

4. OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

- The cilomilast clinical development program included 66 studies, 12 of which were conducted in patients with COPD.
- Two North American (studies 039 and 156) and two European (studies 042 and 091) pivotal, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies evaluated the use of cilomilast 15mg BID for 24-weeks in patients with COPD.
- Six of the twelve COPD studies were placebo-controlled supporting studies, and two were open-label, long-term extension studies.
- Overall, a total of 4093 patients were randomized in the Phase II and III controlled clinical studies, with 2586 receiving cilomilast and 1507 receiving placebo. In the long-term extension studies safety was evaluated in over 1000 patients for up to three years.

4.1. Summary of Studies

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Table 1 lists the 12 Phase II and Phase III studies conducted in patients with COPD and provides a brief overview of study characteristics.

Table 1 Studies in the Cilomilast Phase II and Phase III clinical development program

Study Number	Duration	Treatment Groups	Dose	Location	Patients Randomized	
					PLA	CIL
Pivotal Efficacy Studies						
039	24 weeks	CIL, PLA	15mg	NA	216	431
156	24 weeks	CIL, PLA	15mg	NA	407	418
042	24 weeks	CIL, PLA	15mg	EU	226	474
091	24 weeks	CIL, PLA	15mg	EU	242	469
Supporting Studies						
Cardiovascular Safety Study						
168	12 weeks	CIL, PLA	15mg	US	94	188
Dose-Ranging Studies						
032	6 weeks	CIL, PLA	5, 10, 15mg	EU	106	318
038	4 weeks	CIL, PLA	2.5, 5mg	NA	75	149
Mechanism of Action Studies						
076	12 weeks	CIL, PLA	15mg	EU	30	29
110	12 weeks	CIL, PLA	15mg	NA	34	31
111	12 weeks	CIL, PLA	15mg	NA	77	79
Long Term Open-Label Extension Studies						
040	Long term	CIL	15mg	EU	n/a	714
041	Long term	CIL	15mg	NA	n/a	355

CIL = cilomilast, PLA = placebo

4.2. Description of Phase II and Phase III Studies

The four 24-week efficacy studies (039, 156, 042, and 091) utilized a double-blind, randomized, placebo-controlled design. Studies 039 and 156 were conducted in North America and studies 042 and 091 were conducted predominately in Europe. Efficacy data from the 24-week studies are presented by each individual study and by pooled North American (NA) studies (039 and 156), pooled European (EU) studies (042 and 091) and by all pooled 24-week studies (039, 156, 042 and 091). The four studies were pooled to estimate the magnitude of effect more accurately. Because of the differences between NA and EU studies for some variables, NA and EU studies were pooled separately as well. Section 5 and Section 6 presents the study design, study population, efficacy and safety results for the pivotal studies.

There were six supporting studies that also utilized a double-blind, randomized, placebo-controlled design. The supporting studies included two Phase II dose-ranging studies (032 and 038), one cardiovascular safety study (168), and three mechanism of action studies (076, 110 and 111).

The Phase II dose ranging studies 032 and 038 were of 6 weeks and 4 weeks duration, respectively. Only data from study 032, which provided the dose rationale for the use of cilomilast 15mg BID in the Phase III pivotal efficacy studies, are presented. The dose rationale for the phase III pivotal studies is discussed in Section 5.1.

The Phase III cardiovascular safety study 168 was 12 weeks in duration and was the first study in the clinical development program to evaluate both reversible and poorly reversible patients with COPD. Section 7.2 presents the study design, study population, efficacy and safety results for study 168.

The Phase III mechanism of action studies, 076, 110 and 111 were 12-weeks in duration. Studies 076 and 110 evaluated the effects of cilomilast on inflammatory cell profile and inflammatory cell mediator concentration in the airways of patients with COPD using induced sputum and bronchial biopsy. Results from studies 076 and 110 are briefly discussed in Section 1.2.1. Study 111 evaluated the effect of cilomilast on static lung volumes. Section 7.3 presents the study design, study population and efficacy results for study 111.

Two Phase III open-label extension studies (040 and 041) evaluated the long-term safety and efficacy of cilomilast. Patients completing EU studies 042 or 091 according to the protocol were eligible for entry into the open label extension study 040, and patients completing NA study 039 were eligible for entry into open-label extension study 041. NA study 156 was conducted at a later time and patients were not eligible to enter the open-label extension study 041. Section 7.1 presents the study design, study population, efficacy and safety results for the open-label extension studies.