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Study No.: SB207499/110		
Title: A 12-week, Multicenter, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Anti-inflammatory Activity of Cilomilast 15 mg Twice Daily in Patients With Chronic Obstructive Pulmonary Disease (COPD)		
Rationale: Cilomilast demonstrated a reduction in pulmonary neutrophilia and edema in LPS-induced animal models. This study was designed to evaluate the activity of cilomilast on cellular and biochemical indices of inflammation in subjects with COPD.		
Phase: III		
Study Period: 26 July 1999 to 20 June 2000		
Study Design: A randomized, double-blind, placebo-controlled, parallel-group, multi-centre study in subjects with COPD.		
Centres: 10 centres in the United States		
Indication: COPD		
Treatment: Subjects received either cilomilast 15mg or matching placebo. One tablet of study medication was taken in the morning and one in the evening, after a meal.		
Objectives: The objectives of this study were to examine, using analysis of induced sputum, the effects of administration of cilomilast 15 mg twice daily and placebo on the inflammatory cell profile and inflammatory mediator concentrations in the airways of subjects with COPD.		
Primary Efficacy Variable: Change from baseline at endpoint in neutrophils as a percentage of total cells in induced sputum.		
Secondary Outcome/Efficacy Variable(s): Clinic FEV ₁ at trough; sputum macrophages, eosinophils, and lymphocytes as a percentage of total cells in induced sputum; total cell counts in induced sputum.		
Statistical Methods: A total of 60 subjects were planned for randomization to obtain 30 evaluable subjects. The study had 90% power to detect a 20% treatment difference in sputum neutrophils, assuming a standard deviation of 15%, at a significance level of 0.05. The assessment of treatment differences for the efficacy variables were based on an analysis of variance (ANOVA) model with effects for centre and treatment group. Least squares means along with associated 95% confidence intervals were calculated, and differences were assessed using t-tests on the least squares means. The primary population analysed for efficacy in this study was the per-protocol (PP) population. Subjects with violations of eligibility criteria were excluded entirely from the analysis, and subjects with violations occurring post-randomization had data excluded only subsequent to the violation. All randomized subjects who received at least one dose of double-blind study medication were evaluated for safety.		
Study Population: Male and female subjects between 40 and 80 years of age (inclusive) with a diagnosis of COPD, as defined by the American Thoracic Society Guidelines; a cigarette-smoking history of at least 10 pack years; pre-salbutamol FEV ₁ to FVC ratio less than or equal to 0.7, post-salbutamol reversibility less than or equal to 15% or 200mL and a post-salbutamol FEV ₁ at least 1.0L and between 30% and 70% of predicted.		
	Placebo	Cilomilast
Number of Subjects:		
Planned, N	30	30
Randomised, N	34	31
Completed, n (%)	33 (97)	30 (97)
Total Number Subjects Withdrawn, N (%)	1 (3)	1 (3)

Withdrawn due to Adverse Events n (%)	0	0
Withdrawn due to Lack of Efficacy n (%)	0	0
Withdrawn for other reasons n (%)	1 (3)	1 (3)
Demographics	Placebo	Cilomilast
N (ITT)	34	31
Females: Males	11:23	5:26
Mean Age, years (SD)	64.4 (8.1)	66.1 (8.1)
Caucasian, n (%)	33 (97)	29 (94)
Current smoker, n (%)	12 (35)	13 (42)
Primary Efficacy Results:		
	Placebo	Cilomilast
Change from Baseline at Endpoint in sputum neutrophil percentage (PP population)		
N	20	19
Baseline mean	69.9	77.3
LS mean change from baseline (SE)	10.9 (6.2)	-4.0 (6.5)
LS mean difference versus placebo		-14.9
95% confidence interval versus placebo		(-30.8, 1.0)
p-value versus placebo		0.065
Secondary Outcome Variables:		
	Placebo	Cilomilast
Change from Baseline at Endpoint in FEV₁ (L) (PP population)		
N	26	20
Baseline mean	1.62	1.69
LS mean change from baseline (SE)	-0.06 (0.04)	0.01 (0.04)
LS mean difference versus placebo		0.07
95% confidence interval versus placebo		(-0.03, 0.16)
Change from Baseline at Endpoint in Sputum Macrophages (%) (PP population)		
N	20	19
Baseline mean	22.9	18.2
LS mean change from baseline (SE)	-9.1 (5.5)	2.3 (5.9)
LS mean difference versus placebo		11.4
95% confidence interval versus placebo		(-2.9, 25.6)
Change from Baseline at Endpoint in Sputum Total Cell Counts (x10⁶) (PP population)		
N	22	20
Baseline mean	1.48	4.31
LS mean change from baseline (SE)	2.79 (2.71)	-1.69 (2.72)
LS mean difference versus placebo		-4.48
95% confidence interval versus placebo		(-11.1, 2.15)
Change from Baseline at Endpoint in Sputum Eosinophils (%) (PP population)		
N	20	19
Baseline mean	2.19	1.17
LS mean change from baseline (SE)	-0.32 (0.83)	1.31 (0.88)
LS mean difference versus placebo		1.63
95% confidence interval versus placebo		(-0.52, 3.77)
Change from Baseline at Endpoint in Sputum Lymphocytes (%) (PP population)		
N	20	19

Baseline mean	1.58	1.26
LS mean change from baseline (SE)	-0.82 (0.37)	-0.30 (0.40)
LS mean difference versus placebo		0.52
95% confidence interval versus placebo		(-0.44, 1.49)
Safety Results:		
	Placebo	Cilomilast
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s), n(%)	20 (59)	24 (77)
Back pain	0	4 (13)
Diarrhea	2 (6)	4 (13)
Dyspepsia	0	4 (13)
Infection viral	1 (3)	4 (13)
Nausea	1 (3)	4 (13)
Abdominal pain	1 (3)	3 (10)
Hypertension	0	3 (10)
Sinusitis	1 (3)	3 (10)
Upper respiratory tract infection	4 (12)	3 (10)
Injury	3 (9)	2 (6)
	Placebo	Cilomilast
Subjects with non-fatal SAEs, n (%)	0	1 (3) [0]
Cardiac failure	0	1 (3)
	Placebo	Cilomilast
Subjects with fatal SAEs, n (%)	0	0

Conclusion: The reduction in the percentage of neutrophils in samples of induced sputum in subjects treated with cilomilast compared with placebo was not statistically significant. In the placebo group 20 subjects reported adverse events with the most frequently reported being upper respiratory tract infection and diarrhea. In the cilomilast treated group 24 subjects reported adverse events. One serious adverse event was reported in the cilomilast group. There were no fatalities reported.

Publications: No publication

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