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Study No.: SB207499/157
Title: A Randomised, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Oral Cilomilast (15 mg bd) When Given as Maintenance Treatment for 12 Months to Subjects 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: III
Study Period: 01 November 2001 to 09 January 2004
Study Design: A randomised, double-blind, placebo-controlled, parallel-group study
Centres: 137 centres from 18 countries
Indication: COPD
Treatment: Subjects who fulfilled the randomisation criteria received either cilomilast 15mg or matching placebo bd. 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 assess the clinical efficacy of oral cilomilast 15mg bd as maintenance treatment for subjects with COPD. This was demonstrated over a 52-week treatment period in subjects with COPD who were poorly reversible to bronchodilators by assessment of reduction in the risk of the occurrence of exacerbations of COPD for subjects treated with cilomilast 15mg bd compared with placebo and assessment of superiority of pulmonary function data (FEV ₁) for subjects treated with cilomilast 15mg bd compared with placebo.
Primary Outcome/Efficacy Variable: There were two primary efficacy endpoints; mean change from baseline in trough pre-bronchodilator FEV ₁ averaged over 52 weeks, and the incidence rate of level II (moderate) and level III (severe) COPD exacerbations during the treatment period.
Secondary Outcome/Efficacy Variable(s): Secondary measures of efficacy were mean change from baseline in trough post-bronchodilator FEV ₁ averaged over 52 weeks, time to first level II (moderate) or level III (severe) COPD exacerbation, time to first COPD exacerbation (all levels), exacerbation incidence for all levels of COPD exacerbations, and quality of life as determined using the St. Georges Respiratory Questionnaire (SGRQ).
Statistical Methods: The planned sample size was 800 subjects to obtain 550 evaluable subjects. The sample size would have greater than 90% power at a significance level of 0.05 to detect a difference of 50mL in FEV ₁ in the change from baseline, assuming a standard deviation of 210mL, and a 30% reduction in exacerbation rate for cilomilast group compared with placebo group, assuming a Poisson distribution for the number of COPD exacerbations (moderate and/or severe) during the treatment period and an exacerbation incidence of 0.8 per patient per year for the placebo group. As both FEV ₁ and exacerbation incidence were required to be positive in this study no multiplicity adjustment was performed for the primary analyses. The primary assessment of FEV ₁ was based on a repeated measures model with fixed effects of treatment, time and country. A compound symmetric correlation structure was used. Least squares means and 95% confidence intervals were calculated for each treatment group and treatment difference. Differences between treatment groups were assessed using t-tests on the least squares means. The primary COPD exacerbation analysis used a maximum likelihood based analysis, assuming a Poisson distribution, with total duration on treatment as an offset variable. Analyses of FEV ₁ included the Intent-to-treat (ITT) Population, composed of all subjects who received at least one dose of double-blind medication and had a baseline and at least one on-therapy FEV ₁ assessment. Analysis of exacerbation data and safety analyses included all randomized subjects.
Study Population: Male or female between 40-80 years old; clinical diagnosis of COPD as

