

6. PIVOTAL STUDIES

- 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.

6.1. Subject Accountability

A summary of the number of patients exposed to cilomilast and placebo and patient disposition in the four pivotal efficacy studies (individually and pooled) is presented in Table 3.

Table 3 Subject accountability in the pivotal efficacy studies - ITT Population

Patient Disposition	Treatment	Study 039	Study 156	Study 042	Study 091 ^a	Pooled NA	Pooled EU	All Pooled
		(N=647) n (%)	(N=825) n (%)	(N=700) n (%)	(N=711) n (%)	(N=1472) n (%)	(N=1411) n (%)	(N=2883) n (%)
Randomized	Placebo	216	407	226	242	623	468	1091
	Cilomilast	431	418	474	469	849	943	1792
Withdrawn	Placebo	52 (24)	96 (24)	51 (23)	65 (27)	148 (23)	116 (25)	264 (24)
	Cilomilast	137 (32)	143 (34)	122 (26)	125 (27) ^b	280 (33)	247 (26)	527 (30)
Completed	Placebo	164 (76)	311 (76)	175 (77)	177 (73)	475 (76)	352 (75)	827 (76)
	Cilomilast	294 (68)	275 (66)	352 (74)	344 (73)	569 (67)	696 (74)	1265 (71)

a. Patient disposition in Study 091 includes the 2-week double-blind run-out period.

b. Includes two patients who completed the 24-week double-blind treatment period but did not enter the 2-week run-out period.

The percentage of patients who withdrew from the pivotal studies was higher in the cilomilast treatment group (ranging from 26% to 34%) than in the placebo treatment group (ranging from 23% to 27%). Overall, across the four pooled pivotal studies, 71% of cilomilast-treated patients and 76% of placebo-treated patients completed the pivotal efficacy studies.

6.2. Demographic and Baseline Characteristics

A summary of demographic and baseline characteristics for patients in the four pivotal efficacy studies (individually and pooled) at Screening is presented in Table 4.

Table 4 Demographic characteristics in the pivotal efficacy studies at Screening – ITT Population

Study/ Treatment Group	N	Sex, %	Race, %	Age, y	COPD Duration, y	History of Chronic Bronchitis, %	Smoking Status, %	Smoking History, pack-years
		M/F	W/B/O	Mean (SD)	Mean (SD)	Hx/No Hx/Unk	Current/Ex	Mean (SD)
039								
Placebo	216	68/32	97/1/2	65 (8)	7 (7)	63/36/1	43/57	56 (29)
Cilomilast	431	59/41	91/4/4	65 (9)	7 (7)	61/39/0	43/57	60 (33)
156								
Placebo	407	62/38	93/6/1	64 (9)	6 (7)	39/58/4	45/55	62 (34)
Cilomilast	418	56/44	94/6/0	65 (8)	6 (7)	36/61/2	46/54	59 (31)
042								
Placebo	226	80/20	99/0/1	65 (9)	8.5 (9)	77/23/0	36/64	46 (23)
Cilomilast	474	81/19	99/0/1	65 (8)	7.8 (8)	81/19/0	41/59	46 (23)
091								
Placebo	242	86/15	98/0/2	63 (9)	9 (8)	90/10/0	36/64	40 (21)
Cilomilast	469	86/14	98/0/2	63 (9)	11 (9)	90/10/0	36/64	41 (22)
Pooled NA								
Placebo	623	64/36	94/5/1	65 (9)	6 (7)	47/50/3	44/56	60 (33)
Cilomilast	849	58/43	93/5/2	65 (8)	7 (7)	49/50/1	44/56	59 (32)
Pooled EU								
Placebo	468	83/17	99/0/2	64 (9)	9 (9)	84/16/0	36/64	43 (22)
Cilomilast	943	83/17	99/0/1	64 (9)	9 (8)	86/15/0	39/62	44 (23)
All Pooled								
Placebo	1091	72/28	96/3/2	64 (9)	7 (8)	63/36/2	41/59	53 (30)
Cilomilast	1792	71/29	96/3/2	64 (9)	8 (8)	68/31/1	41/59	51 (29)

M/F = Male/Female; W/B/O = White/Black/Other; Hx = History; Unk = Unknown; SD = standard deviation; y = years

Overall with the exception of history of chronic bronchitis and gender, demographic characteristics were similar between groups. The percentages of patients with a history of chronic bronchitis were lowest in NA Study 156. The lower percentage of patients with a history of chronic bronchitis in Study 156 may be due to the lack of a symptom requirement for randomization as compared with the other pivotal studies.

6.3. Spirometry and Bronchodilator Response at Screening

A summary of pulmonary function characteristics for patients in the four pivotal efficacy studies (individually and pooled) at Screening is presented in Table 5.

Table 5 Pulmonary function characteristics and medication use in the pivotal efficacy studies at Screening - ITT Population

Study/ Treatment Group	N	FEV ₁ , L ^a Mean (SD)	% Predicted FEV ₁ ^b Mean (SD)	% Reversibility ^b Mean (SD)	Reversibility (mL) ^b Mean	FEV ₁ /FVC ^a Mean (SD)	% Predicted DLCO Mean (SD)	Concomitant IAC
								Use, % Use/No Use
039								
Placebo	216	1.48 (0.55)	50.5 (12.2)	6.7 (7.6)	86	0.51 (0.11)	60.8 (23.2)	44/56
Cilomilast	431	1.37 (0.49)	49.3 (12.6)	7.7 (7.1)	93	0.51 (0.11)	57.3 (21.4)	39/61
156								
Placebo	407	1.45 (0.53)	50.0 (12.1)	8.6 (6.4)	99	0.53 (0.10)	55.7 (20.3)	31/70
Cilomilast	418	1.40 (0.48)	50.3 (11.6)	8.6 (6.4)	101	0.53 (0.10)	56.9 (21.0)	33/67
042								
Placebo	226	1.45 (0.43)	48.9 (10.6)	4.9 (8.6)	58	0.53 (0.10)	71.2 (28.2)	45/55
Cilomilast	474	1.44 (0.42)	49.1 (11.1)	5.2 (9.0)	63	0.54 (0.10)	70.6 (28.6)	43/57
091								
Placebo	242	1.53 (0.46)	50.5 (11.8)	5.4 (8.8)	69	0.54 (0.10)	70.2 (25.5)	43/57
Cilomilast	469	1.53 (0.48)	50.2 (11.9)	4.9 (8.2)	54	0.55 (0.10)	69.9 (25.3)	37/64
NA Pooled								
Placebo	623	1.46 (0.53)	50.2 (12.1)	7.9 (6.9)	94	0.52 (0.11)	57.5 (21.5)	35/65
Cilomilast	849	1.39 (0.49)	49.8 (12.1)	8.2 (6.8)	97	0.52 (0.11)	57.1 (21.2)	36/64
EU Pooled								
Placebo	468	1.49 (0.45)	49.7 (11.3)	5.1 (8.7)	64	0.54 (0.10)	70.7 (26.8)	44/56
Cilomilast	943	1.48 (0.45)	49.6 (11.5)	5.0 (8.6)	63	0.54 (0.10)	70.2 (27.0)	40/60
All Pooled								
Placebo	1091	1.47 (0.50)	50.0 (11.7)	6.7 (7.8)	81	0.53 (0.10)	63.0 (24.8)	39/61
Cilomilast	1792	1.44 (0.47)	49.7 (11.8)	6.5 (7.9)	79	0.53 (0.11)	63.9 (25.3)	38/62

IAC= inhaled anticholinergic

a. pre-bronchodilator

b. post-bronchodilator

Overall with the exception of DLCO and reversibility status, pulmonary function characteristics were similar between groups. DLCO was higher in the EU studies as compared to the NA studies.

As determined by entry criteria, reversibility to albuterol was low with mean reversibility ranging from 4.9% to 8.6%. Percent reversibility was higher in the NA studies as compared to the two EU studies. The absolute reversibility was higher in the NA studies (placebo 94mL; cilomilast 97mL) as compared to the EU studies (placebo 64mL; cilomilast 63mL) which used a higher dose of albuterol for reversibility testing. These findings suggest that there may have been a bias toward a less reversible COPD population in the EU studies.

6.4. 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.

6.4.1. Primary Efficacy Measures

6.4.1.1. FEV₁

Summaries of the mean change from Baseline in trough FEV₁ over 24 weeks in the pivotal efficacy studies as well as in the pooled NA studies, pooled EU studies, and all pooled studies are presented Table 6.

Table 6 Change from Baseline in trough FEV₁ (L) averaged over 24 weeks in the pivotal efficacy studies – ITT Patients

Study	Treatment Group	N	Baseline	Change from Baseline		Comparison to Placebo	
			Mean	Mean	SEM	Mean Difference	p-value
039	Placebo	207	1.42	-0.03	0.01	-	-
	Cilomilast	378	1.34	0.01	0.01	0.04	0.002
156	Placebo	377	1.38	-0.02	0.01	-	-
	Cilomilast	364	1.36	0.01	0.01	0.02	0.024
042	Placebo	219	1.36	-0.00	0.02	-	-
	Cilomilast	440	1.38	0.03	0.01	0.03	0.044 ^a
091	Placebo	230	1.44	-0.03	0.02	-	-
	Cilomilast	435	1.45	0.00	0.02	0.03	0.055
Pooled NA	Placebo	584	1.42	-0.02	0.01	-	-
	Cilomilast	742	1.37	0.00	0.01	0.03	0.001
Pooled EU	Placebo	449	1.42	-0.02	0.01	-	-
	Cilomilast	875	1.44	0.01	0.01	0.03	0.007
All Pooled	Placebo	1033	1.42	-0.02	0.01	-	-
	Cilomilast	1617	1.41	0.01	0.00	0.03	<0.001

a. Not significantly different from placebo after adjustment for multiple comparisons using the modified Bonferroni procedure of Hochberg.

Across the four studies, the mean improvement from Baseline in FEV₁ averaged over 24 weeks was 20mL to 40mL greater in the cilomilast treatment group relative to placebo. In NA Studies 039 and 156, FEV₁ was maintained over 24 weeks with a statistically significant difference between the cilomilast and placebo treatment groups (40mL, p = 0.002 for Study 039; 20mL, p = 0.024 for Study 156). In EU Studies 042 and 091, when averaged over 24 weeks, the improvements in FEV₁ in the cilomilast treatment group relative to placebo were comparable to those observed in the NA studies (30mL in both studies, p = 0.044 and p = 0.055, respectively). In Study 042, the difference from placebo of 30mL had a p-value <0.05 (p = 0.044); however, after adjusting for multiple comparisons this result was not statistically significant.

The difference between cilomilast and placebo widened over the 24-week treatment period. This suggests that Endpoint (last observation carried forward) may be a more appropriate way to evaluate the response at the end of the study.

Summaries of the mean change from Baseline in trough FEV₁ at Endpoint in the pivotal efficacy studies as well as in the pooled NA studies, pooled EU studies, and all pooled studies are presented Table 7.

