# Trial of a preferential phosphodiesterase 4B inhibitor for idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive pulmonary disease characterised by a usual interstitial pneumonia pattern on high-resolution computed tomography (CT) of the chest.[1] A diagnosis of IPF is associated with considerable morbidity and mortality and identification and management of the disease remains a key pillar in modern pulmonary medicine. There are currently only two approved agents for use in IPF; the anti-fibrotic drugs nintedanib and pirfenidone. Both have been shown to slow disease progression in IPF but there remains a need for further drug treatments as our understanding of the disease process continues to grow.

A recent phase 2, double-blind, placebo-controlled trial conducted by Richeldi *et al.*[2] investigated the efficacy and safety of BI 1015550, an oral preferential inhibitor of phosphodiesterase 4B (PDE4). PDE4 inhibition is associated with both anti-inflammatory and antifibrotic properties, which are central to retarding disease progression in IPF. The study, conducted in 22 countries, identified 147 patients. Eligibility criteria included age ≥40 years with guideline-based IPF diagnosis, forced vital capacity (FVC) of ≥45% predicted and diffusion capacity of carbon monoxide (DLCO-corrected for haemoglobin) of between 25% and 80%. Of note, there were 2 arms in the treatment group, one group with background antifibrotic use and one without. The primary end point was a change from baseline standardised FVC at 12 weeks.

The primary endpoint was analysed separately based on background use or non-use of an antifibrotic agent. Overall, in patients without antifibrotic use, the median change in FVC was 5.7 ml (95% credible interval (CI) −39.1 - 50.5) in the treatment group and −81.7 ml (95% CI −133.5 - −44.8) in the placebo group. Among patients with background antifibrotic use, the median change in FVC for the treatment group was 2.7 ml (95% CI −32.8 - 38.2) and -59.2 ml (95% CI −111.8 - −17.9) in the placebo group. Thus, treatment with BI 1015550, either alone or with background antifibrotic use prevented a further decrease in FVC over a 12-week period. The safety profile of the drug appeared to be acceptable although gastrointestinal side effects were observed (typically seen and overlapping with antifibrotic use). Given the nature of a phase-2 trial, limitations were noted including the 12-week duration and inability to include other clinically-important events, such as exacerbations or deaths. Furthermore, pertinent to our setting, no black patients were included. An important takeaway from such a trial, is that in a disease entity typically associated with poor outcomes and limited drug therapeutics, there remain avenues for opportunity as our knowledge surrounding the pathophysiological basis of IPF continues to expand, providing hope where previously, there was little.

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