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Study No.: SB207499/040	
Title: A Multicentre, Open-label Extension Study to Evaluate the Safety, Tolerability and Efficacy of Oral SB-207499 (15 mg twice daily) in Patients with Chronic Obstructive Pulmonary Disease (COPD).	
Rationale	
Phase: III	
Study Period: 14 June 1999 to 19 September 2002	
Study Design: A multi-centre, open-label extension study	
Centres: 130 centres in 10 countries (Australia, South Africa, Belgium, Finland, France, Germany, Netherlands, Norway, Spain and United Kingdom)	
Indication: COPD	
Treatment: Study medication was to be taken orally, twice daily, in the morning after breakfast and in the evening after a meal.	
Objectives: To evaluate the long-term safety and tolerability of cilomilast administered at a dosage of 15mg twice daily.	
Primary Outcome Variable: Adverse experiences. No primary efficacy measure was defined.	
Secondary Outcome Variables: Not applicable.	
Statistical Methods: No formal power calculations were performed since this was an open-label study with the primary purpose of evaluating subject safety. Summaries include all subjects who had received at least one dose of study medication in study 040.	
Study Population: Males or females with COPD who successfully completed study 042 or 091 where subjects received cilomilast 15 mg bd or placebo for 24 weeks in study 042 and 26 weeks in study 091 without tolerability problems. The study excluded subjects from study 042 or 091 who had withdrawn; had a positive faecal occult blood test between Weeks 20 and 24; had a serious adverse event, a gastrointestinal adverse experience or a clinically significant laboratory abnormality which could have been attributed to study medication and still present at the end of those studies.	
	Cilomilast
Number of Subjects:	
Enrolled from Placebo:Cilomilast arms of 042 or 091	243:480
Enrolled into extension study, N	723
Completed, n (%)	427 (59)
Total Number Subjects Withdrawn, N (%)	296 (41)
Withdrawn due to Adverse Events n (%)	135 (19)
Withdrawn due to Lack of Efficacy n (%)	8 (1)
Withdrawn for other reasons n (%)	153 (21)
Demographics	
Cilomilast	
N (ITT)	723
Females: Males	114:609
Mean Age, years (SD)	62.9 (9.0)
Caucasian, n (%)	712 (98)
Current smoker, n (%)	314 (43)
Primary Efficacy Results: Adverse events are displayed in Safety Results.	
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.	
Extent of Exposure, n(%)	
At least 24 weeks	623 (86)
At least 52 weeks	568 (79)
At least 108 weeks	449 (62)
At least 136 weeks	142 (20)

	Cilomilast
Most Frequent Adverse Events – On-Therapy	n (%)
Subjects with any AE(s), n(%)	677 (94)
Chronic obstructive airways disease	494 (68)
Abdominal pain	118 (16)
Diarrhoea	102 (14)
Injury	95 (13)
Back pain	82 (11)
Headache	80 (11)
Rhinitis	77 (11)
Upper respiratory tract infection	73 (10)
Nausea	71 (10)
Dyspepsia	67 (9)
Serious Adverse Events - On-Therapy	
n (%) [n considered by the investigator to be related to study medication]	
	Cilomilast
	n (%) [related]
Subjects with any SAEs, n (%)	203 (28) [6]
Chronic obstructive airways disease	67 (9)
Pneumonia (including lobar pneumonia)	19 (3)
Injury	17 (2)
Pulmonary carcinoma	11 (2)
Angina pectoris	8 (1)
Chest pain	8 (1)
Neoplasm NOS	8 (1)
Respiratory disorder	6 (<1)
Cataract	5 (<1)
Respiratory insufficiency	5 (<1)
Aneurysm	4 (<1)
Carcinoma	4 (<1)
Herpes zoster	4 (<1)
Intestinal obstruction	4 (<1)
Myocardial infarction	4 (<1)
Urinary retention	4 (<1)
Abdominal pain	3 (<1) [2]
Cardiac arrest	3 (<1)
Cellulitis	3 (<1)
Cerebrovascular disorder	3 (<1)
Diverticulitis	3 (<1)
Fibrillation atrial	3 (<1) [1]
Gastrointestinal disorder NOS	3 (<1)
Gastrointestinal haemorrhage	3 (<1) [2]
Hyperthyroidism	3 (<1)
Sepsis	3 (<1)
Adenocarcinoma NOS	2 (<1)
Angina pectoris aggravated	2 (<1)
Arrhythmia atrial	2 (<1)
Arthropathy	2 (<1)
Asthenia	2 (<1)
Bladder carcinoma	2 (<1)
Bronchitis	2 (<1)
Cardiac failure	2 (<1)