Table 7 Mean change from Baseline in trough FEV₁ (L) at Endpoint in the pivotal efficacy studies – ITT Patients

Table	Treatment Group	n	Baseline	Change from Baseline		Comparison to Placebo	
			Mean	Mean	SEM	Mean Difference	p-value
039	Placebo	208	1.43	-0.07	0.02	-	-
	Cilomilast	394	1.33	0.01	0.01	0.08	<0.001
156	Placebo	383	1.39	-0.04	0.01	-	-
	Cilomilast	377	1.35	-0.00	0.01	0.04	0.013
042	Placebo	220	1.35	-0.00	0.02	-	-
	Cilomilast	448	1.37	0.04	0.02	0.04	0.050
091	Placebo	232	1.45	-0.06	0.02	-	-
	Cilomilast	443	1.46	-0.03	0.02	0.03	0.146
Pooled NA	Placebo	591	1.42	-0.05	0.01	-	-
	Cilomilast	771	1.36	0.00	0.01	0.05	<0.001
Pooled EU	Placebo	452	1.42	-0.02	0.01	-	-
	Cilomilast	891	1.44	0.01	0.01	0.03	0.014
All Pooled	Placebo	1043	1.42	-0.04	0.01	-	-
	Cilomilast	1662	1.40	0.01	0.01	0.04	<0.001

In NA Studies 039 and 156, FEV₁ was maintained over 24 weeks with a difference of 80ml (p<0.001) and 40ml (p=0.013) between the cilomilast and placebo treatment groups, respectively. In EU Studies 042 and 091, the differences in FEV₁ at Endpoint between the cilomilast and placebo treatment groups were 40mL (p = 0.050) and 30mL (p = 0.146), respectively.

The mean change from Baseline in FEV₁ by time and treatment group in the NA pivotal studies is presented graphically in Figure 5 and in Figure 6.

Figure 5 Mean change from Baseline in FEV₁ by time and treatment group- Study 039

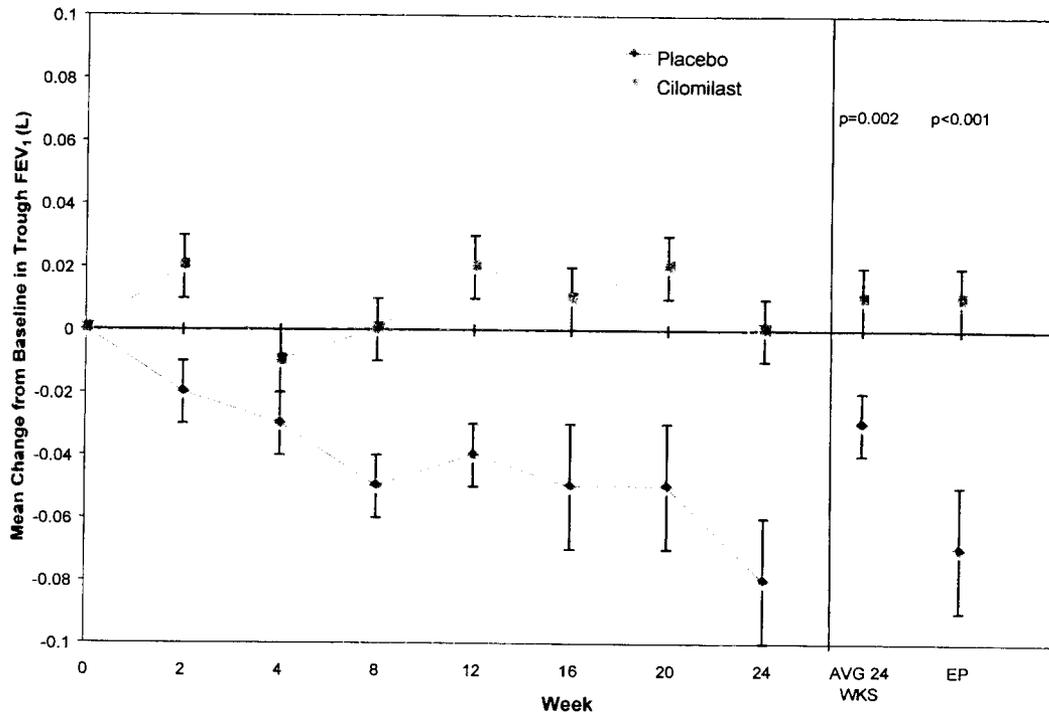
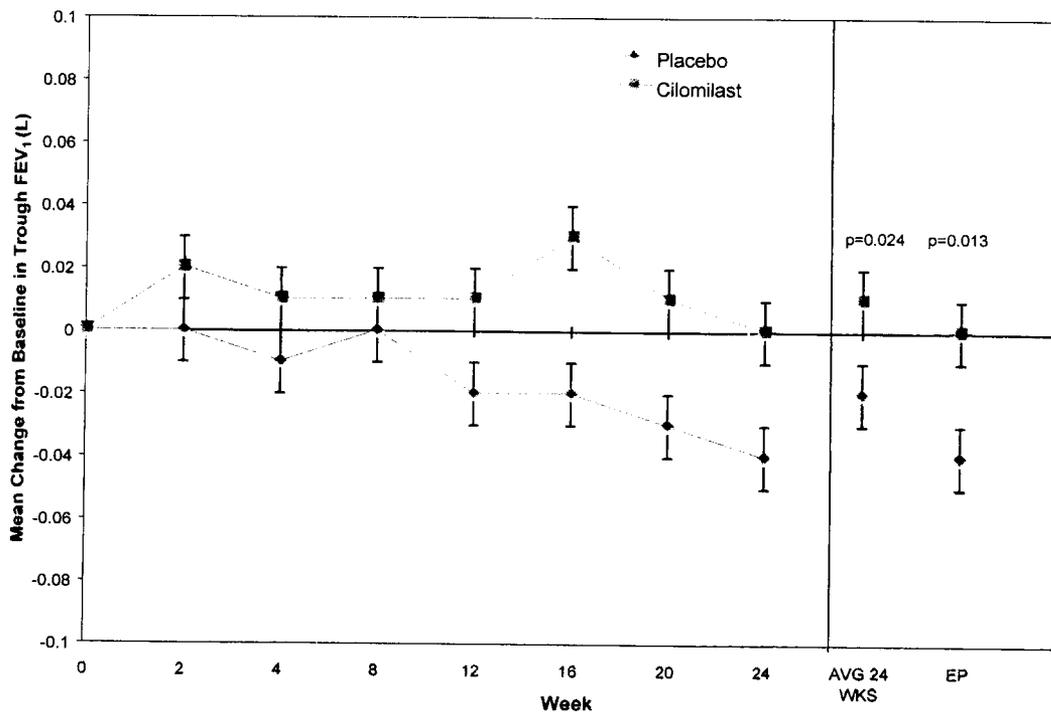


Figure 6 Mean change from Baseline in FEV₁ by time and treatment group- Study 156



As shown in the figures above, in general, the magnitude of the difference in FEV₁ in the cilomilast treatment group relative to placebo increased over time in the NA pivotal studies. Cilomilast-treated patients demonstrated maintenance of FEV₁ relative to Baseline over time while placebo-treated patients generally showed deterioration in FEV₁ relative to Baseline over time.

The mean change from Baseline in FEV₁ by time and treatment group in the EU pivotal studies is presented graphically in Figure 7 and Figure 8.

Figure 7 Mean change from Baseline in FEV₁ by time and treatment group- Study 042

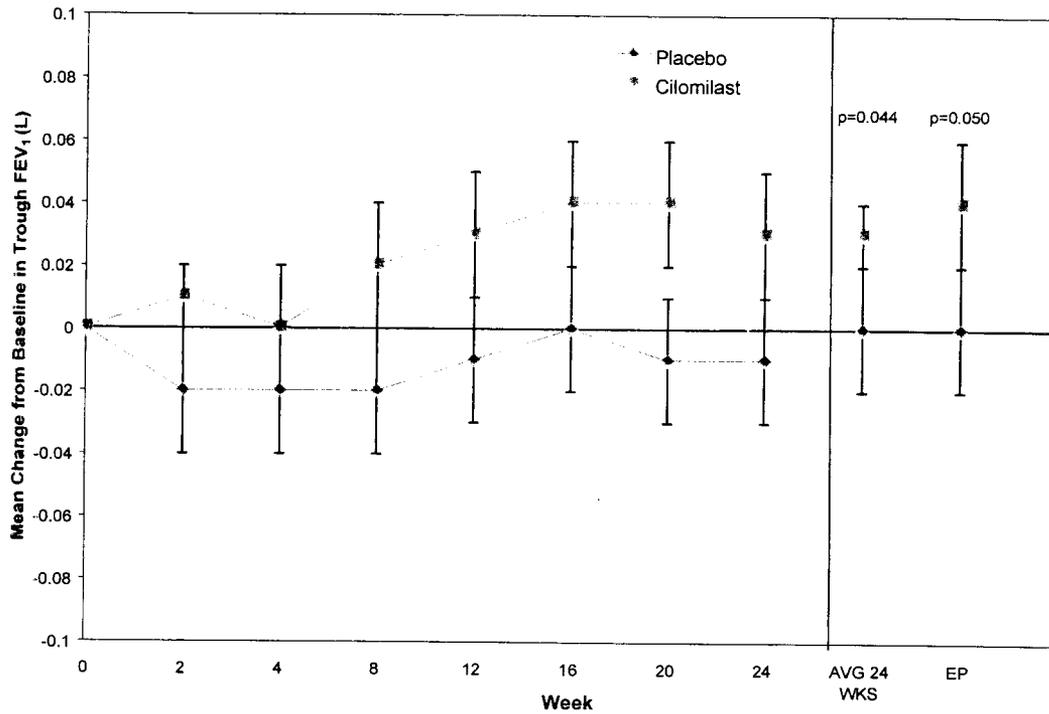
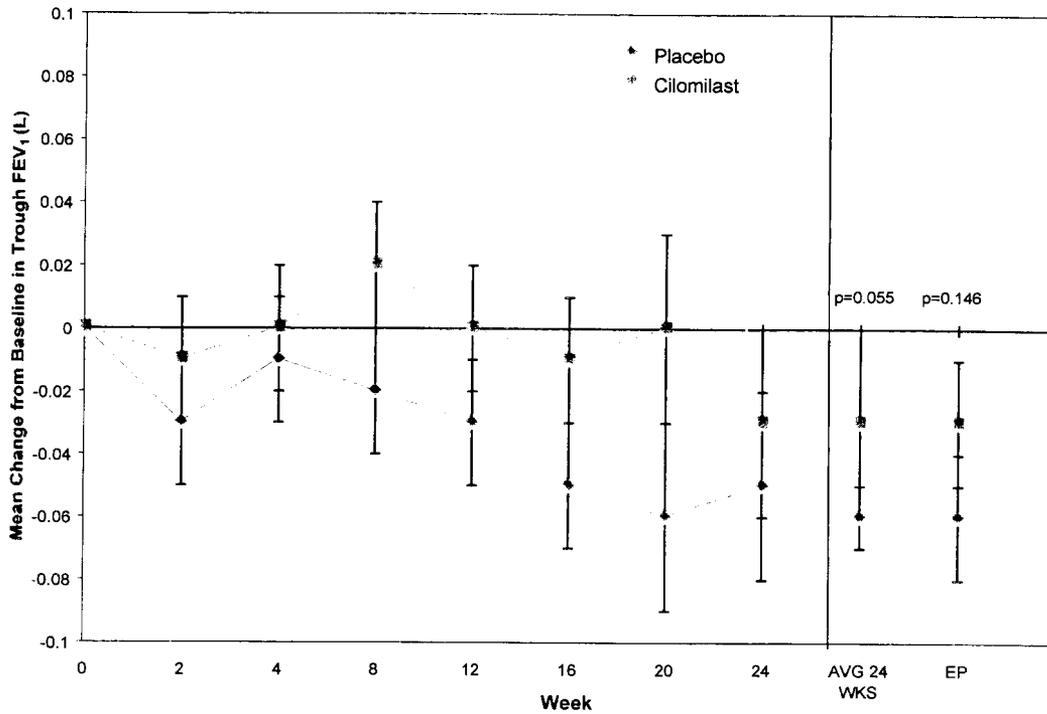


Figure 8 Mean change from Baseline in FEV₁ by time and treatment group- Study 091



As seen in the NA studies, FEV₁ was maintained in the EU studies over 24 weeks in patients receiving cilomilast. The magnitude of effect was similar in the NA and EU studies.

