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Study No.: CIL103657		
Title: A Randomized, 24-week, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Cilomilast (15mg BID) 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: 18 November 2004 – 16 January 2007		
Study Design: a randomized, double-blind, placebo-controlled, multi-centre study		
Centres: 103 centres in the US		
Indication: chronic obstructive pulmonary disease		
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 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 changes from baseline in clinic trough forced vital capacity (FVC), time to first Level 2 or Level 3 COPD exacerbation. A Level 2 exacerbation was defined as an acute worsening of COPD that required additional treatment (e.g., a short course of oral corticosteroids, antibiotics, etc.) prescribed by a physician or other health care provider or as a result of a hospital out-patient visit, and a Level 3 exacerbation was defined as an acute worsening of COPD that required the subject to be admitted to the hospital for treatment.		
Statistical Methods: The planned sample size was 600 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 50mL difference in FEV ₁ and a 4-unit difference in SGRQ total score with 90% joint power. Randomization of 300 subjects per arm achieved at least 90% power for the co-primary endpoints. 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. 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. The Safety Population consisted of all subjects who had received at least one dose of double-blind medication.		
Study Population: Male and female subjects ≥40 years of age with COPD, and a cigarette-smoking history of ≥10 pack-years were eligible. Additional inclusion criteria were pre-albuterol FEV ₁ to FVC ratio ≤70%, post-albuterol reversibility ≤15% or ≤200mL (or both), post-albuterol FEV ₁ ≤70% of predicted normal and at least one COPD exacerbation within the 12 months prior to screening.		
	Placebo	Cilomilast
Number of Subjects:		
Planned, N	300	300

Randomised, N	317	296
Completed, n (%)	240 (76)	191 (65)
Total number subjects withdrawn, n (%)	76 (24)	105 (35)
Withdrawn due to adverse events, n (%)	17 (5)	46 (16)
Withdrawn due to lack of efficacy, n (%)	7 (2)	6 (2)
Withdrawn for other reasons, n (%)	52 (16)	53 (18)
Demographics:		
	Placebo	Cilomilast
N (ITT)	316	296
Females: Males	166:150	160:136
Mean age, years (SD)	63.2 (9.73)	63.1 (9.60)
White, n (%)	297 (94)	282 (95)
Current smoker, n (%)	163 (52)	155 (52)
Primary Efficacy Results:		
	Placebo	Cilomilast
FEV₁ (L)		
Baseline, n	316	296
Mean (SE)	1.188 (0.027)	1.205 (0.032)
Over 24 weeks, n	303	268
LS mean change from baseline (SE)	0.006 (0.005)	0.050 (0.005)
LS mean difference (SE) versus placebo		0.044
95% confidence interval versus placebo		0.033, 0.055
p-value versus placebo		<0.001
SGRQ		
Baseline, n	310	292
Mean (SE)	52.1 (0.93)	52.5 (0.93)
Over 24 weeks, n	296	277
LS mean change from baseline (SE)	-1.84 (0.566)	-1.80 (0.595)
LS mean difference (SE) versus placebo		0.04
95% confidence interval versus placebo		-1.31, 1.39
p-value versus placebo		0.951
Secondary Outcome Variables:		
	Placebo	Cilomilast
Level 2/Level 3 Exacerbation-free Survival at 24 Weeks		
Subjects exacerbation free, n (%)	229 (69.1)	216 (66.2)
95% confidence interval	63.7, 74.6	60.0, 72.4
FVC (L)		
Baseline, n	316	296
Mean (SE)	2.502 (0.041)	2.481 (0.051)
Endpoint, n	303	268
LS mean change from baseline (SE)	-0.002 (0.023)	0.025 (0.026)
LS mean difference (SE) versus placebo		0.027
95% confidence interval versus placebo		-0.030, 0.085
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(%)	232 (73)	234 (79)
Nausea	12 (4)	63 (21)

Upper respiratory tract infection	49 (15)	52 (18)
Diarrhoea	20 (6)	50 (17)
Headache	34 (11)	47 (16)
Vomiting	8 (3)	28 (9)
Nasopharyngitis	28 (9)	25 (8)
Stomach discomfort	3 (<1)	22 (7)
Pharyngolaryngeal pain	17 (5)	19 (6)
Dyspepsia	5 (2)	14 (5)
Lower respiratory tract infection	14 (4)	14 (5)
Sinusitis	14 (4)	14 (5)

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 (%)	23 (7) [2]	17 (6) [0]
Chronic obstructive pulmonary disease	4 (1)	7 (2)
Myocardial infarction	0	2 (<1)
Pneumonia	3 (<1)	2 (<1)
Non cardiac chest pain	2 (<1)	1 (<1)
Cellulitis	2 (<1)	0
Abdominal hernia	1 (<1)	0
Abdominal pain	1 (<1)	0
Alcohol poisoning	0	1 (<1)
Anaemia	1 (<1)	0
Benign prostatic hyperplasia	1 (<1)	0
Breast cancer	0	1 (<1)
Bronchitis acute	1 (<1)	0
Cerebrovascular accident	1 (<1)	0
Chest pain	0	1 (<1)
Constipation	1 (<1)	0
Coronary artery disease	0	1 (<1)
Coronary artery occlusion	0	1 (<1)
Device electrical finding	1 (<1)	0
Diabetic foot	1 (<1)	0
Gastroenteritis	0	1 (<1)
Haemorrhoidal haemorrhage	1 (<1)	0
Hip fracture	1 (<1)	0
Iliac artery stenosis	1 (<1)	0
Large intestine perforation	1 (<1) [1]	0
Lethargy	1 (<1)	0
Mental status changes	1 (<1) [1]	0
Non-small cell lung cancer	1 (<1)	0
Osteoarthritis	0	1 (<1)
Pancreatitis chronic	0	1 (<1)
Rectal haemorrhage	1 (<1)	0
Renal colic	0	1 (<1)
Renal failure acute	1 (<1)	0
Respiratory failure	1 (<1)	0
Small intestinal obstruction	0	1 (<1)
Ventricular fibrillation	0	1 (<1)
Ventricular tachycardia	1 (<1)	0
	Placebo	Cilomilast
Subjects with fatal SAEs, n (%)	0	0

Conclusion:

Cilomilast was shown to have statistically significant effects on one primary endpoint of FEV1; however, it did not demonstrate a significant improvement in SGRQ compared with placebo when administered at 15mg twice daily over a 24-week treatment period. Other measures of efficacy did not demonstrate a positive treatment benefit of cilomilast, based on evaluations of FVC and COPD exacerbations. In the placebo group 232 subjects reported adverse events with the most frequently reported being upper respiratory tract infection and headache. In the cilomilast treated group 234 subjects reported adverse events with the most frequently reported being nausea and

upper respiratory tract infection. Twenty-three subjects in the placebo group reported serious adverse events and seventeen subjects in the cilomilast group reported serious adverse events. There were no fatalities reported.

Publications: No publication

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