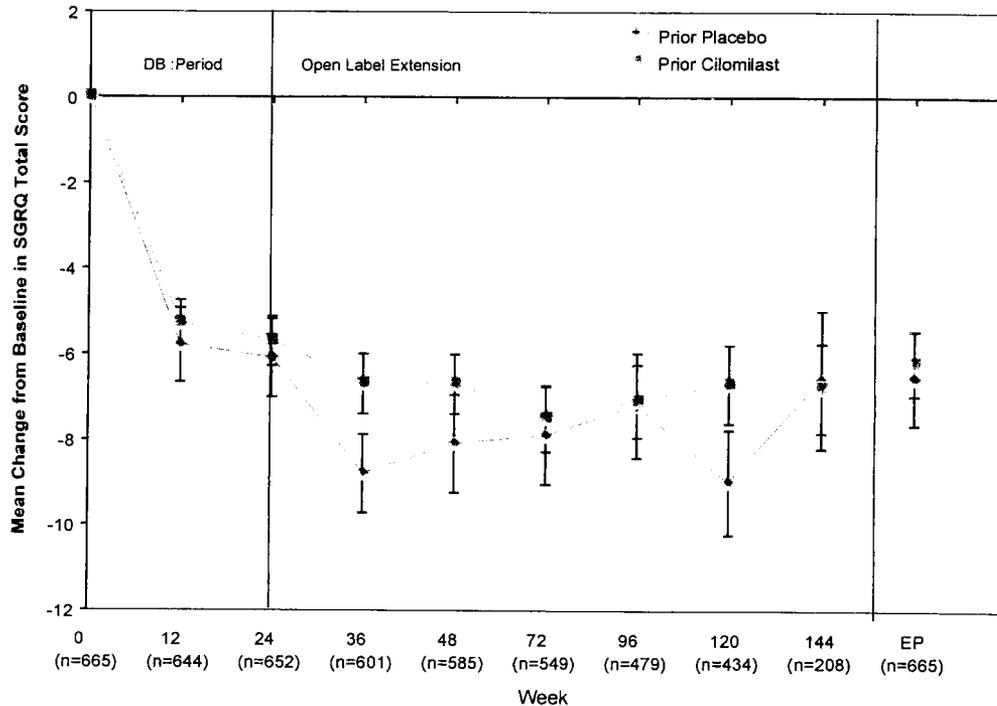
#### 7.1.12.2. SGRQ

A summary of the mean change from Baseline in total score of the SGRQ in the open-label extension studies in 041 and 040 is presented in Figure 21 and Figure 22.

**Figure 21** Mean (SEM) Change from Baseline in SGRQ Total Score in the open-label extension study 041 and the corresponding double-blind feeder study 039



**Figure 22 Mean (SEM) Change from Baseline in SGRQ Total Score in the open-label extension study 040 and the corresponding double-blind feeder study 042 and 091**



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.

**7.1.12.3. COPD Exacerbations**

A summary of the rate of level 2 or 3 COPD exacerbations per patient-year in the open-label extension studies is presented in Table 28.

**Table 28 Level 2 or 3 COPD exacerbation rates (per patient-year) in the open-label extension studies for patients who received cilomilast**

Prior Treatment <sup>a</sup>	Rate/Patient-Year <sup>b</sup>	95% CI
Placebo	0.915	(0.840, 0.996)
Cilomilast	0.859	(0.808, 0.912)

The rate of exacerbations in both groups were low and less than expected compared to published literature where the average ranges between 1-3 exacerbations/patient-year [Anthonisen, 1987 (1.3 exacerbations/patient-year); Seemungal, 1998 (2.7

exacerbations/patient-year), Seemungal, 2000 (2.4 exacerbations/patient-year), Seemungal, 2001 (2.9 exacerbations/patient-year)].