6.4.1.2. SGRQ

The changes in SGRQ total score averaged over 24-weeks in the pivotal efficacy studies are presented in Table 8. The SGRQ was assessed at Baseline, Week 12 and Week 24 (or early withdrawal), therefore, no notable differences were observed between average over 24-weeks and Endpoint.

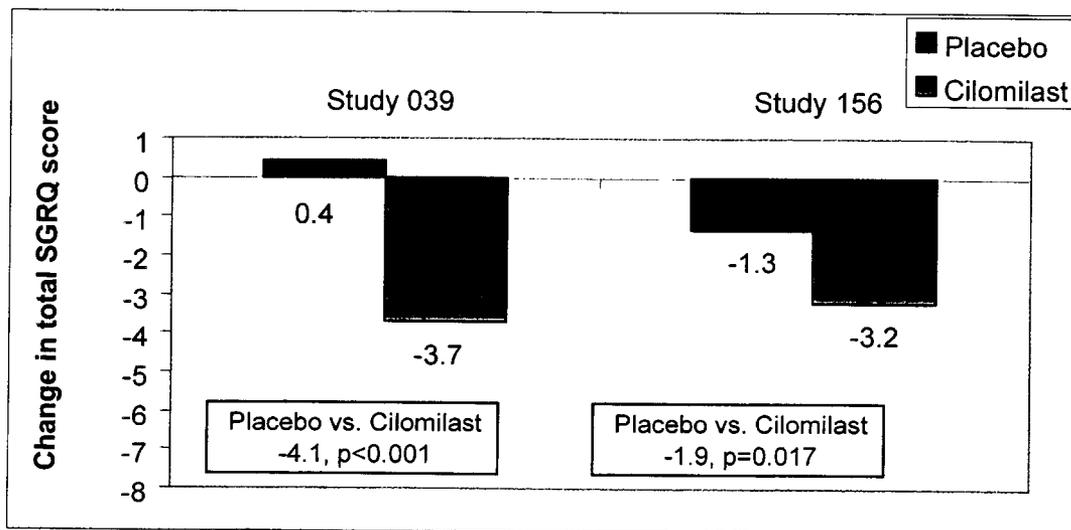
Table 8 Change in the SGRQ total score averaged over 24 weeks in the pivotal efficacy studies – ITT Patients

Study	Treatment Group ^a	n ^b	Baseline	Change from Baseline		Comparison to Placebo	
			Mean	Mean	SEM	Mean Difference	p-value
039	Placebo	181	44.81	0.35	0.84	-	-
	Cilomilast	310	45.07	-3.74	0.67	-4.09	0.000
156	Placebo	337	43.18	-1.32	0.60	-	-
	Cilomilast	304	44.35	-3.22	0.64	-1.90	0.017
042	Placebo	190	45.92	-4.87	0.97	-	-
	Cilomilast	375	43.79	-4.17	0.79	0.70	0.473
091	Placebo	197	42.09	-2.28	1.17	-	-
	Cilomilast	369	42.74	-2.66	1.10	-0.38	0.711
Pooled NA	Placebo	518	43.73	-0.95	0.45	-	-
	Cilomilast	614	44.71	-3.61	0.40	-2.67	0.000
Pooled EU	Placebo	387	43.38	-4.29	0.58	-	-
	Cilomilast	744	42.54	-4.20	0.42	0.10	0.894
Pooled	Placebo	905	43.48	-2.52	0.36	-	-
	Cilomilast	1358	43.59	-3.85	0.29	-1.34	0.004

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. However, in both EU studies, patients receiving placebo also experienced an improvement from Baseline in SGRQ.

Summaries of the mean change from Baseline in the total score of the SGRQ over 24 weeks in NA studies 039 and 156 are presented in Figure 9.

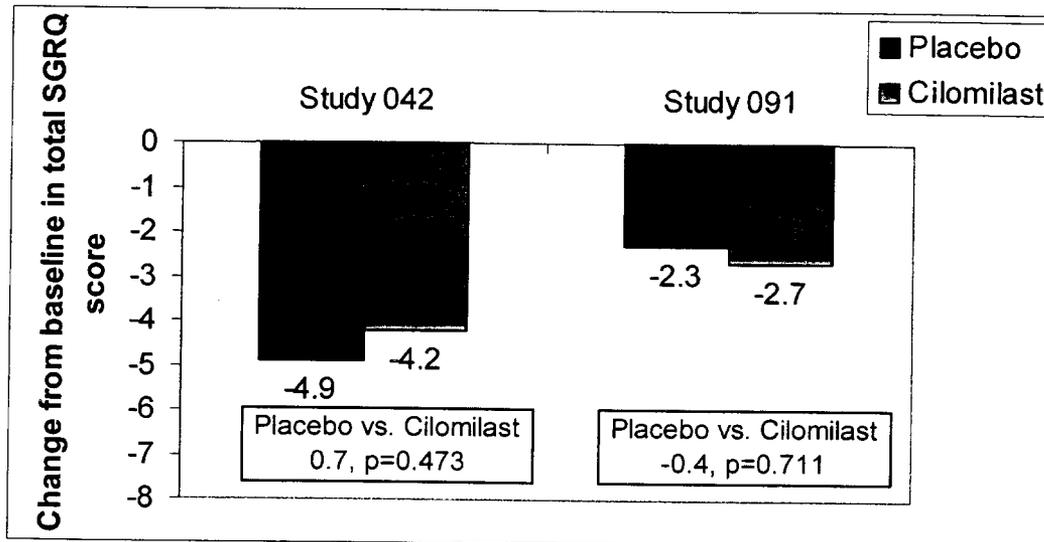
Figure 9 Change from baseline in total SGRQ scores: NA studies



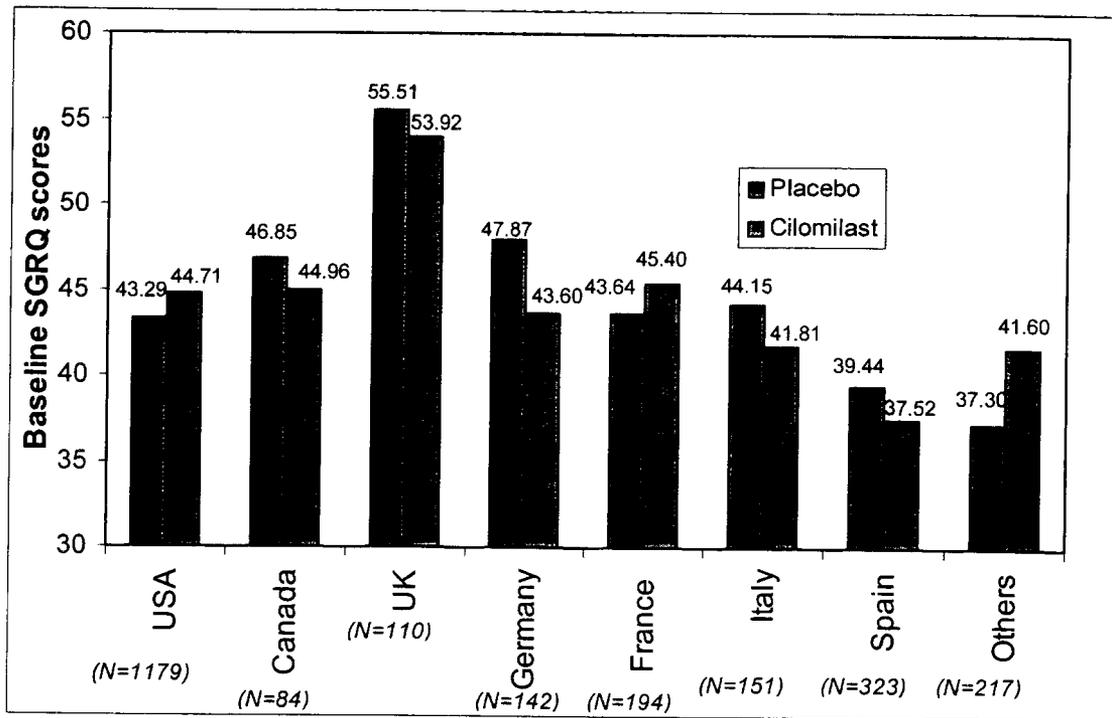
In NA Study 039, patients in the cilomilast group experienced an improvement in QOL (as measured by SGRQ) from baseline of -3.7 points while patients in placebo group experienced a QOL deterioration of 0.4 points. When compared to patients in placebo group, patients in cilomilast group experienced a clinically meaningful improvement of -4.1 points in total SGRQ scores that was statistically significant ($p < 0.001$). Similarly, patients in the cilomilast group in NA study 156 experienced a QOL improvement of -3.2 from baseline. Unlike Study 039, patients in the placebo group of Study 156 experienced a QOL improvement of -1.3 points. The difference between cilomilast and placebo was statistically significant (-1.9, $p = 0.017$), but did not reach the clinically meaningful difference of -4.0. Overall, in the NA studies the cilomilast treated patients demonstrated a consistent improvement from baseline in QOL.

Summaries of the mean change from Baseline in the total score of the SGRQ over 24 weeks in EU studies 091 and 042 are presented in Figure 10.

Figure 10 Change from baseline in total SGRQ scores: EU Studies



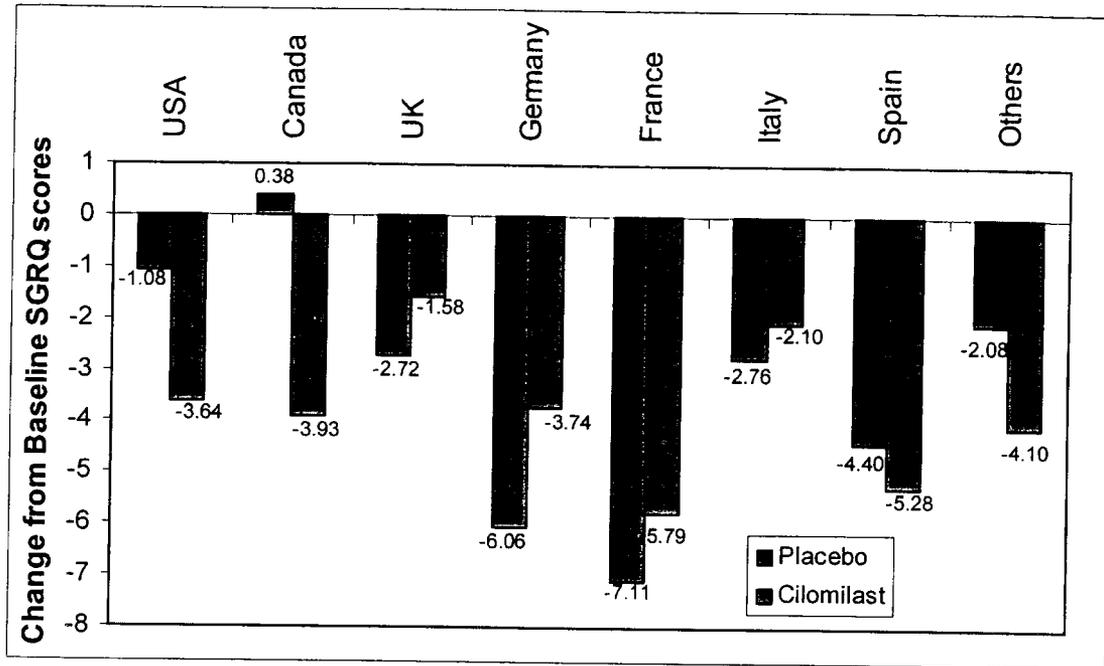
In the two EU studies, Study 042 and Study 091, patients in both the cilomilast and the placebo groups showed improvements in QOL from baseline as measured by the SGRQ. In Study 042, patients in the cilomilast group improved by -4.2 points while patients in the placebo group improved by -4.9 points (see Figure 10). Similarly, in Study 091, patients in cilomilast group improved by -2.7 points while patients in the placebo group improved by -2.3 points (see Figure 10). The effect of cilomilast versus placebo on patient's QOL in the EU studies 042 and 091 needs to be interpreted in context to the large baseline differences between countries (see Figure 11).

