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Study No.: SB207499/181		
Title: A 13-week randomised, double-blind, parallel group, multicentre study to compare the bronchial anti-inflammatory activity of oral cilomilast (15 mg bd) with placebo twice daily in subjects with Chronic Obstructive Pulmonary Disease (COPD)		
Rationale: To explore further the potential for cilomilast to demonstrate anti-inflammatory effects in subjects with COPD.		
Phase: III		
Study Period: 10 March 2003 to 29 April 2004		
Study Design: A randomised, double-blind, parallel group, multi-centre study		
Centres: 27 centres in Australia, Canada, Finland, Ireland, Lithuania, Norway, Romania, Slovakia, Slovenia, South Africa, Sweden and the United Kingdom.		
Indication: COPD		
Treatment: Subjects received either cilomilast 15 mg or placebo. One tablet of study medication was taken twice daily, in the morning immediately after breakfast and in the evening immediately after a meal.		
Objectives: The primary objective of the study was to compare the numbers of inflammatory cells of distinct immuno and ultrastructural phenotypes after treatment with cilomilast 15 mg twice daily (bd) and with placebo bd in subjects with COPD, using bronchial biopsy.		
Primary Efficacy Variable: Change from baseline at endpoint in CD68+ (macrophages) and CD8+ (cytotoxic T-lymphocytes) per unit area of tissue.		
Secondary Efficacy Variable(s): Change from baseline in numbers of sub-epithelial cells per unit area in biopsy for neutrophil elastase positive (ne+) cells, CD4+, IL-8 mRNA positive cells, TNF-alpha mRNA positive cells.		
Statistical Methods: The planned sample size was 116 to obtain 86 subjects for the per-protocol analysis. The sample size had 90% power to detect a difference of 175 (assumed common standard deviation of 230) in CD8+ (cytotoxic T-lymphocytes) and a difference of 80 (assumed common standard deviation of 75) in CD68+ (macrophages) between cilomilast and placebo at a significance level of 2.5%. The primary analysis was based on an analysis of variance (ANOVA) model, controlling for centre effect and treatment. Primary comparisons were performed using Hochberg multiple comparison adjustment with an overall alpha level of 0.05. Efficacy analyses were based on the per-protocol population; subjects with violations of eligibility criteria were excluded entirely, and subjects with post-randomisation violations had only the data collected subsequent to the violation excluded.		
Study Population: Male or female between 40 and 80 years of age, inclusive; clinical diagnosis of COPD as defined by GOLD guidelines (2001) guidelines; smoking history of 10 or more pack years; pre-bronchodilator FEV ₁ to FVC ratio less than or equal to 0.7 at screening; post-bronchodilator FEV ₁ between 40% and 80% of predicted normal at screening; poor reversibility of airway obstruction (no more than 10% increase in FEV ₁ predicted normal or 200mL increase in FEV ₁ at screening)		
	Placebo	Cilomilast
Number of Subjects:		
Planned, N	58	58
Randomised, N	62	65
Completed, n (%)	56 (90)	57 (88)
Total Number Subjects Withdrawn, N (%)	6 (10)	8 (12)