## **7.2. Study 168**

### **7.2.1. Introduction**

Study 168 was primarily a cardiovascular safety study. The Holter data from study 168 were integrated with Holter data from studies 039, 042 and 091 and presented in Section 6.5.5.2. In addition, the overall safety profile in study 168 was similar to that observed in the pivotal efficacy studies and is not discussed further.

Study 168 was the first study to evaluate reversible and poorly reversible patients. 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  $\text{FEV}_1$  post-bronchodilator). In general, patients who are poorly reversible have a decreased magnitude of  $\text{FEV}_1$  response to COPD medications as compared to a more reversible population.

### **7.2.2. Methods**

Study 168 was a 12-week randomized, double-blind, placebo-controlled, parallel-group study stratified by reversibility primarily designed to assess cardiovascular safety and tolerability of cilomilast 15mg BID in COPD through 24-hour continuous ambulatory electrocardiography (Holter) monitoring. With the exception of bronchodilator reversibility, all entry criteria were similar to that of the pivotal studies. Although  $\text{FEV}_1$  was designated as a key efficacy variable in Study 168, the study was not powered to detect statistical significance. All efficacy analyses for this study were performed for the ITT population, the reversible population, and the poorly reversible population.

### **7.2.3. Demographics**

With the exception of reversibility to albuterol (approximately 7% in the pivotal studies and 18% in study 168), there were no marked differences in demographic or pulmonary function characteristics between study 168 and the pivotal studies.

### **7.2.4. Efficacy Results**

#### **7.2.4.1. Key Efficacy Endpoint**

##### ***FEV<sub>1</sub>***

The primary measure of efficacy was the change from baseline in trough pre-bronchodilator  $\text{FEV}_1$  at endpoint.

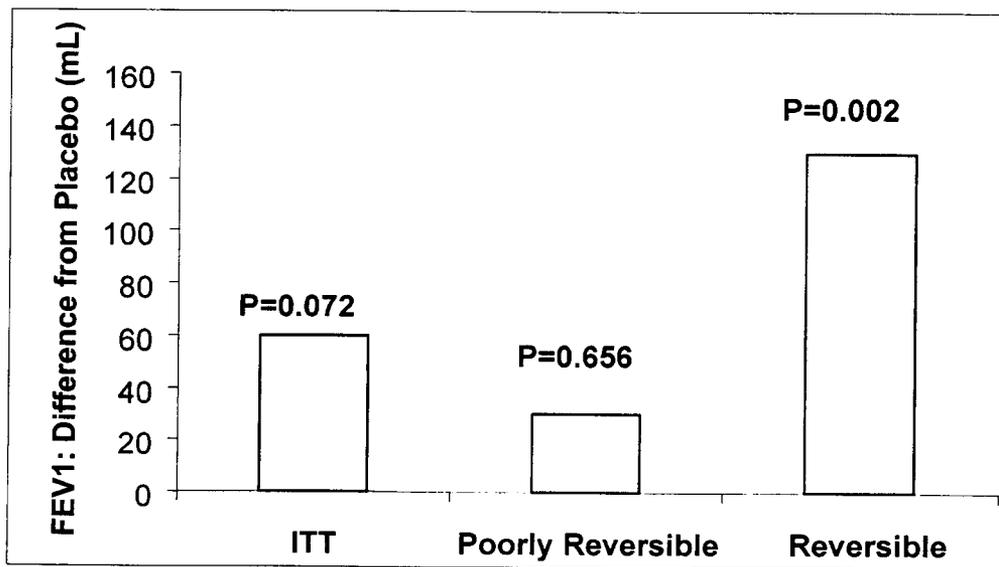
Table 29 presents the mean change from baseline in trough  $\text{FEV}_1$  at endpoint for ITT, Reversible and Poorly reversible Populations.