Figure 11 SGRQ scores at Baseline by Country

Substantial differences in Baseline total SGRQ score were observed across the EU countries ranging from 37.52 in Spain to 55.51 in United Kingdom. In contrast, the baseline total SGRQ score in the two NA countries, US and Canada ranged from 43.29 in US to 46.85 in Canada.

An additional confounder in the EU studies was the inconsistency in SGRQ response observed across different EU countries in both cilomilast and placebo groups (see Figure 12). A consistent improvement in QOL was seen across the NA countries and in the NA studies, a statistically significant improvement in QOL was observed for cilomilast treated patients as compared to placebo.

Figure 12 Change from Baseline in Total SGRQ scores by Country



6.4.2. Secondary Efficacy Measures

6.4.2.1. COPD Exacerbations

All levels of COPD exacerbations were evaluated in the pivotal studies (level 1, level 2 and level 3). However, level 2 or level 3 exacerbations are the most clinically relevant as they required physician intervention and are presented below.

A summary of exacerbation-free survival rates and the relative risk of experiencing at least one level 2 or 3 COPD exacerbation in the cilomilast treatment group versus placebo in the pivotal studies as well as in the pooled NA studies, pooled EU studies, and all pooled studies is presented in Table 9.

Table 9 Exacerbation-free survival and relative risk of experiencing at least one level 2 or 3 COPD exacerbation in the pivotal efficacy studies – ITT Patients

Study	Treatment Group	Number at Risk on Day 1	% Exacerbation-free at 24 weeks	Relative Risk Cilomilast vs. Placebo		
				Relative Risk	(95% CI)	p-value
039	Placebo	216	69.7	-	-	-
	Cilomilast	431	81.7	0.60	(0.42, 0.85)	0.0037
156	Placebo	407	79.5	-	-	-
	Cilomilast	418	75.6	1.22	(0.89, 1.68)	0.2113
042	Placebo	226	71.0	-	-	-
	Cilomilast	474	70.9	0.96	(0.71, 1.30)	0.7912
091	Placebo	242	64.3	-	-	-
	Cilomilast	469	75.5	0.68	(0.50, 0.91)	0.0094
Pooled NA	Placebo	623	76.1	-	-	-
	Cilomilast	849	78.7	0.90	(0.71, 1.14)	0.3766
Pooled EU	Placebo	468	67.5	-	-	-
	Cilomilast	943	73.2	0.81	(0.65, 1.00)	0.0462
All Pooled	Placebo	1091	72.3	-	-	-
	Cilomilast	1792	75.7	0.88	(0.75, 1.03)	0.1008

In studies 039 and 091, the relative risk of experiencing at least one level 2 or 3 COPD exacerbation was reduced by 40% and 32% in cilomilast patients compared to placebo, respectively. In Study 042 the relative risk of experiencing a level 2 or 3 exacerbation was comparable between cilomilast and placebo treated patients. In Study 156, although not statistically significant, the relative risk of experiencing a level 2 and level 3 exacerbation was in favor of placebo. Study 156 was the only study that did not require patients to be symptomatic at entry. There were fewer patients with one or more exacerbations in the placebo group of Study 156 (20.5%) as compared to the other pivotal studies (range 29.0%-35.7%) which may explain why no difference in COPD exacerbations was observed between treatment groups.

The results are shown graphically in Figure 13, Figure 14, Figure 15 and Figure 16.