Withdrawn due to Adverse Events n (%)	3 (5)	6 (9)
Withdrawn due to Lack of Efficacy n (%)	0	1 (2)
Withdrawn for other reasons n (%)	3 (5)	1 (2)
Demographics	Placebo	Cilomilast
N (ITT)	62	65
Females: Males	15:47	18:47
Mean Age, years (SD)	63.4 (9.1)	61.4 (8.4)
Caucasian, n (%)	60 (97)	62 (95)
Current smoker, n (%)	28 (45)	32 (49)
Primary Efficacy Results:		
	Placebo	Cilomilast
Change from Baseline in CD68+ (macrophages) per unit area of tissue (cells/mm²), Per-protocol Population		
N	49	54
Baseline mean	143.6	121.4
LS mean change from baseline (SE)	-50.0 (13.7)	-20.8 (12.2)
LS mean difference versus placebo		29.2
95% confidence interval versus placebo		(-5.0, 63.3)
p-value versus placebo		0.093
Change from Baseline in CD8+ (cytotoxic T-lymphocytes) per unit area of tissue (cells/mm²), Per-protocol Population		
N	49	54
Baseline mean	213.5	201.9
LS mean change from baseline (SE)	-69.8 (13.6)	-75.3 (12.0)
LS mean difference versus placebo		-5.5
95% confidence interval versus placebo		(-39.3, 28.2)
p-value versus placebo		0.744
Secondary Outcome Variables:		
Change from Baseline in sub-epithelial neutrophils (ne+) per unit area of tissue (cells/mm²), Per-protocol Population		
N	49	54
Baseline mean	46.9	38.0
LS mean change from baseline (SE)	-21.6 (6.5)	-2.2 (5.8)
LS mean difference versus placebo		19.4
95% confidence interval versus placebo		(3.3, 35.6)
Change from Baseline in sub-epithelial CD4+ lymphocytes per unit area of tissue (cells/mm²), Per-protocol Population		
N	49	54
Baseline mean	122.9	102.3
LS mean change from baseline (SE)	-21.6 (12.0)	-8.1 (10.6)
LS mean difference versus placebo		13.6
95% confidence interval versus placebo		(-16.2, 43.3)
Change from Baseline in sub-epithelial IL-8 mRNA+ cells per unit area of tissue (cells/mm²), Per-protocol Population		
N	49	54
Baseline mean	44.4	36.1
LS mean change from baseline (SE)	-24.8 (4.7)	-13.2 (4.2)

LS mean difference versus placebo		11.6
95% confidence interval versus placebo		(-0.1, 23.3)
Change from Baseline in sub-epithelial TNFα mRNA+ cells per unit area of tissue (cells/mm²), Per-protocol Population		
N	49	54
Baseline mean	70.3	63.5
LS mean change from baseline (SE)	-42.5 (5.7)	-34.9 (5.1)
LS mean difference versus placebo		7.6
95% confidence interval versus placebo		(-6.6, 21.8)
Change from Baseline in sub-epithelial CD45+ cells per unit area of tissue (cells/mm²), Per-protocol Population		
N	49	54
Baseline mean	393.1	396.1
LS mean change from baseline (SE)	-90.7 (18.8)	-99.4 (16.6)
LS mean difference versus placebo		-8.6
95% confidence interval versus placebo		(-55.2, 37.9)
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.		
	Placebo	Cilomilast
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s), n(%)	36 (58)	41 (63)
Headache	12 (19)	9 (14)
Nasopharyngitis	8 (13)	8 (12)
Nausea	4 (6)	6 (9)
Diarrhoea	2 (3)	5 (8)
Pharyngolaryngeal pain	2 (3)	5 (8)
Vomiting	1 (2)	5 (8)
Cough	2 (3)	3 (5)
Dyspepsia	0	3 (5)
Back pain	0	2 (3)
Dizziness	0	2 (3)
Gastritis	0	2 (3)
Loose stools	0	2 (3)
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 SAE(s), n(%)	1 (2) [0]	2 (3) [0]
Anxiety	0	1 (2)
Atrial flutter	0	1 (2)
Chronic obstructive airways disease exacerbated	1 (2)	0
	Placebo	Cilomilast
Subjects with fatal SAEs, n (%)	0	0

Conclusion: Cilomilast failed to show statistically significant effects on change from baseline compared with placebo for CD68+ cells and CD8+ cells when administered at 15mg twice daily over a 13 week treatment period. In the placebo group 36 subjects reported adverse events with the most frequently reported being headache and nasopharyngitis. In the cilomilast treated group 41 subjects reported adverse events with the most frequently reported being headache and

nasopharyngitis. One subject in the placebo group and two subjects in the cilomilast group reported serious adverse events. There were no fatalities reported.

Publications: No publications

Date updated: 14-Jul-2008