defined by GOLD guidelines (2000); smoking history of 10 or more pack years; pre-bronchodilator FEV ₁ to FVC ratio less than or equal to 0.7 at screening; poor reversibility of airway obstruction, defined by less than or equal to 10% of predicted normal or less than or equal to 200mL (or both) increase in FEV ₁ after administration of salbutamol 400mcg via MDI at screening; post-salbutamol FEV ₁ of between 30%-70% predicted normal at screening		
	Placebo	Cilomilast
Number of Subjects:		
Planned, N	400	400
Randomised, N	452	455
Completed, n (%)	331 (73)	288 (63)
Total Number Subjects Withdrawn, N (%)	121 (27)	167 (37)
Withdrawn due to Adverse Events n (%)	46 (10)	80 (18)
Withdrawn due to Lack of Efficacy n (%)	18 (4)	8 (2)
Withdrawn for other reasons n (%)	57 (13)	79 (17)
Demographics		
	Placebo	Cilomilast
N (ITT)	452	455
Females: Males	122:330	98:357
Mean Age, years (SD)	63.3 (8.9)	64.6 (8.7)
Caucasian, n (%)	433 (96)	436 (96)
Current smoker, n (%)	188 (42)	196 (43)
Primary Efficacy Results:		
	Placebo	Cilomilast
Change from Baseline in Pre-bronchodilator FEV₁ (L) Averaged Over 52 Weeks		
N	416	395
Baseline mean	1.42	1.34
LS mean change from baseline (SE)	-0.047 (0.009)	-0.006 (0.009)
LS mean difference versus placebo		0.041
95% confidence interval versus placebo		(0.019, 0.063)
p-value versus placebo		<0.001
Incidence Rate of Level 2/Level 3 COPD Exacerbations		
N	437	442
Per patient per year rate of incidence	0.448	0.483
Incidence density ratio (Cilomilast v placebo)		1.078
95% confidence interval, density ratio		(0.827, 1.405)
p-value versus placebo		0.580
Secondary Outcome Variable(s):		
	Placebo	Cilomilast
Change from Baseline in Post-bronchodilator FEV₁ (L) Averaged Over 52 Weeks		
N	411	390
Baseline mean (SE)	1.42	1.33
LS mean change from baseline (SE)	-0.002 (0.009)	0.032 (0.010)
LS mean difference versus placebo		0.034
95% confidence interval versus placebo		(0.011, 0.057)
Incidence Rate of All COPD Exacerbations		
N	437	442
Per patient per year rate of incidence	0.909	0.867
Incidence density ratio (Cilomilast v placebo)		0.954
95% confidence interval, density ratio		(0.775, 1.173)

Level 2/Level 3 Exacerbation-free Survival at 52 Weeks		
N	452	455
Subjects exacerbation free, n (%)	318 (69.6)	329 (68.4)
95% confidence interval	(65.0, 74.2)	(63.5, 73.3)
Exacerbation-free Survival at 52 Weeks		
N	452	455
Subjects exacerbation free, n (%)	240 (50.7)	263 (51.2)
95% confidence interval	(45.7, 55.7)	(46.0, 56.5)
Change from Baseline in SGRQ Averaged Over 52 Weeks		
N	369	347
Baseline mean (SE)	39.2 (0.99)	39.4 (1.02)
LS mean change from baseline (SE)	-1.49 (0.75)	-1.29 (0.80)
LS mean difference versus placebo		0.20
95% confidence interval versus placebo		(-1.70, 2.10)
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(%)	343 (76)	351 (77)
Exacerbation of COPD	209 (46)	191 (42)
Nausea	14 (3)	44 (10)
Nasopharyngitis	54 (12)	43 (9)
Headache	22 (5)	35 (8)
Diarrhoea	13 (3)	33 (7)
Vomiting	8 (2)	21 (5)
Anorexia	1 (<1)	18 (4)
Dyspepsia	6 (1)	18 (4)
Cough	11 (2)	14 (3)
Influenza	17 (4)	14 (3)
Abdominal pain upper	5 (1)	13 (3)
Dizziness	5 (1)	13 (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(%)	55 (12) [0]	53 (12) [5]
Chronic obstructive airways disease exacerbated	18 (4)	19 (4)
Atrial fibrillation	1 (<1)	3 (<1)
Atrial flutter	0	2 (<1)
Duodenal ulcer	0	2 (<1) [1]
Coronary artery disease	1 (<1)	2 (<1)
Myocardial ischaemia	2 (<1)	2 (<1)
Pneumonia	2 (<1)	2 (<1)
Myocardial infarction	1 (<1)	1 (<1)
Ileus	1 (<1)	1 (<1)
Lung neoplasm malignant	1 (<1)	1 (<1)
Syncope	2 (<1)	1 (<1)
Tachycardia	2 (<1)	0

