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REGULATORY WATCH

Surprise setback for lung fibrosis drug highlights trial challenges

Following mixed results from two Phase III trials, the US FDA turned down InterMune's application for the use of its drug pirfenidone in the treatment of idiopathic pulmonary fibrosis (IPF) in May, despite the recommendation of an advisory committee to grant approval.

IPF is a fatal disease that is characterized by progressive scarring of the lungs and has a median survival time of ~3 years. In 2008, pirfenidone was granted marketing approval in Japan for the treatment of IPF (see *Nature Rev. Drug Discov.* **7**, 966–967; 2008), based on the results of a Phase III trial conducted in that country.

However, in the United States and Europe, treatment options are currently limited to corticosteroids, immunosuppressants and antioxidants, often in combination, which slow but do not arrest disease progression (see *Nature Rev. Drug Discov.* **9**, 129–140; 2010). If approved, pirfenidone would have been the first treatment in the United States specifically for IPF. Following the FDA's decision, InterMune's stock price fell by approximately 80%, representing a US$2 billion loss.

The two pivotal trials that formed the basis of the application to the FDA, known as CAPACITY 1 and CAPACITY 2, involved 344 and 435 patients, respectively, with participants randomized to receive pirfenidone or placebo. In both trials, the drug was generally well tolerated, but the primary end point of an improvement in forced vital capacity (FVC) — a measure of lung function — was met only in CAPACITY 2. Although two positive pivotal trials are typically required for a drug to be approved, an FDA advisory committee nevertheless recommended that pirfenidone receive approval, presumably owing to the lack of effective treatment options for IPF. However, in their complete response letter to InterMune's new drug application, the FDA have requested a further set of trial data supporting pirfenidone's efficacy.

Ron du Bois, Imperial College, London, UK, and co-chair of the CAPACITY trials steering committee, explains the problems that are inherent to clinical trials of IPF drugs: "The key challenge in developing a drug for IPF is to convince clinicians and regulators that the outcome measures that are used to assess efficacy are clinically meaningful. This poses problems in a disease in which the predominant pathology at any one time — fixed fibrosis — means that the best outcome that might be achieved is disease stability." William J. Calhoun, Chair of the FDA advisory committee, adds that "because the rate of progression varies from patient to patient, the variance in any given efficacy metric is high, which generally translates into a prolonged study period and/or large numbers of patients."

Both du Bois and Calhoun suggest that survival could be an important end point to consider in future trials, although this would require long follow-up times. However, "there is accumulating evidence for the use of other indicators of progression-free survival, particularly now that even small changes in physiological indices such as FVC and the distance walked in 6 minutes have been shown to be associated with an increased risk of mortality," notes du Bois. Overall, "studies with longer follow-up times, focused on outcomes that are important to patients, will be most informative," concludes Calhoun.