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Study No.: SB207499/042		
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: 16 November 1998 to 2 December 1999		
Study Design: A randomized, double-blind, placebo-controlled, parallel-group, multicentre study		
Centres: 98 centres in Australia and New Zealand, Germany, Spain, South Africa and the United Kingdom		
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, after a meal.		
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 clinic forced vital capacity (FVC) at trough, post-exercise breathlessness, summary symptom score, , exercise performance (six-minute walk test) 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 gave at least 90% power to detect a 4 unit difference in total SGRQ score (average of 12 and 24 week assessments at an adjusted significance level of 0.025 and assuming standard deviation of 12 units). For FEV ₁ , there was at least 90% power to detect a difference of 120mL assuming a standard deviation of 270mL. To account for co-primary endpoints the Hochberg method was used to adjust the significance level in the test for treatment effect. The primary endpoints were analyzed using a repeated measures model to compare the average change over 24 weeks. Additional comparisons using analysis of variance (ANOVA) 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 patients 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	226	474
Completed, n (%)	175 (77)	352 (74)

Total Number Subjects Withdrawn, N (%)	51 (23)	122 (26)
Withdrawn due to Adverse Events n (%)	22 (10)	71 (15)
Withdrawn due to Lack of Efficacy n (%)	2 (<1)	5 (1)
Withdrawn for other reasons n (%)	27 (12)	46 (10)
Demographics	Placebo	Cilomilast
N (ITT)	226	474
Females: Males	46:180	92:382
Mean Age, years (SD)	64.7 (8.5)	64.5 (8.1)
Caucasian, n (%)	224 (99)	471 (99)
Current smoker, n (%)	87 (38)	213 (45)
Primary Efficacy Results:		
	Placebo	Cilomilast
Change from Baseline in FEV₁ (L) Averaged Over 24 Weeks		
N	219	440
Baseline mean	1.35	1.37
LS mean change from baseline (SE)	-0.00 (0.02)	0.03 (0.01)
LS mean difference versus placebo		0.03
97.5% confidence interval versus placebo		(0.00, 0.06)
p-value versus placebo		0.044
Change from Baseline in SGRQ Averaged Over 24 Weeks		
N	190	375
Baseline mean	46.0	43.9
LS mean change from baseline (SE)	-4.9 (1.0)	-4.2 (0.8)
LS mean difference versus placebo		0.7
97.5% confidence interval versus placebo		(-1.5, 2.9)
p-value versus placebo		0.473
Secondary Outcome Variables:		
	Placebo	Cilomilast
FVC (L) at Endpoint		
N	220	448
Baseline mean (SE)	2.75 (0.06)	2.76 (0.05)
LS mean change from baseline (SE)	-0.02 (0.03)	0.03 (0.03)
LS mean difference versus placebo		0.05
95% confidence interval versus placebo		(-0.01, 0.11)
Post-Exercise Breathlessness (Borg scale) at Endpoint		
N	206	422
Baseline mean (SE)	3.54 (0.14)	3.73 (0.12)
LS mean change from baseline (SE)	-0.11 (0.13)	-0.29 (0.10)
LS mean difference versus placebo		-0.18
95% confidence interval versus placebo		(-0.43, 0.07)
Summary Symptom Score at Endpoint		
N	212	435
Baseline mean (SE)	4.77 (0.13)	4.71 (0.10)
LS mean change from baseline (SE)	-0.59 (0.13)	-0.41 (0.11)
LS mean difference versus placebo		0.18
95% confidence interval versus placebo		(-0.09, 0.45)
Distance Walked (m) at Endpoint		
N	207	423
Baseline mean (SE)	397.6 (10.9)	421.1 (8.8)

LS mean change from baseline (SE)	22.2 (7.6)	5.8 (6.1)
LS mean difference versus placebo		-16.4
95% confidence interval versus placebo		(-31.3,-1.4)
Exacerbation-free Survival at 24 Weeks		
N	226	474
Subjects exacerbation free, n (%)	143 (61.3)	299 (58.8)
95% confidence interval	(54.6, 68.1)	(54.0, 63.5)
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(%)	154 (68)	340 (72)
Chronic obstructive airways disease	83 (37)	176 (37)
Nausea	9 (4)	56 (12)
Headache	14 (6)	44 (9)
Diarrhoea	8 (4)	38 (8)
Abdominal Pain	10 (4)	37 (8)
Dyspepsia	8 (4)	29 (6)
Upper respiratory tract infection	11 (5)	29 (6)
Back pain	6 (3)	22 (5)
Injury	11 (5)	22 (5)
Vomiting	0	17 (4)
Hypertension	6 (3)	17 (4)
Rhinitis	6 (3)	17 (4)
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 non-fatal SAEs, n (%)	13 (6) [1]	28 (6) [2]
Chronic obstructive airways disease	5 (2)	6 (1) [1]
Bladder carcinoma	0	2 (<1)
Pulmonary carcinoma	0	2 (<1)
Myocardial infarction	1 (<1)	2 (<1)
Aneurysm	1 (<1)	1 (<1)
Angina pectoris	1 (<1)	1 (<1)
Confusion	1 (<1)	1 (<1)
Abdominal pain	0	1 (<1) [1]
Bladder papilloma	0	1 (<1)
Bronchitis	1 (<1)	0
Carcinoma	0	1 (<1)
Cardiac failure	1 (<1)	0
Cerebrovascular disorder	0	1 (<1)
Convulsions	0	1 (<1)
Convulsions grand mal	1 (<1)	0
Collagenosis	1 (<1)	0
Coronary artery disorder	0	1 (<1)
Cystitis	1 (<1)	0
Dementia	0	1 (<1)
Dyspnea	0	1 (<1)
Gall bladder disorder	1 (<1)	0

Hematuria	0	1 (<1)
Injury	0	1 (<1)
Neoplasm	0	1 (<1)
Pancreatitis	0	1 (<1)
Peripheral ischemia	0	1 (<1)
Therapeutic response increased	0	1 (<1)
Urticaria	1 (<1) [1]	0
Urinary tract infection	0	1 (<1)
Vascular 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)
Aneurysm	1 (<1)	0
Chronic obstructive airways disease	0	1 (<1)
Respiratory insufficiency	0	1 (<1)

Conclusion: After adjustment for multiple comparisons, cilomilast failed to show statistically significant effects on the co-primary endpoint of FEV₁ compared with placebo when administered at 15mg twice daily over a 24-week treatment period. Cilomilast also failed to show statistically significant effects for SGRQ. In the placebo group, 154 subjects reported adverse events with the most frequently reported being chronic obstructive airways disease and headache. In the cilomilast treated group, 340 subjects reported adverse events with the most frequently reported being chronic obstructive airways disease and nausea. Thirteen subjects in the placebo group and twenty-eight subjects in the cilomilast group reported serious adverse events. There were two fatalities reported in the placebo group and two fatalities reported in the cilomilast group.

Publications: No publication

Date updated: 16-Jul-2008