Figure 13 Percent of Patients Exacerbation Free (Level 2/3): Study 039

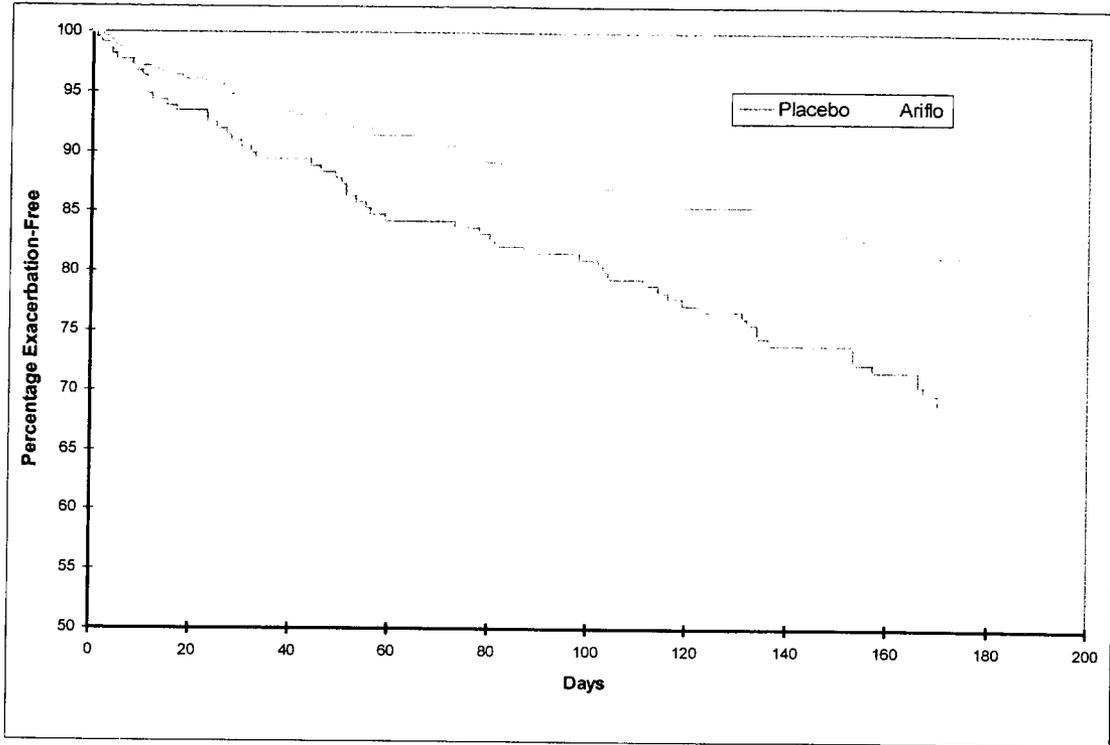


Figure 14 Percent of Patients Exacerbation Free (Level 2/3): Study 156

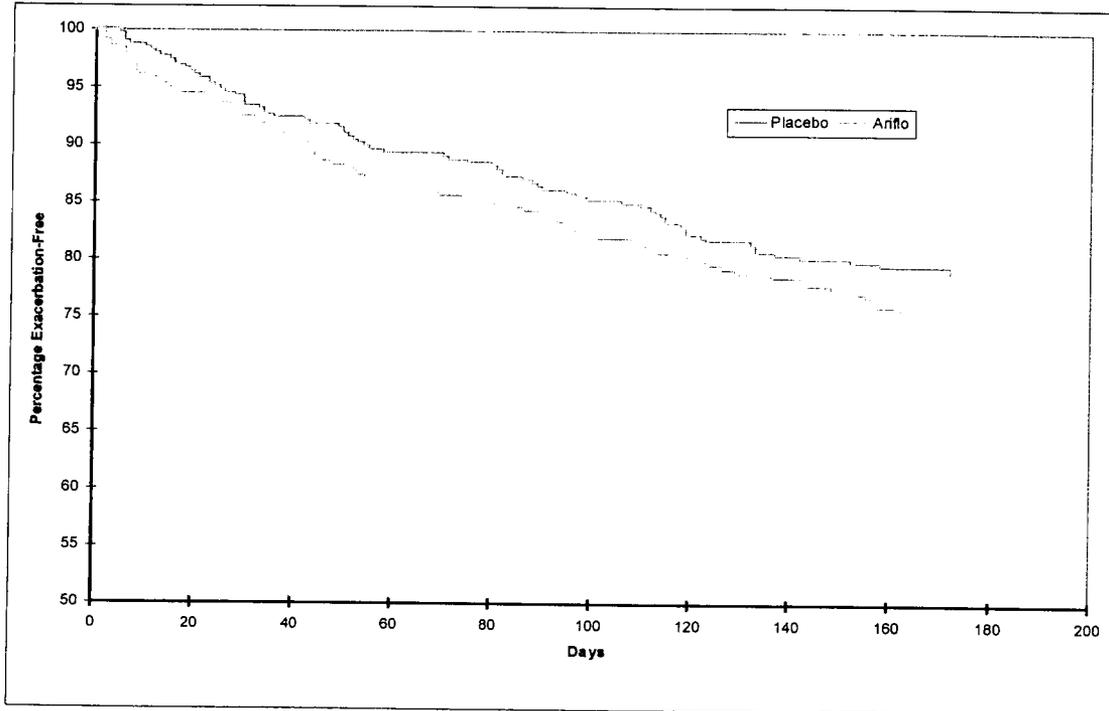


Figure 15 Percent of Patients Exacerbation Free (Level 2/3): Study 091

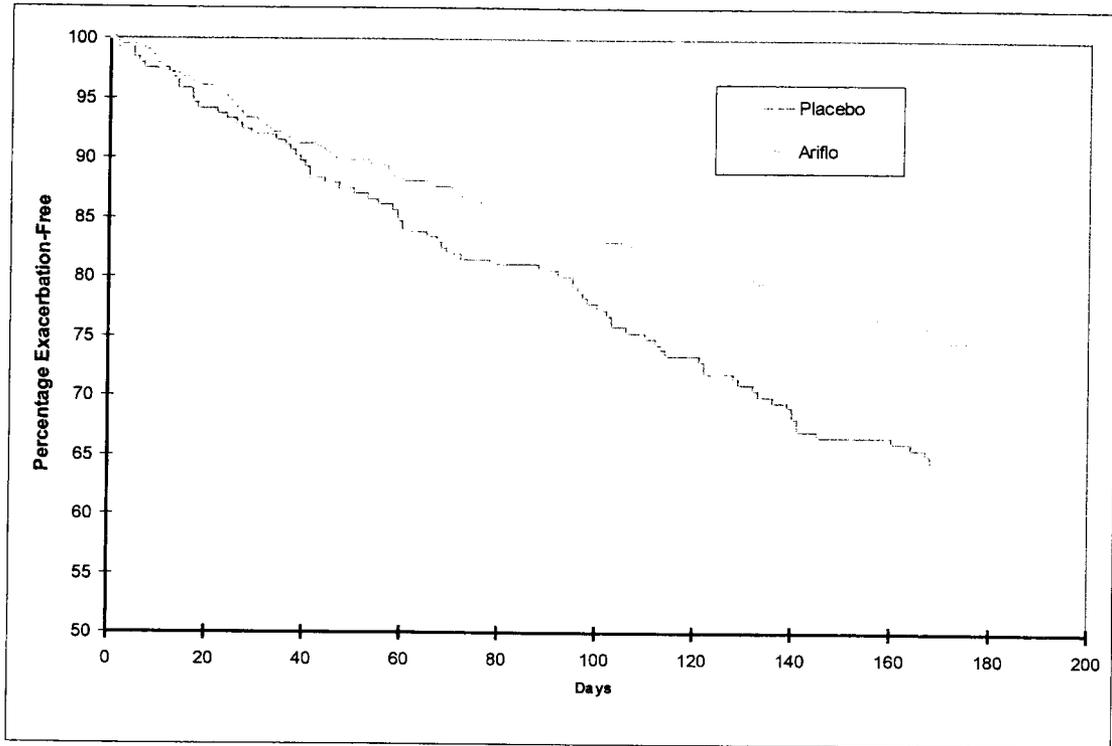
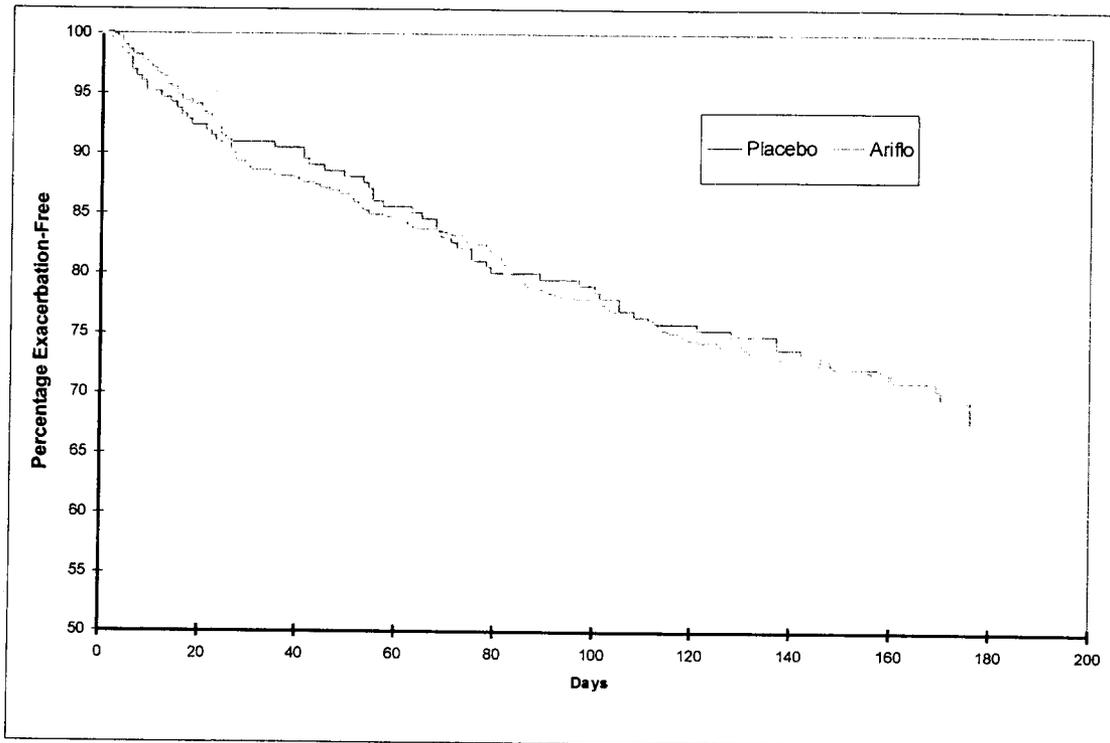
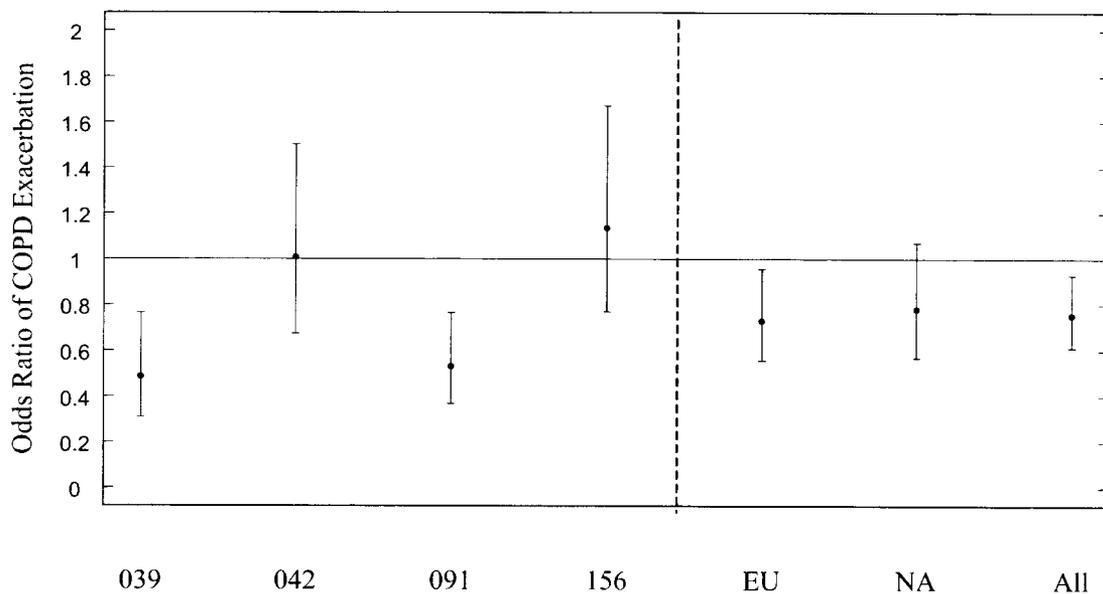


Figure 16 Percent of Patients Exacerbation Free (Level 2/3): Study 042



The primary analysis of time to first COPD exacerbation does not take frequency and duration of COPD exacerbations into account. In order to include frequency and duration of COPD exacerbations, a post-hoc analysis was performed to compare the percentage of patients experiencing an exacerbation on any given day throughout the pivotal studies. Using the pooled data from all pivotal trials, cilomilast reduced the percent of patients experiencing a level 2/3 COPD exacerbation on any given day by 24% as compared with placebo (odds ratio = 0.754, relative risk = 0.760, p-value = 0.0078) See Figure 17.

Figure 17 Odds Ratio (95% CI) of a Level 2 or 3 COPD Exacerbation on Any Given Day in the Pivotal Studies



Statistical Methods: repeated measures logistic regression using generalized estimating equations with covariates of gender, age, baseline FEV₁ percent predicted as a marker for disease severity, protocol and treatment were used.

In the pooled population, the percentage of patients experiencing a COPD exacerbation on any given day was significantly reduced as compared to placebo even when data from studies 042 and 156 were included in the analysis. This supports the overall benefit of cilomilast on COPD exacerbations.

6.4.2.2. FVC

Across the four studies, the mean improvement in FVC was 50mL to 110mL greater in the cilomilast treatment group relative to placebo. In NA Studies 039 and 156, there was an improvement in FVC in the cilomilast treatment group relative to placebo at Endpoint (110mL, p = 0.001 for Study 039; 60mL, p = 0.022 for Study 156). In EU Studies 042 and 091, the differences in FVC at Endpoint between cilomilast and placebo were 50mL (p = 0.129) and 60mL (p = 0.073), respectively.

There were improvements in FVC at Endpoint in the cilomilast-treated patients of 80mL (p<0.001), 50mL (p = 0.018), and 70mL (p<0.001) relative to placebo in the pooled NA, pooled EU, and all pooled pivotal studies, respectively.

6.4.2.3. Summary Symptom Score, Exercise Tolerance and Post Exercise Breathlessness

There were no differences from placebo in summary symptom score and six minute walk test in cilomilast-treated patients in the pivotal efficacy studies.

Across all four studies, there were small improvements in post-exercise breathlessness scores at Endpoint in the cilomilast treatment group relative to placebo ranging from -0.18 to -0.32 points.

6.4.3. Efficacy in Population Subgroups

Analyses in the sub-populations were performed in the pooled NA, pooled EU, and all pooled pivotal studies, and were restricted to the following efficacy endpoints: FEV₁, total score of the SGRQ, and COPD exacerbations. The sub-populations of age, sex, race, weight, body mass index (BMI), % predicted FEV₁ (disease severity), % predicted carbon monoxide diffusing capacity (DLCO), history of chronic bronchitis, smoking status, pack year smoking history, prior ICS use and concomitant inhaled anticholinergic use were evaluated and only clinically relevant differences are presented below.

In the NA studies subgroup analyses suggested that cilomilast treated patients with more severe disease experienced greater improvements in QOL. Patients with severe COPD (FEV₁ <35% predicted) had greater improvements in total score of the SGRQ than mild or moderate disease following treatment with cilomilast in the pooled NA studies (difference from placebo; mild:-2.35, moderate: -2.21, severe: -5.06). The presence of a history of chronic bronchitis was associated with a greater improvement in total score of the SGRQ (difference from placebo; history: -3.90, no history: -1.67) in the NA studies. In the NA studies, longer pack year smoking history (i.e., ≥42 pack years) was associated with greater improvements in total score of the SGRQ (difference from placebo: <42 pack-years: -0.53; ≥42 pack-years: -3.66).

In all pivotal studies the presence of a history of chronic bronchitis correlated with a greater reduction in the risk of a level 2 or 3 COPD exacerbation following treatment with cilomilast (relative risk cilomilast vs. placebo; history: 0.79, no history: 1.09).

6.5. Safety Results

- The safety of cilomilast was extensively evaluated throughout the clinical development program with nearly 3,000 patient years exposure to cilomilast.
- Extensive cardiac monitoring throughout the clinical development program (> 70,000 ECGs, >1,000 holters) 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 the majority were mild to moderate in intensity.
- While a number of patients may experience gastrointestinal discomfort 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.
- The incidence of SAEs reported by placebo and cilomilast treated patients was low and similar, except that SAEs attributed to chronic lung disease occurred more frequently in the placebo group.
- Laboratory values, vital signs and other safety monitoring did not reveal any other concerns.

6.5.1. Extent of exposure

The extent of exposure to study medication in the Phase III pivotal studies (Studies 039, 042, 091, and 156) is summarized in Table 10.

Table 10 Duration of exposure in Phase III pivotal studies

Exposure ^a (days)	Treatment Group	
	Placebo (N = 1091) n (%)	Cilomilast 15mg BID (N = 1792) n (%)
1	1091 (100.0)	1792 (100.0)
> 1	1084 (99.4)	1775 (99.1)
≥ 14	1040 (95.3)	1631 (91.0)
≥ 28	1002 (91.8)	1554 (86.7)
≥ 60	945 (86.6)	1437 (80.2)
≥ 90	908 (83.2)	1381 (77.1)
≥ 180	254 (23.3)	418 (23.3)
Mean (SD)	148.4 (54.6)	139.2 (63.3)
Median	170	169
Range	1 - 220	1 - 231

a Calculation of exposure: (Date of last dose of study medication – Date of first dose of study medication) + 1.

Among cilomilast-treated patients with COPD, there were 1631 patients (91.0%) with ≥ 14 days of cilomilast exposure, 1437 patients (80.2%) with ≥ 60 days of exposure, and 418 patients (23.3%) with ≥ 180 days of exposure. The overall mean duration of exposure to cilomilast in the Phase III pivotal studies was 139.2 days. The exposure for patients who received placebo (mean, 148.4 days) in these studies was similar to that for patients who received cilomilast.

