

## Tralokinumab Reduced Acute Exacerbations in a Phase 2 Study of Severe Asthma

Written by Mary Mosley

Tralokinumab, a human immunoglobulin-G4 monoclonal antibody, potently and specifically neutralizes interleukin (IL)-13, a pleiotropic cytokine thought to be a central mediator of asthma [Mitchell J et al. *Curr Opin Investig Drugs* 2010]. Christopher E. Brightling, MBBS, University of Leicester, Leicester, United Kingdom, presented the overall results from A Phase 2b, Randomized, Double-Blind Study to Evaluate the Efficacy of Tralokinumab in Adults With Asthma [NCT01402986; Brightling CE et al. *Am J Crit Care Med* 2014]. In brief, the study showed that acute exacerbation rates (AERs) were reduced with the every-2-week (Q2W), but not the every-4-week (Q4W), tralokinumab dosing regimen compared with placebo and that tralokinumab was well tolerated and safe, with similar rates of adverse events in all groups.

Eligible patients at screening had severe asthma with forced expiratory volume in 1 second (FEV<sub>1</sub>) reversibility of  $\geq 12\%$  and  $\geq 200$  mL within 3 years of screening and  $\geq 2$  exacerbations in the prior year. Following a 5-week run-in period, subjects with FEV<sub>1</sub> of 40% to 80% predicted or Asthma Control Questionnaire 6 (ACQ-6) scores  $\geq 1.5$  were randomly assigned to receive subcutaneous tralokinumab 300 mg every 2 weeks for 52 weeks (Q2W group; n=150) or every 4 weeks for 12 weeks and then every 4 weeks to Week 48 (Q4W group; n=151) or placebo (n=151). Subjects received fluticasone 500  $\mu$ g and salmeterol 50  $\mu$ g or equivalent and were continued on prestudy control medications. The primary end point was the AER over 52 weeks, with secondary end points of FEV<sub>1</sub>, ACQ-6 scores, and safety.

The mean age of the study patients was 50 years, 65% were women, 56% were Caucasian, and 34% were Asian. The average baseline FEV<sub>1</sub> was 68.6%.

The primary efficacy endpoint of AER, defined as the use or increase in dose of systemic corticosteroids for  $\geq 3$  consecutive days for asthma symptoms, at 52 weeks was not significantly reduced in either tralokinumab dosing regimen (Q2W, 7%; 95% CI, -30% to 33% [p=0.67]; Q4W, -2%; 95% CI, -46% to 29% [p=0.91]) in the intention-to-treat analysis.

The secondary end point of percentage change in FEV<sub>1</sub> increased significantly in the Q2W group (7.10%; 95% CI, 2.35% to 11.84%; p=0.003) but not the Q4W group (1.57%; 95% CI, -3.22% to 6.35%; p=0.52). There were trends for improvements in measures of health status, measured

by the ACQ-6 and Asthma Quality of Life Questionnaire (AQLQ) in the overall study.

Investigation of biomarkers in predefined subgroups revealed a trend toward a reduction in AER in patients with FEV<sub>1</sub> reversibility and elevated levels of periostin or dipeptidyl peptidase-4 (DPP-4) treated with Q2W tralokinumab compared with placebo. In the Q2W group, there were greater improvements in ACQ-6 and AQLQ scores in the patients with FEV<sub>1</sub> reversibility and high levels of periostin and DPP-4.

The frequency of treatment-emergent serious adverse events or adverse events was similar within the safety population (tralokinumab Q2W, 89.3%; tralokinumab Q4W, 84.8%; placebo, 84.8%).

Although there was not an overall reduction in AER in either tralokinumab dosing regimen compared with placebo, the trends toward improvements in AER in the predefined subgroup analysis in subjects with airway reversibility and high levels of periostin or DPP-4 are hypothesis generating and suggest populations that may benefit from IL-13 blockade in future studies.

## Phase 3 Trial Confirms Benefits of Pirfenidone for IPF

Written by Brian Hoyle

The Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis trial [ASCEND; King TE et al. *N Engl J Med* 2014] was a Phase 3, multinational, double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis (IPF). The findings were presented by Talmadge E. King, Jr, MD, University of California, San Francisco, San Francisco, California, USA.

IPF is a chronic, progressive, and irreversible lung disease characterized by pulmonary scarring that ultimately leads to pulmonary dysfunction and death. The prognosis is poor, with a median survival time from diagnosis of 2 to 5 years. Two of 3 prior Phase 3 studies with pirfenidone demonstrated a reduction in lung deterioration and progression-free survival (PFS) [Taniguchi H et al. *Eur Respir J* 2010; Noble PW et al. *Lancet* 2011]. On the basis of the inconsistent Phase 3 data, it was recommended by US regulatory authorities that the ASCEND trial be undertaken.

In the ASCEND trial, 555 eligible patients with IPF (summarized in Table 1) were randomized 1:1 to receive oral pirfenidone (2403 mg/day; n=278) or placebo (n=277) for 52 weeks. Clinical follow-up included assessments at Day 1 and Weeks 13, 26, 39, and 52 on therapy as well as 28 days after the last dose of study drug. The primary end point was the change in forced



## CLINICAL TRIAL HIGHLIGHTS

vital capacity (FVC;  $\geq 10\%$  predicted) or death at Week 52. Secondary end points were change in 6-minute walk distance (6MWD) at Week 52, PFS (time to first occurrence of death, confirmed  $\geq 10\%$  decline in FVC, or confirmed  $\geq 50\text{-m}$  decline in 6MWD), dyspnea, all-cause mortality, and treatment-related mortality.