**Table 29 Mean Change from Baseline In Trough FEV<sub>1</sub> (L) – ITT, Reversible and Poorly Reversible Patients**

Time Point	Treatment Group	N	Assessment	Change from Baseline		Comparison with Placebo	
			Mean	Mean	SEM	Mean Difference	p-value
<b>ITT Population</b>							
Baseline	Placebo	90	1.33	-	-	-	-
	Cilomilast	174	1.35	-	-	-	-
Endpoint	Placebo	90	1.30	-0.03	0.03	-	-
	Cilomilast	174	1.38	0.03	0.02	<b>0.06</b>	<b>0.072</b>
<b>Reversible Population</b>							
Baseline	Placebo	39	1.30	-	-	-	-
	Cilomilast	69	1.32	-	-	-	-
Endpoint	Placebo	39	1.29	-0.01	0.03	-	-
	Cilomilast	69	1.44	0.12	0.03	<b>0.13</b>	<b>0.002</b>
<b>Poorly reversible Population</b>							
Baseline	Placebo	51	2.63	-	-	-	-
	Cilomilast	105	2.74	-	-	-	-
Endpoint	Placebo	51	2.57	-0.06	0.06	-	-
	Cilomilast	105	2.71	-0.03	0.04	<b>0.03</b>	<b>0.656</b>

A greater magnitude of response was observed in the reversible (difference from placebo 130ml, p=0.002) as compared to the poorly reversible patients (difference from placebo 30ml, p=0.656). See Figure 23.

**Figure 23 Mean Difference from Placebo in FEV<sub>1</sub> (L) for ITT, Poorly Reversible and Reversible Patients**



### **7.3. Study 111**

#### **7.3.1. Introduction**

Although the measurement of FEV<sub>1</sub> is of unquestionable diagnostic utility, and has been an accepted measure of disease severity in COPD, there is evidence to indicate that FEV<sub>1</sub> 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]. Static or dynamic lung volume measurements may be a more useful tool in assessing degree of functional impairment in patients with COPD especially those who are poorly reversible [O'Donnell, 2001].

Study 111 was designed to evaluate the effect of cilomilast on static lung volumes. In the small airways of patients with COPD, there is an increased number of inflammatory cells, which correlates with reduced expiratory airflow and lung hyperinflation [Turato, 2002]. Changes in lung volume measurements indicative of hyperinflation of the lungs provide complementary information to FEV<sub>1</sub> results when evaluating therapeutic responses in COPD. Hyperinflation of the lungs is common in patients with COPD. Hyperinflation is characterized by increases in total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV) despite a reduction in slow vital capacity (SVC). Of these, the increases in FRC and RV are the more detrimental effects because they significantly reduce the respiratory reserve necessary for ambulatory function and increase the work of breathing in patients with COPD. Hyperinflation results from reductions in elastic recoil of the lungs and expiratory muscle strength, as well as the airway obstruction associated with COPD [Crapo, 1998].

The loss of elastic recoil and expiratory muscle strength reduce the force favoring reduction of lung volume against the unchanged force favoring increased lung volume, i.e., chest wall recoil. 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 increases in both FRC and RV. This is exacerbated during activity when expiratory time is shortened even more and FRC and RV continually increase, as they become a dynamic measurement, dependent upon expiratory time. Another important observation is that following inhaled bronchodilator, more severely obstructed and hyperinflated patients showed the greatest response, by reducing hyperinflation, while at the same time responding only minimally as measured by FEV<sub>1</sub> [O'Donnell, 2001].

#### **7.3.2. Study Design**

This was a 12-week randomized, double-blind, placebo-controlled, parallel-group, multicenter study in patients with COPD. Patients were required to have a Baseline RV (from plethysmography)  $\geq 120\%$  of predicted RV. Other entry criteria were similar to that of the pivotal studies.

