The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: SB207499/121
Title: A Randomized, 24-week, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of cilomilast (15mg BID) in Patients with Chronic Obstructive Pulmonary Disease (COPD).
Rationale: This study was designed to further evaluate the efficacy and safety of cilomilast versus placebo in subjects with COPD.
Phase: II/III
Study Period: 07 January 2003 to 30 November 2004
Study Design: A randomized, double-blind, placebo-controlled, multicentre study
Centres: 22 centres in China
Indication: COPD
Treatment: Double-blind study medication was dispensed as one tablet of either cilomilast (15mg) or matched placebo taken immediately after breakfast and after the evening meal.
Objectives: The primary objective of the study was to demonstrate the clinical efficacy of cilomilast (15mg BID) versus placebo in subjects with COPD by change from baseline to endpoint in forced expiratory volume in one second (FEV_1) at trough drug levels.
Primary Outcome/Efficacy Variable: The primary efficacy endpoint in this study was the change from baseline to Endpoint in trough pre-bronchodilator FEV_1.
Secondary Outcome/Efficacy Variables: Secondary efficacy endpoints included time to first Level 2 or Level 3 COPD exacerbation, defined as acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics, etc) or hospital outpatient visit (Level 2), or requires admission to the hospital for treatment (Level 3), change from baseline to endpoint in residual volume (RV) and functional residual capacity (FRC) performed by body box plethysmography, and change from baseline in total score of the St. George's Respiratory Questionnare (SGRQ).
Statistical Methods: The planned sample size was 900 subjects in a ratio of 2:1 for (cilomilast:placebo) to obtain 840 subjects with both baseline and at least one post-baseline FEV_1. The sample size calculation was based on the two-sided t-test to achieve an overall power of 90% at type I error of 0.05 for change from baseline averaged over 24 weeks in FEV_1. This study was designed to detect a 50mL difference in FEV_1 (assuming a standard deviation of 210mL). The primary endpoint was analyzed using an ANOVA model with fixed effects for treatment and centre. Baseline was also included in the model as a covariate. Least squares means along with 95% confidence intervals were calculated for each treatment group and for the treatment difference. The difference between treatment groups were assessed using t-tests on the least squares mean. Exacerbation-free survival at 24 weeks was estimated using the Kaplan-Meier product limit. Analyses were performed for the Intent-to-treat (ITT) Population, composed of all subjects who received at least one dose of double-blind medication. Descriptive statistics were provided for safety parameters. The Safety Population consisted of all subjects who had received at least one dose of double-blind medication.
Study Population: Male/female subjects 40-75 years old with a clinical diagnosis of COPD as defined by the American Throacic Society Guidelines, a smoking history of ≥ 10 pack-years, a documented history of COPD exacerbations each year for 3 years prior to screening and at least one in the last year that required oral corticosteroids and/or antibiotics, a pre-salbutamol $FEV_1/FVC < 0.7$ at screening, a post-salbutamol FEV_1 between 25% and 70% of the predicted normal value and a % predicted FRC of ≥120% for subjects at a subset of sites conducting plethysmography.