6.5.2. Adverse Events

The numbers (%) of patients in the pivotal Phase III studies with the most frequently reported on-therapy AEs, occurring in $\geq 5\%$ of patients in either treatment group (cilomilast or placebo), are summarized in Table 11 below.

Table 11 Number (%) of patients with the most frequently reported adverse events (greater than or equal to 5.0% patients in either treatment group) – Phase III pivotal studies

Adverse Event (Preferred Term)	Treatment Group	
	Placebo (N = 1091) n (%)	Cilomilast 15mg BID (N = 1792) n (%)
Total	839 (76.9)	1404 (78.3)
Chronic Obstructive Airways Disease	395 (36.2)	545 (30.4)
Nausea	55 (5.0)	281 (15.7)
Diarrhea	86 (7.9)	258 (14.4)
Abdominal Pain	77 (7.1)	210 (11.7)
Upper Respiratory Tract Infection	112 (10.3)	157 (8.8)
Headache	76 (7.0)	147 (8.2)
Dyspepsia	27 (2.5)	122 (6.8)
Vomiting	18 (1.6)	110 (6.1)
Injury	55 (5.0)	96 (5.4)
Coughing	58 (5.3)	63 (3.5)

A total of 78.3% of patients (1404 of 1792) treated with cilomilast and 76.9% of patients (839 of 1091) treated with placebo reported one or more on-therapy AEs in the Phase III pivotal studies. Gastrointestinal intolerance occurred more frequently in patients treated with cilomilast while, placebo patients experienced more respiratory adverse events.

Among the patients who reported AEs (one or more), the majority of patients treated with either cilomilast 15mg BID or placebo reported AEs with a maximum intensity of mild or moderate: 83.9% (1178 of 1404 patients) for cilomilast and 84.4% (708 of 839 patients) for placebo.

6.5.2.1. Adverse events leading to withdrawal

The numbers (%) of patients with adverse events leading to withdrawal of $\geq 0.5\%$ in any treatment group are summarized in Table 12.

Table 12 Adverse events leading to withdrawal of greater than or equal to 0.5% in any treatment group– Phase III pivotal studies

Adverse Event (Preferred Term)	Treatment Group	
	Placebo (N = 1091) n (%)	Cilomilast 15mg BID (N = 1792) n (%)
Total	128 (11.7)	314 (17.5)
Nausea	5 (0.5)	92 (5.1)
Abdominal Pain	8 (0.7)	77 (4.3)
Diarrhea	7 (0.6)	65 (3.6)
Chronic Obstructive Airways Disease	42 (3.8)	40 (2.2)
Vomiting	3 (0.3)	25 (1.4)
Dyspepsia	1 (0.1)	18 (1.0)
Dizziness	2 (0.2)	16 (0.9)
Headache	1 (0.1)	16 (0.9)
Flatulence	1 (0.1)	9 (0.5)

A total of 314 cilomilast-treated patients (17.5%) and 128 placebo-treated patients (11.7%) were withdrawn from the Phase III pivotal studies due to an on-therapy AE. Gastrointestinal intolerance led to withdrawal more frequently in patients treated with cilomilast while, patients treated with placebo withdrew more frequently due to chronic obstructive airways disease.

6.5.2.2. Serious Adverse Events

The numbers (%) of patients with the most commonly reported SAEs (SAEs reported in two or more patients) are shown in Table 13.

Table 13 Number (%) of patients with the most frequently reported SAEs (greater than or equal to 2 patients in any treatment group) – Phase III pivotal studies

Adverse Event (Preferred Term)	Treatment Group	
	Placebo (N = 1091)	Cilomilast 15mg BID (N = 1792)
	n (%)	n (%)
Total	96 (8.8)	104 (5.8)
Chronic Obstructive Airways Disease	22 (2.0)	21 (1.2)
Cerebrovascular Disorder	1 (0.1)	5 (0.3)
Myocardial Infarction	6 (0.5)	5 (0.3)
Abdominal Pain	0 (0.0)	4 (0.2)
Aneurysm	2 (0.2)	4 (0.2)
Injury	3 (0.3)	4 (0.2)
Basal Cell Carcinoma	4 (0.4)	3 (0.2)
Bladder Carcinoma	2 (0.2)	3 (0.2)
Carcinoma	1 (0.1)	3 (0.2)
Pulmonary Carcinoma	2 (0.2)	3 (0.2)
Urinary Retention	0 (0.0)	3 (0.2)
Vascular Disorder	1 (0.1)	3 (0.2)
Alcohol Intolerance	0 (0.0)	2 (0.1)
Cholecystitis	1 (0.1)	2 (0.1)
Coronary Artery Disorder	0 (0.0)	2 (0.1)
Dyspnea	1 (0.1)	2 (0.1)
Neoplasm Nos	3 (0.3)	2 (0.1)
Pneumonia	5 (0.5)	2 (0.1)
Pneumothorax	2 (0.2)	2 (0.1)
Pulmonary Edema	1 (0.1)	2 (0.1)
Respiratory Disorder	0 (0.0)	2 (0.1)
Syncope	1 (0.1)	2 (0.1)
Angina Pectoris	4 (0.4)	1 (0.1)
Cardiac Failure	7 (0.6)	1 (0.1)
Chest Pain	4 (0.4)	1 (0.1)
Atrial Fibrillation	3 (0.3)	1 (0.1)
Thrombosis Coronary	2 (0.2)	1 (0.1)
Colitis	2 (0.2)	0 (0.0)
Intestinal Obstruction	2 (0.2)	0 (0.0)

In the Phase III pivotal studies, SAEs were reported in 96 placebo-treated patients (8.8%) and 104 cilomilast-treated patients (5.8%). The patterns of SAEs reported by placebo- and cilomilast-treated patients were similar, except that complications of chronic lung disease (COAD, pneumonia, and cardiac failure) occurred more frequently in the placebo group.

SAEs 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. SAEs of gastrointestinal bleeding occurred in 4 placebo and 2 cilomilast treated patients (placebo: GI hemorrhage, hemorrhage rectum, gastric ulcer hemorrhagic, hemorrhoids; cilomilast: hematemesis, hemorrhoids). Thus, GI intolerance observed did not lead to serious GI sequelae.

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 treated with placebo during the Phase III pivotal studies. Brief descriptions of the events are provided below.

Patient 156.495.16160, in study 156 (after 10 days of treatment with placebo), was hospitalized for abdominal pain and hypotension and developed bowel ischemia resulting in withdrawal from the study.

Patient 156.402.19351, in study 156 (after 121 days of treatment with placebo), experienced an upset stomach and severe diarrhea like cramping. A CT scan was reported to show "a slowing of blood flow to the intestines due to a plaque". The patient was later admitted to the hospital and underwent an aortic angiogram, which showed an occlusion of the celiac and superior mesenteric arteries. The final diagnosis was mesenteric ischemia.

6.5.2.3. Deaths

Fatal AEs reported during the Phase III pivotal studies are listed in Table 14.

Table 14 Patient deaths – Phase III pivotal studies

Age (years)	Sex	Days on Randomized Medication/ Days Post Study	Cause of Death	Fatal SAE ^a	Relationship
ON-THERAPY - Placebo					
75	F	157/0	Myocardial infarction	Cardiac failure Myocardial infarction Thrombosis coronary	Not related Not related Not related
ON THERAPY - Cilomilast 15mg BID					
73	M	151/0	Possible MI as per coroner	Myocardial infarction	Not related
71	F	72/1	Myocardial infarction and congestive heart failure	Myocardial infarction	Unlikely
67	M	148/0	Aneurysm (abdomen)	Aneurysm Constipation	Not related Unlikely
72	M	174/1	Cerebral aneurysmal rupture	Aneurysm	Unlikely
POST-THERAPY – Placebo					
75	M	137/5	CHF	Cardiac failure	Unlikely
77	M	9/2	Ruptured aortic aneurysm	Aneurysm	Unlikely
58	M	193/64	Heart Failure	Cardiac Failure	Unlikely
57	F	27/5	Natural causes	Myocardial infarction	Unlikely
POST-THERAPY - Cilomilast 15mg BID					
63	M	172/23	Myocardial infarction (ischemic cardiomyopathy)	Myocardial ischemia	Unlikely
79	M	26/19	COPD exacerbation, respiratory insufficiency	Chronic obstructive airways disease Respiratory insufficiency	Not related Not related
80	M	128/7	Cardiorespiratory uncompensation	Cardiac failure	Not related

a. Preferred term

Twelve patients died during double blind treatment period of the phase III pivotal studies or during the post-therapy follow-up period. Five were treated with placebo and seven with cilomilast. All of the on-therapy fatal AEs were due to cardiovascular causes and not unexpected in the population studied. The investigators judged all the fatal AEs not related or unlikely related to study medication.

6.5.2.4. Additional Assessments of Gastrointestinal Safety

GI adverse events are a known class effect of non-selective and 1st generation PDE4 inhibitors. Non-clinical data with cilomilast showed medial necrosis of the mesenteric arteries in the rat. This is a class finding in rats with PDE4 inhibitors, including caffeine, which is thought to be related to a relaxing effect on rat mesenteric arterial muscle. This finding was not seen in non-rodents and was not associated with any pathologic consequences in the rat GI tract.

Based on the class effects of PDE inhibitors and non-clinical findings in rodents, the FDA requested that extensive gastrointestinal monitoring be performed in the clinical development program.

To 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 pivotal studies.

At visit 1, patients were issued a fecal occult blood test kit and were instructed to contact the Investigator as soon as possible if they experienced gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, vomiting) which cause the patient concern or interfere with usual activity (including eating and sleeping) at any time during the study. The patient was required to report these adverse events within 24 hours of occurrence. Therefore, the reporting of GIAEs was enhanced as patients were instructed prior to the start of the study to closely monitor GI events.

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, in Study 156, 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 of Concern

The numbers (%) of patients with the most frequently reported on-therapy GIAEs of concern in the Phase III pivotal studies, as defined by occurring in $\geq 0.5\%$ of patients in either treatment group (cilomilast or placebo), are summarized in Table 15 below.

Table 15 **Number (%) of patients with most frequently reported gastrointestinal adverse events of concern (greater than or equal to 0.5% of patients in either treatment group) – Phase III pivotal studies**

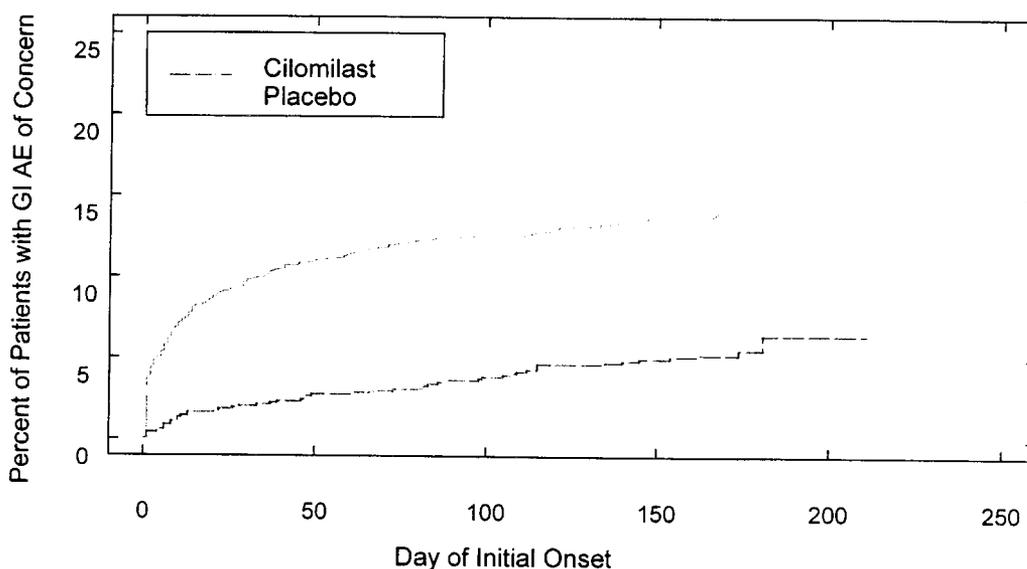
Adverse Event (Preferred Term)	Treatment Group	
	Placebo (N = 1091) n (%)	Cilomilast 15mg BID (N = 1792) n (%)
Total	52 (4.8)	231 (12.9)
Abdominal Pain	28 (2.6)	106 (5.9)
Diarrhea	23 (2.1)	94 (5.2)
Nausea	7 (0.6)	77 (4.3)
Vomiting	6 (0.5)	52 (2.9)
Dyspepsia	3 (0.3)	28 (1.6)
Melena	9 (0.8)	17 (0.9)
Flatulence	2 (0.2)	16 (0.9)

A higher percentage of GIAEs of concern were reported in patients treated with cilomilast (12.9% of 1792 patients) in the Phase III pivotal studies than in patients treated with placebo (4.8% of 1091 patients).