**7.3.3. Demographics**

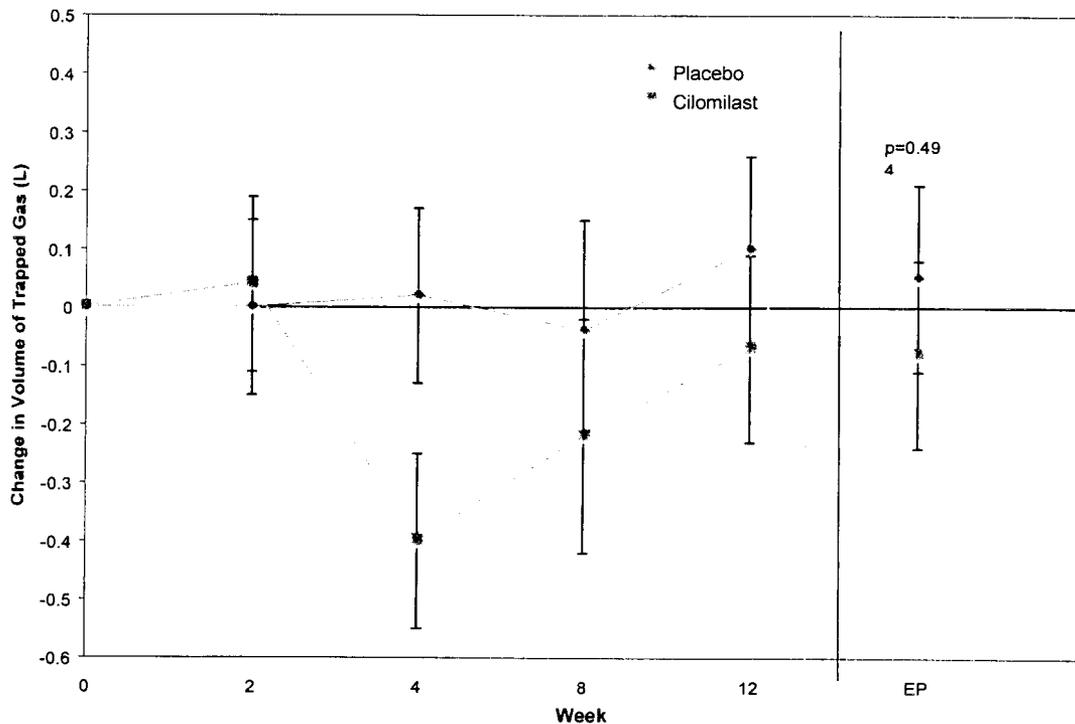
The demographic and pulmonary function characteristics were similar between groups and consistent with the pivotal studies.

**7.3.4. Efficacy Results**

**7.3.4.1. Volume of Trapped Gas**

The primary efficacy variable was the change in volume of trapped gas at Endpoint. Trapped gas volume was calculated as the difference between total lung capacity (TLC) determined by body plethysmography and single-breath helium dilution methods. When calculated in this way, the difference in the mean volume of trapped gas between the cilomilast treatment group and the placebo treatment group at Endpoint favored cilomilast treatment (-140mL), although the difference was not statistically significant (see Figure 24).