Cholecystitis	2 (<1)
Cholelithiasis	2 (<1)
Convulsions	2 (<1)
Haemorrhoids	2 (<1)
Neoplasm malignant	2 (<1)
Neuralgia	2 (<1)
Pancreatitis	2 (<1)
Pyelonephritis	2 (<1)
Renal failure acute	2 (<1)
Syncope	2 (<1)
Therapeutic response increased	(<1)
Urinary tract infection	2 (<1)
Weight decrease	2 (<1)
Arthritis rheumatoid aggravated	1 (<1)
Arthrosis	1 (<1)
Basal cell carcinoma	1 (<1)
Bone disorder	1 (<1)
Bursitis	1 (<1)
Coma	1 (<1)
Colon carcinoma	1 (<1)
Depression	1 (<1)
Dermatitis	1 (<1)
Diarrhoea	1 (<1) [1]
Dizziness	1 (<1)
Dysphagia	1 (<1)
Epistaxis	1 (<1)
Fibrillation ventricular	1 (<1)
Gastric carcinoma	1 (<1)
Gastroenteritis	1 (<1)
Gastrointestinal neoplasm malignant	1 (<1) [1]
Goitre	1 (<1)
Hematemesis	1 (<1)
Hematuria	1 (<1)
Hepatic cirrhosis	1 (<1)
Hypertension pulmonary	1 (<1)
Infection	1 (<1)
Laryngitis	1 (<1)
Leukocytosis	1 (<1)
Lymphoma malignant	1 (<1)
Malaise	1 (<1)
Myalgia	1 (<1)
Myocardial ischemia	1 (<1)
Nasal polyp	1 (<1)
Nausea	1 (<1)
Neuropathy	1 (<1)
Orchitis	1 (<1)
Osteonecrosis	1 (<1)
Otitis externa	1 (<1)
Pain	1 (<1)
Palpitation	1 (<1)
Pelvic inflammation	1 (<1)
Peritonitis	1 (<1)

Pleural effusion	1 (<1)
Pleurisy	1 (<1)
Pneumothorax	1 (<1)
Renal calculus	1 (<1)
Renal function abnormal	1 (<1)
Renal pain	1 (<1)
Retinal detachment	1 (<1)
Sinusitis	1 (<1)
Skin disorder	1 (<1)
Suicide attempt	1 (<1)
Tendon disorder	1 (<1)
Thrombophlebitis deep	1 (<1)
Thrombosis retinal artery	1 (<1)
Thrombosis coronary	1 (<1)
Vertigo	1 (<1)
Vomiting	1 (<1) [1]
	Cilomilast
	n (%) [related]
Subjects with fatal SAEs, n (%)	23 (3)
Chronic obstructive airways disease	5 (<1)
Cardiac arrest	4 (<1)
Pneumonia	4 (<1)
Pulmonary carcinoma	3 (<1)
Neoplasm malignant	2 (<1)
Myocardial infarction	1 (<1)
Cardiac failure	1 (<1)
Circulatory failure	1 (<1)
Neoplasm NOS	1 (<1)
Respiratory insufficiency	1 (<1)
Suicide attempt	1 (<1)

Conclusion: Six hundred seventy-seven subjects reported adverse events with the most frequently reported being chronic obstructive airways disease and abdominal pain. Two hundred three subjects reported serious adverse events. There were twenty fatalities reported.

Publications: No publication

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