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Study No.: SB207499/168		
Title: A Randomized, 12-week, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Safety and Tolerability of Cilomilast 15mg Twice Daily in Patients with Chronic Obstructive Pulmonary Disease (COPD)		
Rationale: This study was conducted to increase the population of subjects evaluated by Holter monitoring in cilomilast studies per regulatory requirement.		
Phase: III		
Study Period: 06 July 2001 to 23 August 2002		
Study Design: A randomized, double-blind, placebo-controlled, parallel-group multicentre study		
Centres: The study was conducted at 42 centres in the United States.		
Indication: COPD		
Treatment: Cilomilast 15mg or matching placebo tablets were provided. One tablet was taken in the morning and one in the evening, after a meal.		
Objectives: The primary objective was to further define the clinical safety and tolerability of cilomilast through assessments of 24-hour Holter electrocardiogram (ECG) monitoring.		
Primary Outcome Variable: No primary efficacy or safety analyses were defined. Descriptive statistics for change from baseline in mean heart rate via 24-hour Holter monitoring is reported.		
Secondary Outcome Variables: No secondary efficacy or safety analyses were defined. Descriptive statistics for change from baseline in minimum and maximum heart rate via 24-hour Holter monitoring is reported.		
Statistical Methods: The planned sample size was 300 subjects, randomized at 2:1 (cilomilast:placebo) to obtain 177 subjects with three evaluable Holters. Evaluation of safety data included all randomized subjects. Descriptive statistics for safety parameters were calculated. Endpoint was defined as the last on-therapy evaluation in the double-blind period.		
Study Population: Male and female subjects with COPD who had pre-albuterol FEV ₁ to FVC ratio of 0.7 or less and a post-albuterol FEV ₁ between 30% and 70% of predicted normal.		
	Placebo	Cilomilast
Number of Subjects:		
Planned, N	100	200
Randomised, N	103	203
Completed, n (%)	89 (86)	142 (70)
Total Number Subjects Withdrawn, N (%)	14 (14)	61 (30)
Withdrawn due to Adverse Events n (%)	8 (8)	36 (18)
Withdrawn due to Lack of Efficacy n (%)	1 (<1)	1 (<1)
Withdrawn for other reasons n (%)	5 (5)	24 (12)
Demographics	Placebo	Cilomilast
N (ITT)	103	203
Females: Males	37:66	60:143
Mean Age, years (SD)	64.3 (9.5)	65.0 (8.5)
Caucasian, n (%)	92 (89)	188 (93)
Current smoker, n (%)	41 (40)	97 (48)
Primary Outcome Variables:		
	Placebo	Cilomilast
Change from Baseline, Average Heart Rate via 24-hour Holter Monitoring (All Randomized Subjects)		
N	83	170
Baseline mean (SD)	79.5 (10.0)	80.1 (11.3)

Mean change from baseline at endpoint (SD)	-0.5 (4.9)	-0.0 (6.9)
Median (Min-Max)	0 (-16, 10)	-1 (-27, 28)
Secondary Outcome Variables:		
	Placebo	Cilomilast
Change from Baseline, Minimum Heart Rate via 24-hour Holter Monitoring (All Randomized Subjects)		
N	83	170
Baseline mean (SD)	57.2 (10.0)	58.6 (12.3)
Mean change from baseline at endpoint (SD)	0.3 (8.3)	0.7 (8.3)
Median (Min-Max)	0 (-48, 19)	1 (-24, 37)
Change from Baseline, Maximum Heart Rate via 24-hour Holter Monitoring (All Randomized Subjects)		
N	83	170
Baseline mean (SD)	120.6 (19.2)	117.9 (16.5)
Mean change from baseline at endpoint (SD)	-0.7 (13.2)	1.0 (14.6)
Median (Min-Max)	0 (-48, 42)	1 (-36, 51)
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. 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.		
	Placebo	Cilomilast
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s), n(%)	76 (74)	136 (67)
Chronic obstructive airways disease	18 (17)	28 (14)
Diarrhea	7 (7)	28 (14)
Nausea	2 (2)	28 (14)
Abdominal pain	6 (6)	19 (9)
Upper respiratory tract infection	18 (17)	18 (9)
Dyspepsia	6 (6)	15 (7)
Dizziness	2 (2)	9 (4)
Sinusitis	4 (4)	9 (4)
Vomiting	1 (<1)	9 (4)
Headache	4 (4)	8 (4)
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 non-fatal SAEs, n (%)	4 (4) [0]	7 (4) [0]
Chronic obstructive airways disease	1 (<1)	3 (2)
Bronchitis	0	1 (<1)
Chest pain	0	1 (<1)
Colitis	0	1 (<1)
Coronary artery disease	1 (<1)	0
Depression aggravated	0	1 (<1)
Gastritis	0	1 (<1)
Injury	1 (<1)	0
Syncope	1 (<1)	0
	n (%) [related]	n (%) [related]
Subjects with fatal SAEs, n (%)	0	0

Conclusion: Cardiac monitoring (Holter and ECG) showed no difference in average heart rate

change from baseline for cilomilast. In the placebo group 76 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 136 subjects reported adverse events with the most frequently reported being chronic obstructive airways disease exacerbated, diarrhoea, and nausea. Four subjects in the placebo group reported serious adverse events and seven subjects in the cilomilast group reported serious adverse events. There were no fatalities reported.

Publications: No publication

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