In the majority of patients treated with either cilomilast or placebo who reported GIAEs of concern, the maximum intensity of the AE was mild or moderate (80.8% of 231 patients for cilomilast; and 78.8% of 52 patients for placebo).

For the majority of patients treated with cilomilast the time of onset of the event was during the first 4 weeks of double-blind treatment. 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 (see Figure 18).

Figure 18 Cumulative Incidence of GIAEs of Concern by Time of Initial Onset



Fecal Occult Blood Results in Patients with GIAEs of Concern

Of these 205 cilomilast treated patients who had FOB tests performed, only 7.8% (16 patients) had a positive test result. Similarly, of the 42 placebo-treated patients who had FOB tests performed, 11.9% (5 patients) tested positive for fecal occult blood.

Of the 133 cilomilast treated patients who had FOB tests performed within 14 days of the event, only 9.8% (13 patients) had a positive test result. Of the 28 placebo-treated patients who had FOB tests performed within 14 days of the event, 17.9% (5 patients) tested positive for fecal occult blood.

Orthostatic Vital Signs from Patients with GIAEs of Concern

A total of 139 patients treated with cilomilast and 39 patients treated with placebo who reported one or more GIAEs of concern underwent orthostatic vital sign evaluation. For each of the three vital signs assessments, the overwhelming percentages of both

cilomilast- and placebo-treated patients exhibited normal values: systolic blood pressure, 88.5% for cilomilast, and 94.9% for placebo; diastolic blood pressure, 95.7% for cilomilast, and 100.0% for placebo; and heart rate, 97.0% for cilomilast, and 94.9% for placebo.

Overview of Colonoscopy Results

Study 156 was amended to include a requirement for a colonoscopy to be performed on patients who reported GIAEs of concern and a positive fecal occult blood test or melena during the double-blind treatment period. A total of 12 patients had colonoscopies performed due to events that occurred during study 156. Seven patients (3 placebo-treated and 4 cilomilast-treated patients) who experienced one or more GIAEs of concern had a colonoscopy performed. Five additional patients, three cilomilast-treated and 2 placebo-treated patients with AEs of the gastrointestinal system or gastrointestinal symptoms that were not considered GIAEs of concern also had colonoscopies 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 safety concerns related to cilomilast.

Routine Fecal Occult Blood Measurements (including FOBs performed for GIAEs of concern)

In the Phase III pivotal studies, routine FOBs were conducted at Screening and at the end of the treatment period or early withdrawal. In addition, FOBs were conducted at any time during the study for GIAEs of concern.

Overall, a total of 788 (72.2%) of 1091 patients who received placebo and 1256 (70.1%) of 1792 patients who received cilomilast had FOB tests during double-blind treatment of the Phase III pivotal studies. Of these patients, 777 placebo-treated and 1246 cilomilast-treated patients had negative FOB results at baseline. A total of 12 (1.5%) of 777 patients who received placebo and 27 (2.2%) of 1246 patients who received cilomilast and who had negative FOB results at baseline, shifted to positive during double-blind treatment.

6.5.3. Clinical Laboratory Tests

In each of the phase III pivotal studies, extensive laboratory evaluations, including hematology (hemoglobin, hematocrit, white blood cell count, total or absolute neutrophil count, total or absolute eosinophil count, and platelet count) and serum chemistries (AST, ALT, GGT, total bilirubin, alkaline phosphatase, creatinine, blood urea nitrogen, sodium, potassium, random glucose, and uric acid), were performed at baseline and at all study visits. The laboratory values were summarized by mean values and by sponsor defined threshold values (transitions from normal to low, low concern, high and high concern) (See Appendices).

6.5.3.1. Mean Changes in Clinical Laboratory Values

Hematology

Small mean decreases in hemoglobin and hematocrit were observed for patients treated with cilomilast (mean changes of -0.26g/L and -0.06%, respectively), compared with small mean increases for patients treated with placebo (mean changes of 0.23g/L and 0.08%). Mean changes in white blood cell, absolute neutrophil count, and absolute eosinophil count were also small, and similar for placebo- and cilomilast-treated patients. Small increases in platelet counts were observed for both placebo-treated and cilomilast-treated groups.

Clinical Chemistry

Mean changes for liver enzymes (AST, ALT, GGT) and alkaline phosphatase were less than one international unit in size for both placebo- and cilomilast-treated groups, except for a GGT change of 2.02 IU/L seen in placebo-treated patients. The mean changes in total bilirubin were also small, and similar for the two treatment groups.

Cilomilast-treated patients had a small decrease in serum creatinine (mean change of -0.46 μ mol/L) compared with a mean increase among placebo-treated patients (3.22 μ mol/L). Mean changes in blood urea nitrogen were small and similar between treatment groups.

Mean changes in random glucose values were 0.00 among cilomilast-treated patients and 0.11mmol/L among placebo-treated patients. Mean changes in uric acid values were -1.05 μ mol/L among cilomilast-treated patients and 6.86 μ mol/L among placebo-treated patients. Mean changes for serum sodium and serum potassium were small and similar for the two treatment groups.

6.5.3.2. Transitions from Baseline in Laboratory Values Concern values

Hematology

For hemoglobin, hematocrit, white blood cell, absolute neutrophil count, absolute eosinophil count, and platelet count, the numbers of patients transitioning from baseline normal values to low or high values, or to low or high values of concern were similar among patients treated with placebo and patients treated with cilomilast. For each of the selected hematologic parameters, no more than 1% of patients in either treatment group transitioned to low or high values of concern.

Clinical Chemistry

For the liver enzymes (AST, ALT, GGT), total bilirubin, and alkaline phosphatase, as well as for creatinine and blood urea nitrogen, the numbers of patients transitioning from baseline normal values to high values, or to high values of concern were similar among patients treated with placebo and patients treated with cilomilast. For each of these parameters reflecting liver or kidney function, less than 1% of patients in either treatment group transitioned to high values of concern.

For sodium, potassium, random serum glucose, and uric acid, similar numbers of placebo-treated and cilomilast-treated patients transitioned to abnormal values or abnormal values of concern.

6.5.4. Vital signs

In the Phase III pivotal studies, blood pressure and heart rate were measured at all visits after the patient had been sitting for 5 minutes. Orthostatic changes in vital signs were measured at predefined visits, including Screening, Baseline, Endpoint, at early withdrawal and at visits associated with GIAEs of concern. Vital signs and orthostatic vital signs were summarized by mean values and by sponsor defined threshold values (transitions from normal to low, low concern, high and high concern) (See Appendices).

6.5.4.1. Sitting vital signs

Overall, mean changes in sitting vital signs were small and similar between treatment groups. There were no differences between treatment groups in the numbers of patients transitioning from baseline normal values to low or high values, or to low or high values of concern for systolic pressure, diastolic blood pressure or heart rate changes.

6.5.4.2. Orthostatic vital signs

Small and similar changes in mean orthostatic vital signs were recorded at Baseline and study Endpoint in placebo and cilomilast patients. The numbers and percentages of patients with transitions in orthostatic vital signs from normal range at Baseline to outside the normal range or to values of concern on-therapy were comparable between the cilomilast and placebo treatment groups. A higher proportion of cilomilast patients had a systolic pressure decrease from normal to high concern (cilomilast 1.5%; placebo 0.1%). However, there were no differences for diastolic blood pressure or heart rate.

6.5.5. Cardiovascular monitoring

Extensive cardiovascular monitoring during the development program included frequent ECGs (>70,000 ECGs with over 6,000 obtained at C_{max}). Additionally, 24-hour Holter monitoring evaluations (>1000 Holters), including Baseline and two on-therapy observations, were obtained in 3 of the 4 pivotal trials (039, 042, and 091) and in the 168 cardiovascular safety trial.

6.5.5.1. ECGs

In the Phase III pivotal studies, a 12-lead ECG was performed during run-in visits and double-blind treatment periods, upon early withdrawal and at Safety Follow-up (if there were ECG abnormalities at the previous visit) and an ECG was also recorded 3 hours after administration of study medication (estimated C_{max}). 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).

Overall, there were no differences in mean changes in trough and Cmax ECG values between treatment groups.

ECG values of concern are defined in Table 16.

Table 16 Electrocardiographic values of clinical concern

Parameter	Low Concern	Low	High	High Concern
QRS interval	NA	NA	120 – 199msec	≥200msec
PR interval	NA	NA	200 – 249msec	≥250msec
Atrial rate	<50 bpm and 2 bpm lower than nadir from baseline or <45 bpm	45–55 bpm	100 – 120 bpm	>120 bpm
Ventricular rate	<50 bpm and 2 bpm lower than nadir from baseline or <45 bpm	45–55 bpm	100 – 120 bpm	>120 bpm
Prolonged QT (corrected) ^a	NA	NA	male 430 – 450msec (borderline) female 450 – 470msec (borderline)	male >450msec (prolonged) female >470msec (prolonged)
Prolonged QT (corrected) ^a Change from baseline	NA	NA	increase 30 – 60msec	Increase >60msec
QT uncorrected	NA	NA	NA	≥500msec

QT corrected by Bazett's formula.

The numbers (%) of patients from the Phase III pivotal studies with transitions from baseline ECG parameters to values outside the normal range or to values of clinical concern for placebo- and cilomilast-treated patients on-therapy are presented in Table 17.