**Figure 24 Mean (SEM) Change from Baseline in Volume of Trapped Gas**

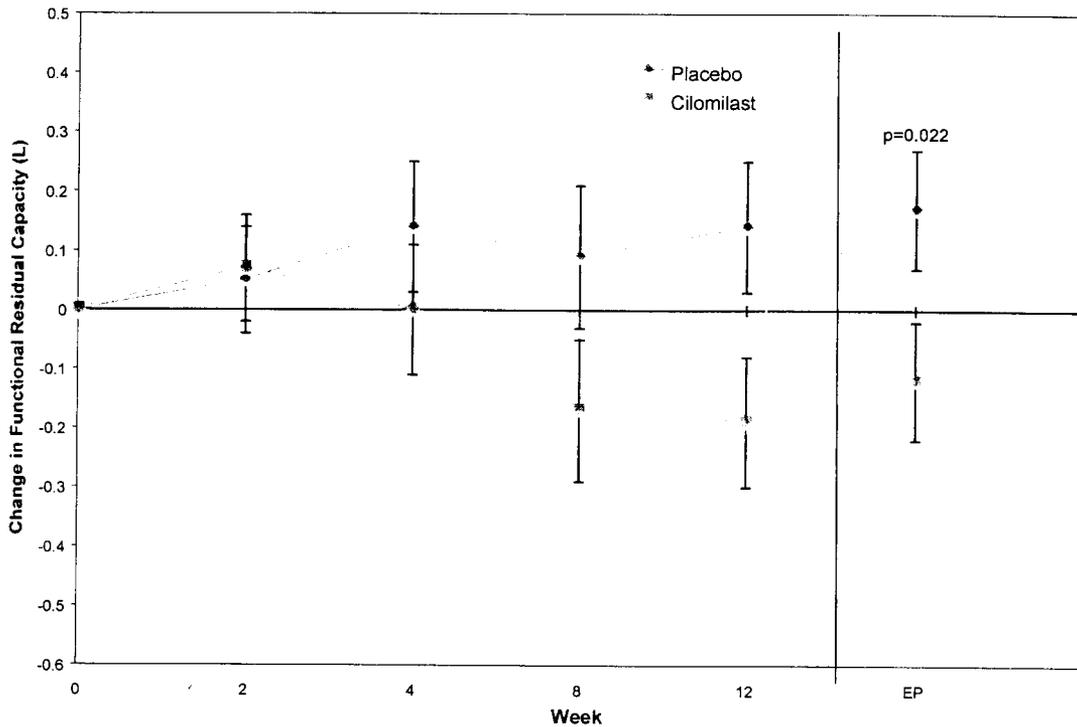


Since the single-breath helium dilution method used consistently underestimates lung volumes in patient with COPD [Kendrick, 1996; Miller, 1986; Brugman, 1986; Burns, 1984], the results from body plethysmography are shown below in Figure 25.

**7.3.4.2. Thoracic Gas Volume at Functional Residual Capacity (FRC)**

Mean FRC decreased from Baseline to Endpoint in the cilomilast treatment group (-120mL) and increased in the placebo treatment group (170mL). The mean difference in FRC between the cilomilast and placebo treatment groups increased from Week 4 through Week 12 and at Endpoint. The differences in mean FRC between the cilomilast and placebo treatment groups were -330mL at Week 12, ( $p = 0.019$ ) and -290mL at Endpoint ( $p = 0.022$ ) (see Figure 25).

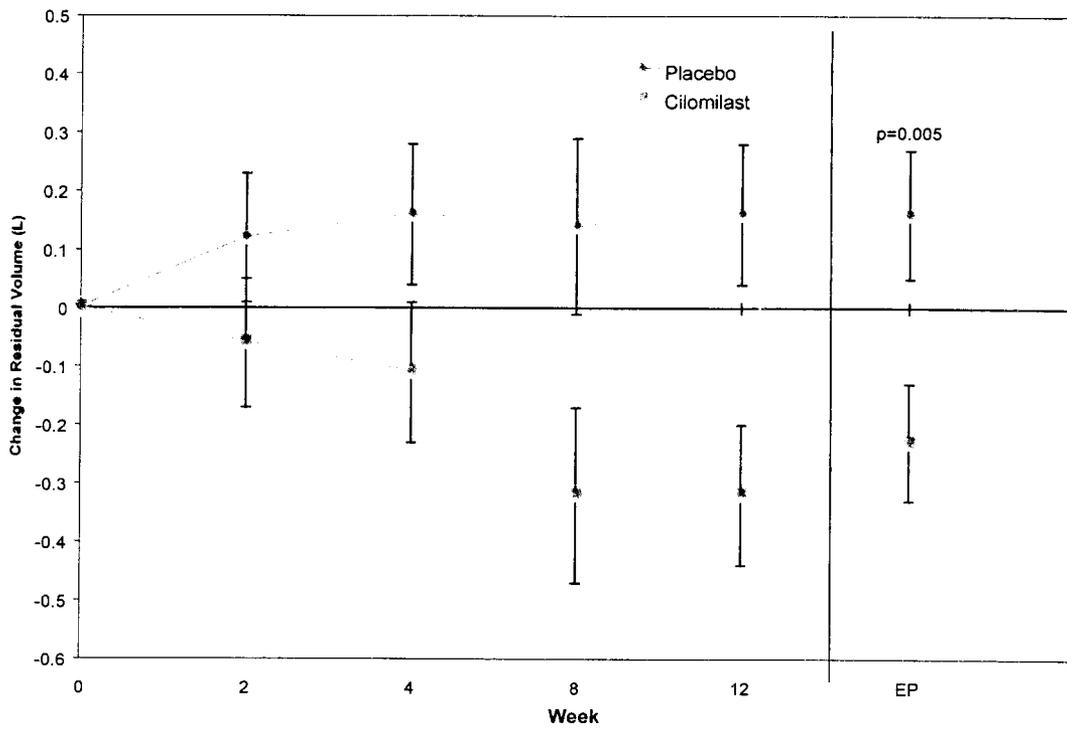
**Figure 25 Mean (SEM) Change from Baseline in Functional Residual Capacity**