Acute myocardial infarction	0	1 (<1)
Acute respiratory failure	0	1 (<1)
Alcohol poisoning	1 (<1)	0
Anaphylactic shock	1 (<1)	0
Angina pectoris	0	1 (<1)
Angina unstable	1 (<1)	0
Aortic aneurysm	0	1 (<1)
Aortic dissection	0	1 (<1)
Basal cell carcinoma	1 (<1)	0
Bladder cancer	0	1 (<1)
Blood in stool	0	1 (<1)
Bradyarrhythmia	0	1 (<1)
Bronchopneumonia	1 (<1)	0
Calculus bladder	1 (<1)	0
Cardiac failure	0	1 (<1)
Cardiac failure acute	0	1 (<1)
Carpal tunnel syndrome	1 (<1)	0
Cataract	1 (<1)	0
Cerebral thrombosis	1 (<1)	0
Cerebrovascular accident	1 (<1)	0
Chest pain	1 (<1)	0
Cholelithiasis	0	1 (<1)
Colonic haemorrhage	0	1 (<1)
Convulsion	0	1 (<1)
Depression	1 (<1)	0
Dermatitis medicamentosa	1 (<1)	0
Diarrhoea	0	1 (<1) [1]
Diverticulum	0	1 (<1)
Dyspnoea	0	1 (<1)
Encephalopathy	1 (<1)	0
Epididymitis	0	1 (<1)
Gastritis	0	1 (<1) [1]
Gastric cancer	1 (<1)	0
Gastroenteritis	1 (<1)	0
Headache	0	1 (<1)
Herpes zoster	1 (<1)	0
Hip fracture	1 (<1)	0
Hypersensitivity	1 (<1)	0
Inguinal hernia	0	1 (<1)
Intestinal obstruction	1 (<1)	0
Intestinal perforation	1 (<1)	0
Iron deficiency anaemia	1 (<1)	0
Lobar pneumonia	1 (<1)	0
Lumbar spinal stenosis	0	1 (<1)
Mania	1 (<1)	0
Metastasis	1 (<1)	0
Neuropathy	1 (<1)	0
Pancreatitis	0	1 (<1) [1]
Pneumonia bacterial	1 (<1)	0
Pneumothorax	1 (<1)	0
Prostate cancer	1 (<1)	0
Proteinuria	1 (<1)	0

Pulmonary fibrosis	1 (<1)	0
Reflux oesophagitis	0	1 (<1) [1]
Renal cell carcinoma stage unspecified	1 (<1)	0
Respiratory alkalosis	0	1 (<1)
Rib fracture	1 (<1)	0
Syncope vasovagal	1 (<1)	0
Thermal burn	1 (<1)	0
Thrombophlebitis	1 (<1)	0
Thyroid gland cancer	1 (<1)	0
Ventricular tachycardia	0	1 (<1) [1]
Viral labyrinthitis	1 (<1)	0
	Placebo	Cilomilast
Subjects with fatal SAEs, n (%)	8 (2) [0]	4 (<1) [0]
Myocardial infarction	2 (<1)	0
Acute myocardial infarction	0	1 (<1)
Aortic aneurysm rupture	1 (<1)	0
Cardiac failure acute	0	1 (<1)
Chronic obstructive airways disease exacerbated	1 (<1)	0
Coma	1 (<1)	0
Death	0	1 (<1)
Gastric cancer	1 (<1)	0
Prostate cancer	1 (<1)	0
Pulmonary embolism	1 (<1)	0
Renal insufficiency	1 (<1)	0
Respiratory failure	0	1 (<1)

Conclusion: Cilomilast was shown to have statistically significant effects on FEV₁ compared with placebo when administered at 15mg twice daily over a 52-week treatment period, but did not show statistically significant effects on exacerbation rates. In the placebo group 343 subjects reported adverse events with the most frequently reported being exacerbation of COPD and nasopharyngitis. In the cilomilast treated group 351 subjects reported adverse events with the most frequently reported being exacerbation of COPD and nausea. Fifty-five subjects in the placebo group and fifty-three subjects in the cilomilast group reported serious adverse events. Fatalities were reported for eight subjects in the placebo group and four subjects in the cilomilast group.

Publications: No publication

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