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<b>Study No.:</b> SB207499/111		
<b>Title:</b> A 12-week, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Investigate the Effect of Cilomilast (15 mg Twice Daily) on Trapped Gas Volume in Patients With Chronic Obstructive Pulmonary Disease		
<b>Rationale:</b> Air trapping that leads to hyperinflation is a common finding in subjects with COPD. This study investigated the effects of cilomilast on hyperinflation, exercise limitation and reductions in ventilatory capacity.		
<b>Phase:</b> III		
<b>Study Period:</b> 07 September 1999 to 30 August 2000		
<b>Study Design:</b> A randomized, double-blind, placebo-controlled, parallel group, multicenter study in subjects with COPD		
<b>Centres:</b> 32 centres in the United States, Canada and Australia.		
<b>Indication:</b> COPD		
<b>Treatment:</b> Subjects received tablets containing 15mg of cilomilast or matching placebo. One tablet was taken in the morning and one in the evening, after a meal.		
<b>Objectives:</b> To evaluate the efficacy of cilomilast versus placebo on hyperinflation (as assessed by the degree of gas trapping) in subjects with COPD, and to evaluate the efficacy on clinical endpoints that result from hyperinflation and gas trapping, including measures of exercise limitation and respiratory muscle strength.		
<b>Primary Efficacy Variable:</b> Change from baseline to endpoint in Volume of trapped gas (D), calculated as the difference of pre-albuterol plethysmography and single-breath helium dilution determinations of total lung capacity (TLC): $D = TLC_{\text{box}} - LC_{\text{He}}$ (where $TLC_{\text{box}} = TGV_{\text{FRC}} + IC$ ).		
<b>Secondary Efficacy Variables:</b> Lung volume measurements, including slow vital capacity (SVC) and residual volume (RV), exercise tolerance (six-minute walk test) and exertional dyspnea.		
<b>Statistical Methods:</b> The planned sample size was 150 subjects to obtain 110 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 assessment of treatment difference for the primary efficacy variable (volume of trapped gas) was based on an analysis of variance (ANOVA) model with factors of centre and treatment group. Secondary variables 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.		
<b>Study Population:</b> 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, and a cigarette-smoking history of at least 10 pack years. Additional inclusion criteria were pre-albuterol FEV <sub>1</sub> to FVC ratio of 0.7 or less, post-albuterol reversibility less than 15% and/or 200mL, residual volume (RV) from plethysmography at least 120% of predicted RV and post-albuterol FEV <sub>1</sub> between 30% and 70% of predicted normal.		
	<b>Placebo</b>	<b>Cilomilast</b>
Number of Subjects:		
Planned, N	75	75
Randomised, N	77	79
Completed, n (%)	63 (82)	64 (81)
Total Number Subjects Withdrawn, N (%)	14 (18)	15 (19)

