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Study No.: SB207499/039		
Title: A Randomized, 24-week, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Cilomilast (15mg Twice Daily) in Patients with Chronic Obstructive Pulmonary Disease (COPD).		
Rationale: This study was designed to further evaluate the efficacy and safety of cilomilast versus placebo in subjects with COPD.		
Phase: III		
Study Period: 09 November 1998 – 13 March 2000		
Study Design: A randomized, double-blind, placebo-controlled, multicentre study		
Centres: 102 centres in the United States, Canada and Mexico		
Indication: COPD		
Treatment: subjects received either 15mg of cilomilast or matching placebo tablet twice daily (BID), one tablet in the morning and one tablet in the evening, with food.		
Objectives: The primary objective of the study was to demonstrate the clinical efficacy of cilomilast (15mg BID) versus placebo by assessment of forced expiratory volume in one second (FEV ₁) measured at trough drug levels and the total score of the St. George's Respiratory Questionnaire (SGRQ) in mean change from baseline over 24 weeks in subjects with COPD.		
Primary Outcome/Efficacy Variable: The primary efficacy variables were changes from baseline in trough pre-bronchodilator FEV ₁ and in total score of the SGRQ averaged over 24 weeks.		
Secondary Outcome/Efficacy Variable(s): Secondary measures of efficacy were post-exercise breathlessness, summary symptom score, clinic trough forced vital capacity (FVC), exercise performance (six-minute walk) and COPD exacerbation rates		
Statistical Methods: The planned sample size was 645 subjects, randomized at a 2:1 ratio (cilomilast:placebo), to obtain 450 evaluable subjects. The sample size calculation was based on the two-sided t-test to achieve an overall power of 90% at type I error of 0.05 for change from baseline averaged over 24 weeks in FEV ₁ and SGRQ total score. This study was designed to detect a 120mL difference in FEV ₁ (assuming a standard deviation of 270mL) and a 4-unit difference in SGRQ total score (assuming a standard deviation of 12 units) with 90% joint power. The primary endpoints were analyzed using a repeated measures model to compare the average change over 24 weeks. Additional comparisons using analysis of covariance (ANCOVA) were made at individual time points and at endpoint, defined as the last on-therapy post-baseline value. Exacerbation-free survival at 24 weeks was estimated using the Kaplan-Meier product limit. Analyses were performed for the Intent-to-treat (ITT) Population, composed of all subjects who received at least one dose of double-blind medication. Descriptive statistics were provided for safety parameters. The Safety Population consisted of all subjects who had received at least one dose of double-blind medication.		
Study Population: Male and female subjects between 40 and 80 years of age (inclusive) with COPD, a cigarette-smoking history of at least 10 pack years, a pre-salbutamol FEV ₁ to FVC ratio less than or equal to 0.70, post-salbutamol reversibility less than or equal to 15% or 200 ml (or both) and a post-salbutamol FEV ₁ of 30 to 70% of predicted normal.		
	Placebo	Cilomilast
Number of Subjects:		
Planned, N	215	430
Randomised, N	216	431
Completed, n (%)	164 (76)	294 (68)
Total Number Subjects Withdrawn, N (%)	52 (24)	137 (32)

Withdrawn due to Adverse Events n (%)	35 (16)	94 (22)
Withdrawn due to Lack of Efficacy n (%)	4 (2)	7 (2)
Withdrawn for other reasons n (%)	13 (6)	36 (8)
Demographics	Placebo	Cilomilast
N (ITT)	216	431
Females: Males	70:146	178:253
Mean Age, years (SD)	64.9 (8.4)	65.4 (8.6)
Caucasian, n (%)	209 (97)	394 (91)
Current smoker, n (%)	101 (47)	191 (44)
Primary Efficacy Results:		
	Placebo	Cilomilast
Change from Baseline in FEV₁ (L) Averaged Over 24 Weeks		
N	207	378
Baseline mean	1.42	1.34
LS mean change from baseline (SE)	-0.03 (0.01)	0.01 (0.01)
LS mean difference versus placebo		0.04
95% confidence interval versus placebo		(0.01, 0.06)
p-value versus placebo		0.002
Change from Baseline in SGRQ Averaged Over 24 Weeks		
N	181	310
Baseline mean	44.8	45.1
LS mean change from baseline (SE)	0.4 (0.8)	-3.7 (0.7)
LS mean difference versus placebo		-4.1
95% confidence interval versus placebo		(-6.0, -2.2)
p-value versus placebo		<0.001
Secondary Outcome Variables:		
	Placebo	Cilomilast
FVC (L) at Endpoint		
N	208	394
Baseline mean (SE)	2.78 (0.06)	2.72 (0.05)
LS mean change from baseline (SE)	-0.12 (0.03)	-0.01 (0.02)
LS mean difference versus placebo		0.11
95% confidence interval versus placebo		(0.05, 0.18)
Post-Exercise Breathlessness (Borg scale) at Endpoint		
N	196	357
Baseline mean (SE)	3.59 (0.11)	3.24 (0.09)
LS mean change from baseline (SE)	0.19 (0.12)	-0.13 (0.09)
LS mean difference versus placebo		-0.32
95% confidence interval versus placebo		(-0.59, -0.05)
Summary Symptom Score at Endpoint		
N	202	382
Baseline mean (SE)	4.42 (0.14)	4.24 (0.10)
LS mean change from baseline (SE)	-0.12 (0.12)	-0.21 (0.09)
LS mean difference versus placebo		-0.09
95% confidence interval versus placebo		(-0.36, 0.18)
Distance Walked (m) at Endpoint		
N	194	356
Baseline mean (SE)	356.3 (8.1)	356.3 (6.2)
LS mean change from baseline (SE)	9.0 (5.5)	16.1 (4.2)