Table 17 Transitions from normal range at baseline at any timepoint on therapy for trough ECG parameters – Phase III pivotal studies

Parameter	N ^b	On-therapy ^a				
		Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
Atrial rate (bpm)						
Placebo	953	11 (1.2)	96 (10.1)	769 (80.7)	74 (7.8)	8 (0.8)
Cilomilast 15mg BID	1533	20 (1.3)	139 (9.1)	1230 (80.2)	138 (9.0)	10 (0.7)
Ventricular rate (bpm)						
Placebo	956	12 (1.3)	96 (10.0)	773 (80.9)	74 (7.7)	6 (0.6)
Cilomilast 15mg BID	1537	20 (1.3)	141 (9.2)	1232 (80.2)	138 (9.0)	11 (0.7)
QRS (msec)						
Placebo	985	NA NA	NA NA	955 (97.0)	30 (3.0)	0 (0.0)
Cilomilast 15mg BID	1594	NA NA	NA NA	1524 (95.6)	69 (4.3)	1 (0.1)
PR (msec)						
Placebo	974	NA NA	NA NA	925 (95.0)	46 (4.7)	3 (0.3)
Cilomilast 15mg BID	1547	NA NA	NA NA	1432 (92.6)	113 (7.3)	2 (0.1)
QT uncorrected (msec)						
Placebo	1059	NA NA	NA NA	1052 (99.3)	NA NA	7 (0.7)
Cilomilast 15mg BID	1699	NA NA	NA NA	1691 (99.5)	NA NA	8 (0.5)
QTc (absolute values) (msec)^c						
Placebo	775	NA NA	NA NA	484 (62.5)	208 (26.8)	83 (10.7)
Cilomilast 15mg BID	1227	NA NA	NA NA	774 (63.1)	345 (28.1)	108 (8.8)
QTc (change from baseline) (msec)^d						
Placebo	775	NA NA	NA NA	608 (78.5)	144 (18.6)	23 (3.0)
Cilomilast 15mg BID	1227	NA NA	NA NA	994 (81.0)	212 (17.3)	21 (1.7)

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.
- 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.

Except for QTc, a small proportion of patients in both treatment groups had transitions On-therapy to values of high or high concern. A substantial percentage of patients in both groups had absolute QTc values of high (placebo 26.8%; cilomilast 28.1%) or high concern (placebo 10.7%; cilomilast 8.8%) at any timepoint on therapy. However, at endpoint the number of patients with high (placebo 11.3%; cilomilast 12.2%) and high concern (placebo 2.6%; cilomilast 2.4%) QTc values was considerably lower in both groups.

The most frequent (defined as occurring in >5% of patients in any treatment group) on-therapy ECG abnormalities in the Phase III pivotal studies that were not present on ECGs recorded pre-therapy at Screening or Baseline are presented in Table 18.

Table 18 Number (%) of patients with the most frequently reported new-onset ECG abnormalities at trough (greater than 5% of patients in any treatment group) – Phase III pivotal studies

ECG Abnormality	Treatment Group	
	Placebo (N = 1088) n (%) ^a	Cilomilast 15mg BID (N = 1786) n (%) ^a
Sinus Bradycardia	120 (13.6)	209 (14.4)
Q-T Interval Increased	118 (12.4)	192 (12.3)
T-wave Abnormal NOS	123 (13.0)	153 (9.5)
Premature Atrial Contractions NOS	105 (10.3)	154 (9.0)
Intraventricular Block NOS	64 (6.2)	137 (8.1)
S-T Changes Nonspecific	90 (9.4)	130 (8.1)
Poor R-wave Progression	84 (9.0)	119 (7.6)
Sinus Tachycardia	61 (5.8)	103 (6.0)
Premature Ventricular Contractions NOS	30 (2.8)	98 (5.7)
Sinus Arrhythmia	74 (7.1)	97 (5.6)
Left Atrial Hypertrophy (P mitrale)	58 (5.8)	81 (4.9)
PVCs Unifocal	75 (7.2)	79 (4.6)

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

There were no clinically relevant differences in new onset of specific ECG abnormalities between treatment groups.

***C_{max}* ECGs**

Over 6000 ECGs were obtained at C_{max} in the Phase III controlled trials and in the uncontrolled (long-term) trials. Overall, the results observed with ECGs at C_{max} were similar to that observed with trough ECGs.

6.5.5.2. 24-hour Holter Monitoring

Holter data was collected from 3 of the 4 Phase III pivotal studies (Studies 039, 042, 091), and from study 168. All four studies utilized a 2:1 (cilomilast to placebo) randomization. Table 19 presents the summary number of patients contributing Holter data from each of these studies. Holter monitoring was performed at three different visits in each study. Studies 039, 042, and 091 each collected Holter data for 48 hours at Week -2, then for 24 hours (≥ 18 hours was considered a completed Holter session) at Weeks 1 and 20. Study 168 obtained 24-hour Holter data at Screening, followed by monitoring at Weeks 1 and 12. The Holter recordings were sent to a centralized facility for reading by Board-certified cardiologists.

Table 19 Summary of Holter Patients and Treatment in Each Study

Study	Treatment Group	
	Placebo Safety Population^a	Cilomilast Safety Population^a
039	23	50
042	22	44
091	12	27
168	89	170
Total	146	291

a. Patients with at least one Holter monitoring session (may include patients with or without Baseline).

All Holter sessions listed are ≥ 18 hours.

Overall, the two treatment groups were similar in their demographic characteristics and comparable to the population studied in the four Phase III pivotal trials.

Table 20 presents descriptive statistics for selected event-based ECG parameters from Holter monitoring at Baseline, Week 1, and Endpoint. Each of these parameters is summarized for only the patients who experienced at least one episode of the event.

Table 20 Summary Statistics for Event-Based Holter Monitoring Parameters for Patients with COPD in Phase III Studies that had at Least One On-therapy Holter

Week of Treatment	Treatment Group	N	Mean	(SD)	Median	Min	Max
Average Heart Rate							
Baseline	Placebo	135	79.7	(10.4)	79.7	57	105
	Cilomilast	276	80.2	(11.0)	80	55.5	110
Week 1	Placebo	144	78.60	(10.04)	79	53	101
	Cilomilast	284	80.18	(10.13)	80	54	109
Endpoint	Placebo	145	78.9	(10.3)	78	54	102
	Cilomilast	291	79.7	(10.5)	80	56	111
Episodes of Ventricular Tachycardia							
Baseline	Placebo	11	1.09	(0.30)	1	1	2
	Cilomilast	20	5.90	(9.92)	1	1	42
Week 1	Placebo	13	1.62	(1.19)	1	1	4
	Cilomilast	25	5.52	(10.40)	1	1	50
Endpoint	Placebo	20	1.70	(1.72)	1	1	7
	Cilomilast	36	6.42	(13.6)	1	1	72
Episodes of Supraventricular Tachycardia							
Baseline	Placebo	81	7.9	(19.4)	1	1	107
	Cilomilast	140	15.5	(87.7)	2	1	988
Week 1	Placebo	75	9.48	(22.41)	2	1	140
	Cilomilast	137	22.04	(146.97)	2	1	1660
Endpoint	Placebo	95	14.9	(55.4)	2	1	421
	Cilomilast	172	20.0	(133.3)	2	1	1660
Ventricular Ectopics per 1000 Beats							
Baseline	Placebo	141	5.8	(18.0)	0.3	0	172
	Cilomilast	281	6.7	(22.0)	0.2	0	262.5
Week 1	Placebo	145	6.62	(16.88)	0.44	0	116.14
	Cilomilast	286	7.34	(25.66)	0.33	0	339.89
Endpoint	Placebo	146	7.4	(18.2)	0.4	0	120.1
	Cilomilast	291	7.8	(27.8)	0.2	0	339.9
Supraventricular Ectopics per 1000 Beats							
Baseline	Placebo	141	5.4	(14.7)	0.6	0	95.2
	Cilomilast	281	6.7	(25.4)	0.5	0	248
Week 1	Placebo	145	5.11	(15.29)	0.63	0	132.13
	Cilomilast	286	7.40	(30.27)	0.55	0	303.56
Endpoint	Placebo	146	6.5	(17.3)	0.9	0	132.1
	Cilomilast	291	6.6	(25.8)	0.5	0	286.7
Episodes of Sinus Pause							
Baseline	Placebo	3	2.7	(1.5)	3	1	4
	Cilomilast	10	141.4	(274.7)	9	1	852
Week 1	Placebo	7	18.9	(29.3)	5	1	79
	Cilomilast	11	42.9	(66.8)	13	1	209
Endpoint	Placebo	9	5.2	(9.5)	1	1	30
	Cilomilast	12	41.3	(63.9)	14	1	209
Episodes of Sinus Bradycardia							
Baseline	Placebo	45	100.6	(206.5)	18.0	1	1106.0
	Cilomilast	91	106.1	(205.5)	10.0	1	1449.0
Week 1	Placebo	43	109.49	(187.15)	13	1	737

Week of Treatment	Treatment Group	N	Mean	(SD)	Median	Min	Max
Endpoint	Cilomilast	81	72.93	(140.21)	13	1	888
	Placebo	49	113.8	(191.0)	19.0	1	961.0
	Cilomilast	98	76.2	(134.3)	15.0	1	827.0
Episodes of Atrial Fibrillation							
Baseline	Placebo	1	5.00	-	5	5	5
	Cilomilast	3	1.33	(0.58)	1	1	2
Week 1	Placebo	1	6.00	-	6	6	6
	Cilomilast	5	3.40	(3.21)	2	1	9
Endpoint	Placebo	1	6.00	-	6	6	6
	Cilomilast	5	4.60	(4.04)	2	1	9
Episodes of Atrial Flutter							
Baseline	Placebo	0	-	-	-	-	-
	Cilomilast	2	1.00	(0.00)	1	1	1
Week 1	Placebo	0	-	-	-	-	-
	Cilomilast	1	1.0	-	1	1	1
Endpoint	Placebo	0	-	-	-	-	-
	Cilomilast	2	1.0	(0.00)	1	1	1

No clinically important differences between placebo-treated and cilomilast-treated patients were seen for average heart rate. Episodes of ventricular tachycardia were observed at Baseline and Endpoint in a total of 11 and 20 placebo-treated and 20 and 36 cilomilast-treated patients, respectively. There were no occurrences of sustained ventricular tachycardia (defined as ventricular ectopics lasting ≥ 30 seconds at a rate of ≥ 100 beats per minute).

A substantial number of patients in both groups had ventricular and supraventricular ectopic beats at baseline and Endpoint. The median number of ventricular and supraventricular ectopics per 1000 beats were similar between treatment groups. The number of patients with atrial fibrillation or atrial flutter was low.

Episodes of sinus pause were infrequent and comparable between treatment groups with no patient experiencing a sinus pause greater than 6.1 seconds.

In patients with episodes of sinus bradycardia at Baseline (45 placebo vs. 91 cilomilast) and Endpoint (49 placebo vs. 98 cilomilast) the median number of episodes was similar between treatment groups.

Table 21 summarizes the incidence of new onset cardiac events by treatment group.

Table 21 Incidence of New Onset Cardiac Events Based on 24-Hour Holter Monitoring for Patients with COPD in Phase III Studies that had at Least One On-therapy Holter

Cardiac Event	Onset	Not Present		
		Pre-Therapy	New Onset	
		N	n	(%)
Atrial Fibrillation	Placebo	142	0	(0.0)
	Cilomilast	280	2	(0.7)
Atrial Flutter	Placebo	143	0	(0.0)
	Cilomilast	281	1	(0.4)
First Degree AV Block	Placebo	139	5	(3.6)
	Cilomilast	275	6	(2.2)
Mobitz Type I Second Degree AV Block	Placebo	142	0	(0.0)
	Cilomilast	279	2	(0.7)
Mobitz Type II Second Degree AV Block	Placebo	143	2	(1.4)
	Cilomilast	283	1	(0.4)
Sinus Bradycardia	Placebo	98	12	(12.2)
	Cilomilast	192	29	(15.1)
Sinus Pause	Placebo	140	6	(4.3)
	Cilomilast	273	4	(1.5)
Supraventricular Tachycardia	Placebo	62	29	(46.8)
	Cilomilast	143	65	(45.5)
Ventricular Tachycardia	Placebo	132	11	(8.3)
	Cilomilast	263	23	(8.7)

Percentages for each finding are based on the number of patients with specific finding absent pre-therapy. Each distinct patient counted once per finding.

New onset cardiac events were similar between the **ARIFLO** and placebo treatment groups.