**7.3.4.3. Residual Volume (RV)**

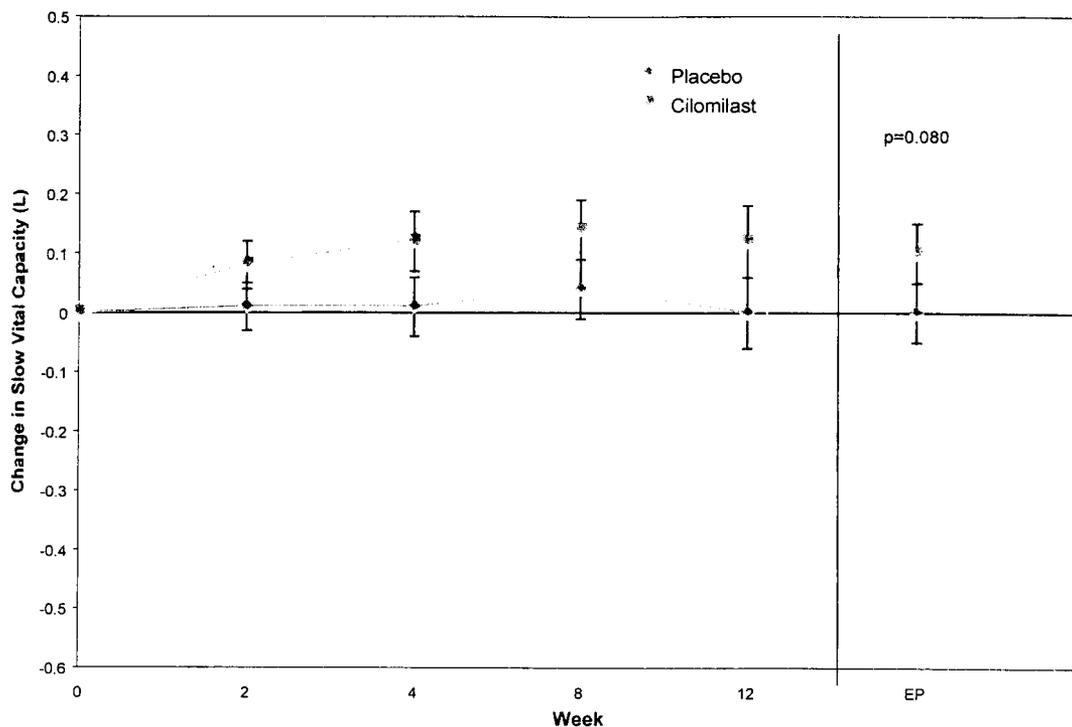
When measured by plethysmography, pre-albuterol RV decreased from Baseline to Endpoint in the cilomilast group (-230mL) and increased in the placebo treatment group (160mL) (see Figure 26). There was a substantial decrease in body plethysmography RV in the cilomilast treatment group compared to placebo at Week 12 (-480mL;  $p = 0.002$ ) and at Endpoint (-390mL;  $p = 0.005$ ).