Table 1. Eligibility Criteria

Age, 40 to 80 years
Diagnosis of IPF on the basis of high-resolution computed tomography
FVC $\geq 50\%$ and $\leq 90\%$ of predicted
Carbon monoxide diffusing capacity $\geq 30\%$ and $\leq 90\%$ of predicted
FEV <sub>1</sub> /FVC ratio $\geq 0.80$

FEV<sub>1</sub>=forced expiratory volume in 1 second; FVC=forced vital capacity; IPF=idiopathic pulmonary fibrosis.

Baseline characteristics were well balanced between treatment groups, with a median age of 68 years, median FVC of 68% predicted, and 6MWDs ranging from 415 to 421 meters. A total of 461 patients (94%) completed the study (pirfenidone, n=261 [93.9%]; placebo, n=261 [94.2%]), and 55 patients (19.8%) in the pirfenidone group and 39 (14.1%) in the placebo group prematurely discontinued study treatment.

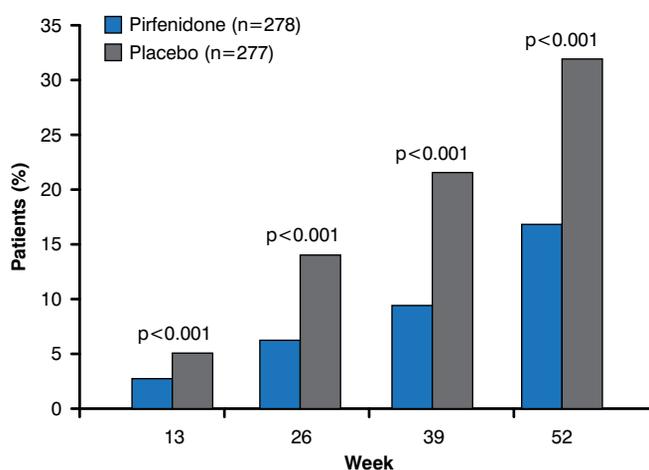
By Week 52, the primary end point, decline in FVC or death, was significantly reduced in the pirfenidone group by 47.9% compared with the placebo group (46 patients [16.5%] vs 88 patients [31.8%],  $p < 0.001$ ; Figure 1). By Week 52, there was a slower decline in FVC (relative difference of 45.1%,  $p < 0.001$ ), fewer subjects with decreased 6MWDs or death ( $p = 0.04$ ), and improved progression-free survival (HR, 0.57; 95% CI, 0.43–0.77;  $p = 0.0001$ ). Dyspnea scores were not significantly improved. Pirfenidone was associated with fewer deaths from any cause (11 [4.0%] vs 20 [7.2%],  $p = 0.01$ ) and death from IPF (3 [1.1%] vs 7 [2.5%],  $p = 0.23$ ); however, the study was not powered for this end point. A prespecified analysis with pooled data from the ASCEND and 2 Phase 3 CAPACITY trials found a 48% reduction in the risk for all-cause mortality in the pirfenidone group compared with the placebo group (HR, 0.52; log rank  $p = 0.0107$ ).

Pirfenidone was associated with fewer deaths from any cause (22 [3.5%] vs 42 [6.7%],  $p = 0.01$ ) and death from IPF (7 [1.1%] vs 22 [3.5%],  $p = 0.006$ ) [Nobel PW et al. *Lancet* 2011].

Treatment with pirfenidone showed a favorable safety profile and was generally well tolerated (Table 2).

The most common adverse events, with higher incidence in the pirfenidone group, were gastrointestinal (nausea, 36.0% vs 13.4%; dyspepsia, 14.7% vs 6.1%)

Figure 1. Primary End point of Decreased FVC or Death



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Table 2. Adverse Events<sup>a</sup>

Adverse Event	Pirfenidone (n=278)	Placebo (n=277)
Any adverse event	277 (99.6)	272 (98.2)
Grade 3 event	58 (20.9)	61 (22.0)
Grade 4 event	8 (2.9)	14 (5.1)
Any serious adverse event	55 (19.8)	69 (24.9)
Worsening IPF	7 (2.5)	27 (9.7)
Treatment emergent all-cause mortality	8 (2.9)	15 (5.4)
Any adverse event leading to treatment discontinuation	40 (14.4)	30 (10.8)

IPF=idiopathic pulmonary fibrosis.

<sup>a</sup>Data are expressed as number (percentage).

and skin related (eg, rash; 28.1% vs 8.7%). These were typically mild to moderate in severity and could be reversed with treatment. Adverse events that prompted discontinuation occurred in 14.4% in the pirfenidone group and 10.8% in the placebo group, most commonly due to worsening of IPF (1.1% and 5.4% in the pirfenidone and placebo groups, respectively). Serious adverse events occurred in 19.8% and 24.9% of patients in the pirfenidone and placebo groups, respectively, and again most often involved worsened IPF (2.5% and 9.7%, respectively).

The authors concluded that pirfenidone was well tolerated and led to a reduction in disease progression or death for patients with IPF.