



# Pirfenidone in idiopathic pulmonary fibrosis

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**ABSTRACT:** Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease without proven effective therapy.

A multicentre, double-blind, placebo-controlled, randomised phase III clinical trial was conducted in Japanese patients with well-defined IPF to determine the efficacy and safety of pirfenidone, a novel antifibrotic oral agent, over 52 weeks. Of 275 patients randomised (high-dose, 1,800 mg·day<sup>-1</sup>; low-dose, 1,200 mg·day<sup>-1</sup>; or placebo groups in the ratio 2:1:2), 267 patients were evaluated for the efficacy of pirfenidone. Prior to unblinding, the primary end-point was revised; the change in vital capacity (VC) was assessed at week 52. Secondary end-points included the progression-free survival (PFS) time.

Significant differences were observed in VC decline (primary end-point) between the placebo group (-0.16 L) and the high-dose group (-0.09 L) ( $p=0.0416$ ); differences between the two groups ( $p=0.0280$ ) were also observed in the PFS (the secondary end-point). Although photosensitivity, a well-established side-effect of pirfenidone, was the major adverse event in this study, it was mild in severity in most of the patients.

Pirfenidone was relatively well tolerated in patients with IPF. Treatment with pirfenidone may decrease the rate of decline in VC and may increase the PFS time over 52 weeks. Additional studies are needed to confirm these findings.

**KEYWORDS:** Idiopathic pulmonary fibrosis, pirfenidone, progression-free survival time, vital capacity

Idiopathic pulmonary fibrosis (IPF) is a devastating, progressive fibrotic lung disease with a median survival of 3–5 yrs without proven effective therapy [1, 2]. Recent studies have suggested that IPF develops from chronic epithelial cell injury and aberrant activation of progressive fibrosis [3, 4]. Therefore, the therapeutic strategy against IPF has shifted from corticosteroids and/or immunosuppressants to antifibrotic agents, as reported in recent clinical trials [5, 6].

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone; Shionogi & Co., Osaka, Japan; MARNAC, Dallas, TX, USA) [7–9] is a promising agent with therapeutic potential for IPF that has combined anti-inflammatory, antioxidant and antifibrotic effects in experimental models of pulmonary fibrosis [10–14]. Following an open-label phase II pioneer study [7] and an open-label 1-yr study in Japan [9], a double-blind, placebo-controlled clinical trial of pirfenidone in Japanese patients with IPF demonstrated a lesser decline of vital capacity (VC) in patients receiving pirfenidone for

9 months [15]. The trial was prematurely terminated by the independent Data and Safety Monitoring Board (DSMB) because of a higher incidence of acute exacerbations in the placebo group than the pirfenidone group. These encouraging results, prompted us to undertake a phase III 1-yr clinical study to examine the therapeutic effects of pirfenidone on lung functional deterioration and disease progression in patients with IPF.

## MATERIALS AND METHODS

### Study subjects

The diagnosis of IPF was in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) Consensus statement [16] and the fourth version of the clinical diagnostic criteria guidelines for idiopathic interstitial pneumonia in Japan [17]. High-resolution computed tomography (HRCT) scans of the chest were reviewed by expert chest radiologists prior to randomisation; two out of six expert radiologists independently evaluated the HRCT images to agree and determine whether the pattern of usual interstitial pneumonia (UIP) was present or not in accordance with the predetermined protocol (see online supplementary material). In cases

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