**Figure 26 Mean (SEM) Change from Baseline in Residual Volume**



**7.3.4.4. Slow Vital Capacity (SVC)**

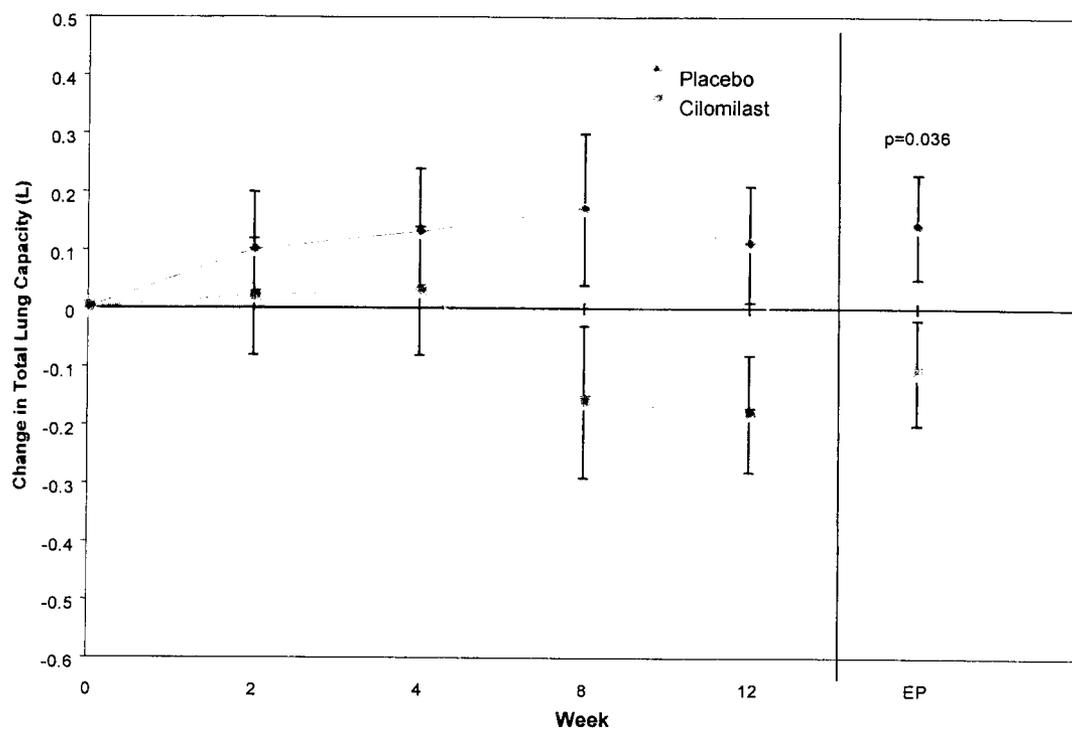
As shown in Figure 27, mean SVC increased from Baseline to Endpoint in the cilomilast treatment group (120mL) whereas there was no change in the placebo treatment group. The difference in mean SVC between the cilomilast treatment group and the placebo treatment group at Endpoint favored cilomilast treatment (110mL;  $p = 0.080$ ).