	Placebo	Cilomilast
Number of Subjects:		
Planned, N	300	600
Randomised, N	340	678
Completed, n (%)	305 (90)	554 (82)
Total Number Subjects Withdrawn, N (%)	35 (10)	124 (18)
Withdrawn due to Adverse Events n (%)	8 (2)	49 (7)
Withdrawn due to Lack of Efficacy n (%)	2 (<1)	11 (2)
Withdrawn for other reasons n (%)	25 (7)	64 (9)
Demographics	**Placebo**	**Cilomilast**
N (ITT)	340	678
Females: Males	29:311	47:631
Asian, n (%)	340 (100)	678 (100)
Mean Age, years (SD)	63.9 (7.5)	64.6 (7.8)
Current smoker, n (%)	77 (23)	160 (24)
Primary Efficacy Results:		
	Placebo	**Cilomilast**
Change from Baseline in FEV_1 (L) at Endpoint		
N	328	622
Baseline adjusted mean (SE)	1.146 (0.024)	1.164 (0.018)
LS mean change from baseline (SE)	-0.006 (0.010)	0.014 (0.007)
LS mean difference versus placebo		0.021
95% confidence interval versus placebo		(-0.003, 0.044)
p-value versus placebo		0.093
Note: Mean values adjusted for centre.		
Secondary Outcome Variable(s):		
	Placebo	**Cilomilast**
Level 2/Level 3 Exacerbation-free Survival at 24 Weeks		
N	340	678
Subjects exacerbation free, n (%)	267 (77.1)	535 (76.3)
95% confidence interval	(72.5, 81.7)	(72.9, 79.7)
Residual Volume (L) at Endpoint		
N	109	213
Baseline adjusted mean (SE)	4.108 (0.098)	4.116 (0.071)
LS mean change from baseline (SE)	-0.050 (0.071)	0.007 (0.051)
LS mean difference versus placebo		0.058
95% confidence interval versus placebo		(-0.109, 0.224)
Functional Residual Capacity (L) at Endpoint		
N	109	213
Baseline mean (SE)	5.196 (0.098)	5.154 (0.071)
LS mean change from baseline (SE)	-0.044 (0.058)	0.038 (0.042)
LS mean difference versus placebo		0.082
95% confidence interval versus placebo		(-0.054, 0.218)
SGRQ Total Score at Endpoint		
N	320	580
Baseline adjusted mean (SE)	44.7 (0.95)	45.0 (0.71)
LS mean change from baseline (SE)	-8.7 (0.82)	-9.0 (0.61)
LS mean difference versus placebo		-0.3
95% confidence interval versus placebo		(-2.3, 1.7)
Note: Mean values adjusted for centre.		
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(%)	245 (72)	518 (76)
Chronic obstructive airways disease exacerbated	178 (52)	297 (44)
Nasopharyngitis	63 (19)	129 (19)
Diarrhoea	20 (6)	94 (14)
Dyspepsia	4 (1)	40 (6)
Nausea	3 (<1)	39 (6)
Abdominal pain	10 (3)	36 (5)
Anorexia	2 (<1)	29 (4)
Flatulence	8 (2)	27 (4)
Abdominal discomfort	2 (<1)	26 (4)
Abdominal distension	0	21 (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(%)	10 (3) [1]	38 (6) [1]
Chronic obstructive airways disease exacerbated	4 (1)	21 (3) [1]
Appendicitis	0	3 (<1)
Atrial fibrillation	0	3 (<1)
Pneumonia	0	2 (<1)
Pneumothorax	0	2 (<1)
Hepatic neoplasm malignant	1 (<1)	1 (<1)
Cardiac failure acute	0	1 (<1)
Cerebral infarction	1 (<1)	0
Cerebrovascular accident	0	1 (<1)
Cholecystitis	0	1 (<1)
Coronary artery disease	0	1 (<1)
Death	1 (<1)	0
Gastritis	1 (<1) [1]	0
Gastroenteritis	1 (<1)	0
Hypertension	0	1 (<1)
Lacunar infarction	0	1 (<1)
Lung infection	0	1 (<1)
Pancreatitis acute	0	1 (<1)
Pelvic fracture	1 (<1)	0
Pulmonary bulla	0	1 (<1)
Retinal vein occlusion	0	1 (<1)
	Placebo	**Cilomilast**
	n (%) [related]	**n (%) [related]**
Subjects with fatal SAEs, n (%)	2 (<1) [0]	1 (<1) [0]
Death	1 (<1)	0
Hepatic neoplasm malignant	1 (<1)	0
Cardiac failure acute	0	1 (<1)

Conclusion: Cilomilast failed to show a statistically significant effect on FEV_1 compared with placebo when administered at 15mg twice daily over a 24-week treatment period. In the placebo group 245 subjects reported adverse events with the most frequently reported being chronic

obstructive airways disease and nasopharyngitis. In the cilomilast treated group 518 subjects reported adverse events with the most frequently reported being chronic obstructive airways disease and nasopharyngitis. Ten subjects in the placebo group and thirty-eight subjects in the cilomilast group reported serious adverse events. There were two fatalities reported in the placebo group and one fatality reported in the cilomilast group.
Publications: No publication

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