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Study No.: SB207499/180		
Title: An 18-week randomized, double-blind, placebo-controlled, multicenter study designed to compare treatment with cilomilast to that with placebo for changes in ventilatory mechanics and function (both at rest and during exercise), as well as related exertional dyspnea and exercise performance, in hyperinflated patients with stable COPD		
Rationale:		
Phase: III		
Study Period: 15 January 2003 to 01 April 2005		
Study Design: Randomized, double-blind, placebo-controlled, multicenter study		
Centres: 34 centres in the United States, Canada, and South America.		
Indication: COPD		
Treatment: Subjects received either cilomilast 15mg or matching 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: To compare treatment with cilomilast to that of placebo for changes in ventilatory mechanics and function (both at rest and during exercise), as well as related exertional dyspnea and exercise performance, in hyperinflated subjects with moderate and severe COPD.		
Primary Efficacy Variable: Change from baseline at endpoint in resting functional residual capacity (FRC).		
Secondary Efficacy Variables: The key secondary analyses of efficacy were the change from baseline at endpoint in Inspiratory capacity (IC) during exercise, exertional dyspnea as measured by the modified Borg scale during exercise and exercise endurance time.		
Statistical Methods: The planned sample size was 200 subjects to obtain 176 evaluable subjects. Based on a two-sided t-test at an alpha level of 0.05, the study had approximately 80% power to detect a 300mL difference in change from baseline at endpoint in FRC, assuming a standard deviation of 700mL. The primary measure was summarized and analysed using analysis of covariance (ANCOVA) adjusting for baseline value, investigator, inhaled corticosteroid use and treatment. Endpoint was defined as the last post-baseline measurement while on treatment. Secondary measures were analysed similarly. All analyses used the Intent-to-Treat (ITT) population, which consisted of all randomized subjects who received at least one dose of study drug.		
Study Population: Male or female at least 40 years of age; clinical diagnosis of COPD in accordance with ATS (1995) 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; baseline FEV ₁ <70% predicted normal; evidence of moderate to severe chronic dyspnea, defined by Baseline Dyspnea Index (BDI) focal score 7 or less at screening; evidence of hyperinflation, defined as FRC at least 140% of predicted FRC at screening; evidence of exercise limitation, defined as peak symptom limited VO ₂ < 75%; ability to complete a work rate of 20 watts during the incremental cycle exercise challenge test at screening		
	Placebo	Cilomilast
Number of Subjects:		
Planned, N	100	100
Randomised, N	102	97
Completed, n (%)	89 (87)	73 (75)
Total Number Subjects Withdrawn, N (%)	13 (13)	24 (25)

Withdrawn due to Adverse Events n (%)	6 (6)	9 (9)
Withdrawn due to Lack of Efficacy n (%)	0	0
Withdrawn for other reasons n (%)	7 (7)	15 (16)
Demographics	Placebo	Cilomilast
N (ITT)	102	97
Females: Males	24:78	30:67
Mean Age, years (SD)	64.7 (8.12)	63.7 (8.10)
Caucasian, n (%)	85 (83)	82 (85)
Current smoker, n (%)	45 (44)	44 (45)
Primary Efficacy Results:		
	Placebo	Cilomilast
Change from Baseline at Endpoint in FRC (mL)		
N	102	96
Baseline mean	5481	5706
LS mean change from baseline (SE)	-84 (87.7)	-212 (101.9)
LS mean difference versus placebo		-128
95% confidence interval versus placebo		(-341, 84)
p-value versus placebo		0.234
Secondary Outcome Variables:		
	Placebo	Cilomilast
Change from Baseline at Endpoint in Peak Exercise IC (L)		
N	86	71
Baseline mean (SE)	1.63	1.66
LS mean change from baseline (SE)	-0.08 (0.035)	-0.06 (0.043)
LS mean difference versus placebo		0.02
95% confidence interval versus placebo		(-0.07, 0.11)
Change from Baseline at Endpoint in Exertional Dyspnea (Borg scale)		
N	97	84
Baseline mean (SE)	5.7	5.8
LS mean change from baseline (SE)	0.0 (0.25)	-0.1 (0.29)
LS mean difference versus placebo		-0.2
95% confidence interval versus placebo		(-0.8, 0.4)
Change from Baseline in Exercise Endurance Time (sec)		
N	102	95
Baseline mean (SE)	426.0	414.0
LS mean change from baseline (SE)	-30.8 (30.36)	-108.0 (35.56)
LS mean difference versus placebo		-77.2
95% confidence interval versus placebo		(-152.6, -1.8)
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(%)	68 (67)	65 (67)
Headache	14 (14)	16 (16)
Nausea	2 (2)	11 (11)
Diarrhoea	3 (3)	9 (9)
Nasopharyngitis	8 (8)	7 (7)
Dyspepsia	1 (<1)	4 (4)

Vomiting	1 (<1)	4 (4)
Stomach discomfort	0	4 (4)
Chronic obstructive airways disease exacerbated	6 (6)	3 (3)
Cough	4 (4)	3 (3)
Upper respiratory tract infection	6 (6)	2 (2)
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(%)	7 (7) [0]	6 (6) [0]
Chronic obstructive airways disease exacerbated	6 (6)	3 (3)
Pneumonia	1 (<1)	1 (1)
Respiratory failure	2 (2)	0
Acute respiratory failure	0	1 (1)
Dyspnoea	0	1 (1)
Femur fracture	1 (<1)	0
Hypotension	0	1 (1)
Periorbital haematoma	0	1 (1)
Pyrexia	0	1 (1)
Rib fracture	0	1 (1)
Supraventricular tachycardia	0	1 (1)
White blood cell count increased	0	1 (1)
	Placebo	Cilomilast
Subjects with fatal SAEs, n (%)	0	0

Conclusion: The difference between cilomilast and placebo in FRC was not statistically significant. In the placebo group 68 subjects reported adverse events with the most frequently reported being headache and nasopharyngitis. In the cilomilast treated group 65 subjects reported adverse events with the most frequently reported being headache and nausea. Seven subjects in the placebo group reported serious adverse events and six subjects in the cilomilast group reported serious adverse events. There were no fatalities reported.

Publications: No publication

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