Withdrawn due to Adverse Events n (%)	8 (10)	14 (18)
Withdrawn due to Lack of Efficacy n (%)	1 (1)	0
Withdrawn for other reasons n (%)	5 (7)	1 (1)
<b>Demographics</b>	<b>Placebo</b>	<b>Cilomilast</b>
N (ITT)	77	79
Females: Males	26:51	28:51
Mean Age, years (SD)	64.2 (8.9)	65.0 (8.3)
Caucasian, n (%)	71 (92)	75 (95)
Current smoker, n (%)	34 (44)	34 (43)
<b>Primary Efficacy Results:</b>		
	<b>Placebo</b>	<b>Cilomilast</b>
<b>Volume of Trapped Gas (L)</b>		
N	72	73
Baseline mean	1.60	1.69
LS mean change from baseline (SE)	0.05 (0.16)	-0.08 (0.16)
LS mean difference versus placebo		-0.14
95% confidence interval versus placebo		(-0.54, 0.26)
p-value versus placebo		0.494
<b>Secondary Outcome Variables:</b>		
	<b>Placebo</b>	<b>Cilomilast</b>
<b>Change from Baseline at Endpoint in Slow Vital Capacity (L)</b>		
N	72	73
Baseline mean (SE)	2.90	2.80
LS mean change from baseline (SE)	0.00 (0.05)	0.12 (0.05)
LS mean difference versus placebo		0.11
95% confidence interval versus placebo		(-0.01, 0.24)
<b>Change from Baseline at Endpoint in Helium Dilution Residual Volume (L)</b>		
N	72	73
Baseline mean (SE)	2.28	2.45
LS mean change from baseline (SE)	0.10 (0.14)	-0.15 (0.14)
LS mean difference versus placebo		-0.25
95% confidence interval versus placebo		(-0.60, 0.10)
<b>Change from Baseline at Endpoint in Body Plethysmography Residual Volume (L)</b>		
N	72	73
Baseline mean (SE)	3.87	4.13
LS mean change from baseline (SE)	0.16 (0.11)	-0.23 (0.10)
LS mean difference versus placebo		-0.39
95% confidence interval versus placebo		(-0.65, -0.12)
<b>Change from Baseline in Distance Walked (m), Six-minute Walk Test</b>		
N	69	73
Baseline mean (SE)	376.9	359.9
LS mean change from baseline (SE)	-3.7 (10.0)	16.1 (9.6)
LS mean difference versus placebo		19.7
95% confidence interval versus placebo		(-5.3, 44.7)
<b>Change from Baseline at Endpoint in Exertional Breathlessness (Borg scale)</b>		
N	69	73
Baseline mean (SE)	3.51	3.23

LS mean change from baseline (SE)	-0.03 (0.20)	0.03 (0.19)
LS mean difference versus placebo		0.07
95% confidence interval versus placebo		(-0.43, 0.56)
<b>Safety Results:</b> 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.		
	<b>Placebo</b>	<b>Cilomilast</b>
<b>Most Frequent Adverse Events – On-Therapy</b>	<b>n (%)</b>	<b>n (%)</b>
Subjects with any AE(s), n(%)	49 (64)	63 (80)
Chronic obstructive airways disease exacerbated	15 (19)	15 (19)
Diarrhoea	3 (4)	14 (18)
Nausea	4 (5)	13 (16)
Dyspepsia	2 (3)	10 (13)
Infection viral	3 (4)	8 (10)
Upper respiratory tract infection	5 (6)	8 (10)
Abdominal pain	0	6 (7)
Rhinitis	4 (5)	5 (6)
Gastroesophageal reflux	0	4 (5)
Myalgia	1 (1)	4 (5)
Sinusitis	3 (4)	4 (5)
<b>Serious Adverse Events - On-Therapy</b>		
<b>n (%) [n considered by the investigator to be related to study medication]</b>		
	<b>Placebo</b>	<b>Cilomilast</b>
	<b>n (%) [related]</b>	<b>n (%) [related]</b>
Subjects with any SAE(s), n(%)	2 (3) [0]	8 (10) [1]
Pulmonary carcinoma	1 (1)	1 (1)
Aneurysm	0	1 (1)
Chronic obstructive airways disease	0	1 (1)
Cerebrovascular disorder	0	1 (1)
Myalgia	0	1 (1)
Myocardial infarction	0	1 (1)
Pneumonia	1 (1)	0
Pneumothorax	0	1 (1)
Therapeutic response increased	0	1 (1) [1]
Vascular disorder	0	1 (1)
	<b>Placebo</b>	<b>Cilomilast</b>
Subjects with fatal SAEs, n (%)	0	2 (3) [0]
Cerebrovascular disorder	0	1 (1)
Myocardial infarction	0	1 (1)

**Conclusion:** There was no statistically significant difference between cilomilast and placebo for the primary efficacy endpoint. In the placebo group 49 subjects reported adverse events with the most frequently reported being chronic obstructive airways disease exacerbated and upper respiratory tract infection. In the cilomilast treated group 63 subjects reported adverse events with the most frequently reported being chronic obstructive airways disease exacerbated and diarrhoea. Two subjects in the placebo group reported serious adverse events and eight subjects in the cilomilast group reported serious adverse events. There were two fatalities reported in the cilomilast group.

**Publications:** No publication

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