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Study No.: SB207499/076		
Title: A 12-week, Multicentre, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Anti-inflammatory Activity of SB207499 15 mg Twice Daily in Patients With Chronic Obstructive Pulmonary Disease (COPD)		
Rationale: This study was designed to evaluate the activity of cilomilast on cellular, biochemical and structural indices of inflammation in patients with COPD by cellular and biochemical analysis of induced sputum and by examination of bronchial biopsies.		
Phase: III		
Study Period: 15 September 1999 to 3 September 2000		
Study Design: A double-blind, placebo-controlled, parallel-group, multicentre study in subjects with COPD.		
Centres: Seven centres in Germany, Italy, the Netherlands, Spain and the United Kingdom		
Indication: COPD		
Treatment: Subjects received either cilomilast 15mg tablets or matching placebo. One tablet of study medication was taken in the morning and one in the evening, both doses after a meal.		
Objectives: Primary objectives were to examine, using analysis of induced sputum, the effects of administration of cilomilast 15mg twice daily compared with placebo on the inflammatory cell profile and inflammatory mediator concentrations in the airways of patients with COPD; using bronchoscopic bronchial biopsy, to examine effects on tissue histology and morphology in patients with COPD; and to further evaluate the clinical efficacy of cilomilast in terms of pulmonary function..		
Primary Efficacy Variable: Change from baseline at endpoint in neutrophils as a percentage of total cells in induced sputum.		
Secondary Outcome/Efficacy Variable(s): Sub-epithelial CD8+ lymphocytes per area tissue, sub-epithelial neutrophils (neutrophil elastase+) per area tissue, sub-epithelial macrophages (CD68+) per area tissue, epithelial neutrophils per area of epithelium, and trough FEV ₁		
Statistical Methods: A total of 60 subjects were planned for randomization. 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 patients 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 European Respiratory Society Consensus Statement; 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, post-salbutamol FEV ₁ at least 1.2L and between 30% and 70% of predicted.		
	Placebo	Cilomilast
Number of Subjects:		
Planned, N	30	30
Randomised, N	30	29
Completed, n (%)	28 (93)	25 (86)
Total Number Subjects Withdrawn, N (%)	2 (7)	4 (14)

Withdrawn due to Adverse Events n (%)	0	4 (14)
Withdrawn due to Lack of Efficacy n (%)	0	0
Withdrawn for other reasons n (%)	2 (7)	0
Demographics	Placebo	Cilomilast
N (ITT)	30	29
Females: Males	5:25	4:25
Mean Age, years (SD)	61.7 (7.6)	61.8 (11.1)
Caucasian, n (%)	29 (97)	29 (100)
Current smoker, n (%)	17 (57)	15 (52)
Primary Efficacy Results:		
	Placebo	Cilomilast
Change from Baseline at Endpoint in sputum neutrophil percentage (PP population)		
N	23	21
Baseline mean	76.9	73.1
LS mean change from baseline (SE)	-1.5 (4.0)	0.7 (4.1)
LS mean difference versus placebo		2.1
95% confidence interval versus placebo		(-8.9, 13.2)
p-value versus placebo		0.697
Secondary Outcome Variables:		
	Placebo	Cilomilast
Change from Baseline at Endpoint in Sub-epithelial CD8+ Lymphocytes/Area Tissue (PP population)		
N	21	16
Baseline mean	304.7	328.3
LS mean change from baseline (SE)	24.4 (55.8)	-132.4 (66.5)
LS mean difference versus placebo		-156.8
95% confidence interval versus placebo		(-316.8, 3.3)
Change from Baseline at Endpoint in Sub-epithelial Neutrophils (ne+)/Area Tissue (PP population)		
N	21	16
Baseline mean	53.4	57.7
LS mean change from baseline (SE)	4.4 (18.9)	-17.9 (22.5)
LS mean difference versus placebo		-22.3
95% confidence interval versus placebo		(-76.4, 31.8)
Change from Baseline at Endpoint in Sub-epithelial Macrophages (CD68+)/Area Tissue (PP population)		
N	20	16
Baseline mean	59.4	102.1
LS mean change from baseline (SE)	33.2 (17.8)	-42.8 (21.0)
LS mean difference versus placebo		-76.0
95% confidence interval versus placebo		(-126.6, -25.4)
Change from Baseline at Endpoint in Epithelial Neutrophils /Area of Epithelium (PP population)		
N	21	16
Baseline mean	7.3	4.3
LS mean change from baseline (SE)	-1.7 (2.6)	-0.0 (3.1)
LS mean difference versus placebo		1.7
95% confidence interval versus placebo		(-5.7, 9.1)
Change from Baseline at Endpoint in FEV₁ (L) (PP population)		
N	23	21

Baseline mean	1.53	1.63
LS mean change from baseline (SE)	-0.07 (0.04)	-0.05 (0.04)
LS mean difference versus placebo		0.02
95% confidence interval versus placebo		(-0.08, 0.12)
Safety Results:		
	Placebo	Cilomilast
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s), n(%)	20 (67)	22 (76)
Diarrhoea	4 (13)	6 (21)
Chronic obstructive airways disease exacerbated	4 (13)	5 (17)
Dyspepsia	1 (3)	5 (17)
Headache	1 (3)	5 (17)
Upper respiratory tract infection	1 (3)	4 (14)
Vomiting	0	4 (14)
Nausea	2 (7)	3 (10)
Abdominal pain	0	3 (10)
Coughing	3 (10)	2 (7)
Chest pain	1 (3)	2 (7)
Influenza-like symptoms	1 (3)	2 (7)
Somnolence	0	2 (7)
Dyspnoea	5 (17)	1(3)
Fatigue	2 (7)	1 (3)
Back pain	3 (10)	0
Rashf	2 (7)	0
	Placebo	Cilomilast
Subjects with non-fatal SAEs, n (%)	1 (3) [0]	2 (7) [0]
Angina pectoris aggravated	0	1 (3)
Chronic obstructive airways disease exacerbated	0	1 (3)
Myocardial infarction	0	1 (3)
Pancreatitis	1 (3)	0
	Placebo	Cilomilast
Subjects with fatal SAEs, n (%)	0	0

Conclusion: Cilomilast failed to show a statistically significant difference versus placebo in change from baseline at endpoint in sputum neutrophil percentage when administered at 15mg twice daily over a 12 week treatment period. In the placebo group, 20 subjects reported adverse events with the most frequently reported being dyspnoea, chronic obstructive airways disease exacerbated and diarrhoea. In the cilomilast treated group, 22 subjects reported adverse events with the most frequently reported being diarrhoea, chronic obstructive airways disease exacerbated, dyspepsia and headache. One subject in the placebo group and two subjects in the cilomilast group reported serious adverse events. There were no fatalities reported.

Publications: No publication

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