LS mean difference versus placebo		7.1
95% confidence interval versus placebo		(-5.7, 19.9)
Exacerbation-free Survival at 24 Weeks		
N	216	431
Subjects exacerbation free, n (%)	141 (62.4)	336 (74.0)
95% confidence interval	(55.5, 69.3)	(69.3, 78.6)
Safety Results: An on-therapy adverse event (AE) was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of study medication. An on-therapy serious adverse event (SAE) was defined as an SAE with onset on or after the start date of study medication and up to 30 days after the last dose of medication.		
	Placebo	Cilomilast
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s), n(%)	176 (81)	373 (87)
Chronic obstructive airways disease	76 (35)	95 (22)
Diarrhea	23 (11)	90 (21)
Nausea	10 (5)	82 (19)
Upper respiratory tract infection	33 (15)	68 (16)
Abdominal pain	20 (9)	61 (14)
Dyspepsia	8 (4)	42 (10)
Vomiting	6 (3)	37 (9)
Headache	14 (6)	36 (8)
Injury	12 (6)	30 (7)
Dizziness	9 (4)	29 (7)
Serious Adverse Events - On-Therapy		
n (%) [n considered by the investigator to be related to study medication]		
	Placebo	Cilomilast
	n (%) [related]	n (%) [related]
Subjects with any SAEs, n (%)	25 (12) [2]	24 (6) [0]
Chronic obstructive airways disease	5 (2)	2 (<1)
Myocardial infarction	1 (<1)	3 (<1)
Cardiac failure	3 (1)	0
Basal cell carcinoma	0	2 (<1)
Urinary retention	0	2 (<1)
Vascular disorder	0	2 (<1)
Aneurysm	1 (<1)	1 (<1)
Pneumonia	1 (<1)	1 (<1)
Pneumothorax	1 (<1)	1 (<1)
Pulmonary edema	1 (<1)	1 (<1)
Angina Pectoris	2 (<1)	0
Bladder carcinoma	2 (<1)	0
Intestinal obstruction	2 (<1)	0
Abdominal pain	0	1 (<1)
Anemia	1 (<1)	0
Arrhythmia atrial	1 (<1) [1]	0
Breast neoplasm malignant female	0	1 (<1)
Bundle branch block	1 (<1)	0
Carcinoma	0	1 (<1)
Cellulitis	0	1 (<1)
Cerebrovascular disorder	0	1 (<1)
Chest pain	1 (<1)	0
Cholecystitis	0	1 (<1)
Colitis	1 (<1)	0

Coronary artery disorder	0	1 (<1)
Diarrhea	0	1 (<1)
Dyspnea	1 (<1)	0
Gastric ulcer hemorrhagic	1 (<1) [1]	0
Hypertension	0	1 (<1)
Injury	1 (<1)	0
Myocardial ischemia	0	1 (<1)
Neoplasm NOS	1 (<1)	0
Paresthesia	1 (<1)	0
Pericardial effusion	1 (<1)	0
Respiratory insufficiency	1 (<1)	0
Schizophrenic reaction	0	1 (<1)
Sepsis	1 (<1)	0
Syncope	0	1 (<1)
Tachycardia ventricular	1 (<1) [1]	0
Thrombosis coronary	1 (<1)	0
Thrombocytopenia	1 (<1)	0
Upper respiratory tract infection	1 (<1)	0
Vein disorder	0	1 (<1)
	n (%) [related]	n (%) [related]
Subjects with fatal SAEs, n (%)	2 (<1) [0]	2 (<1) [0]
Myocardial infarction	1 (<1)	1 (<1)
Cardiac failure	2 (<1)	0
Myocardial ischemia	0	1 (<1)
Thrombosis coronary	1 (<1)	0

Conclusion: See publication below.

Publications:

Rennard, S. Schachter, N. Streck, M. Rickard, K. Amit, O. Cilomilast for COPD: Results of a 6-Month, Placebo-Controlled Study of a Potent, Selective Inhibitor of Phosphodiesterase 4. Chest (2006); 129:56-66.

Date updated: 15-Jul-2008