**Figure 27 Mean (SEM) Change from Baseline in Slow Vital Capacity**

#### 7.3.4.5. Total Lung Capacity ( $TLC_{Box}$ )

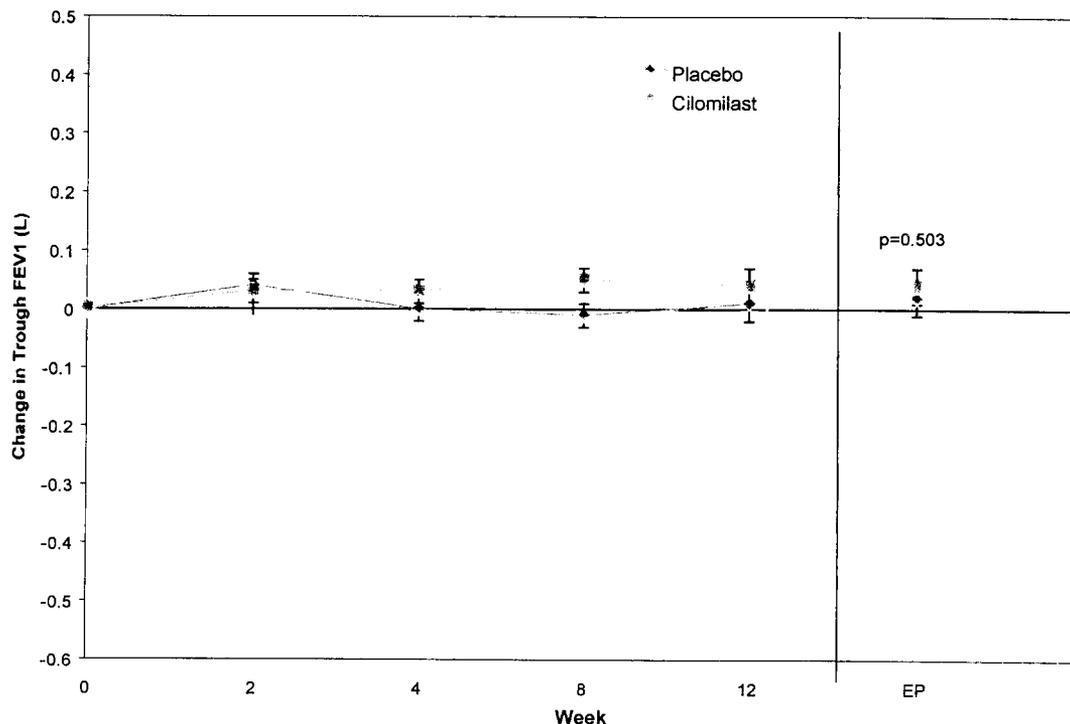
Mean pre-albuterol  $TLC_{Box}$ , as measured by plethysmography, decreased from Baseline to Endpoint in the cilomilast treatment group (-110mL) and increased in the placebo treatment group (140mL) (see Figure 28). The difference in the mean  $TLC_{Box}$  (measured by plethysmography) between the cilomilast and placebo treatment groups was -290mL at Week 12 ( $p = 0.022$ ) and -250mL at Endpoint ( $p = 0.036$ ).

**Figure 28 Mean (SEM) Change from Baseline in Total Lung Capacity**



**7.3.4.6. FEV<sub>1</sub>**

The difference in mean FEV<sub>1</sub> between the cilomilast treatment group and the placebo treatment group at Endpoint favored cilomilast treatment by 20mL (p = 0.503) (see Figure 29).

**Figure 29 Mean (SEM) Change from Baseline in Trough FEV<sub>1</sub>****7.3.4.7. Summary**

In this study, despite substantial improvements in lung volume indices, no significant improvement was observed in FEV<sub>1</sub> when compared to placebo. These findings are consistent with previous studies that showed significant reductions from baseline in lung volumes in response to albuterol in patients with COPD but modest improvements in FEV<sub>1</sub> [Newton, 2002, O'Donnell, 2001]. The changes seen in lung volumes and FEV<sub>1</sub> 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 determine the respiratory reserve necessary for ambulatory activity, and the volume changes seen in our study have been regarded as being clinically beneficial in patients with hyperinflation [O'Donnell, 2001].