Overview of Latest Clinical Trials in IPF

Steven Nathan: I was privileged on Monday to present on behalf of all the co-authors, investigators, coordinators and patients, cumulative data from the ASCEND and CAPACITY studies, of which there are about 1,250 patients. With this particular post-hoc analysis was to look at the most severe patients and how they responded to pirfenidone in terms of quality of life as manifested by the UCSD Shortness of Breath Questionnaire and their functionality as manifested by change in the six-minute walk distance.

What we did is, we looked at patients who had diffusing capacities less than 35% of predicted and/or forced vital capacities less than 50% of predicted. Now, folks might know that the cut-off for inclusion in all three clinical trials in terms of FVC was that an FVC had to be 50% or greater. So the question becomes, how do patients with FVCs less than 50% get into the clinical trial? Well, they had to have an FVC of 50% or greater at screening, but at baseline it could be less than 50%. So there were some patients who came into the study with FVCs less than 50%.

Most of the patients who qualified for this particular analysis qualified on the basis of the DLCO, because the ASCEND study had a DLCO cutoff of 30%, whereas the, the capacity studies had DLCO cutoffs of 35%. At the end of the day, we had about 170 patients or so for analysis, and we looked at changing the six-minute walk distance and change in the UCSD Shortness of Breath Questionnaire. What we showed was that there was a significant difference favoring the pirfenidone group in terms of rate of change in the six-minute walk distance, as well as rate of change in the Shortness of Breath Questionnaire.

So, I think this is important information because it gets to, should we treat patients with more severe disease? And at the onset, at least based on this analysis is yes, there can be benefit based on the function, six-minute walk, and quality of life based on Shortness of Breath Questionnaire. Now, one of the criticisms, and this actually came up as a question from one of the audience members was, well, there's a certain amount of bias because most of your patients weren't included. Namely, patients who had DLs of 25% or FVCs of 45%. And that's true,

however this is as close a look as we can get, in terms of the most severe patients on pirfenidone compared to placebo.

What we would all lack, and this was actually a question that came up as well, what about doing a study of pirfenidone in patients with more severe disease? And personally, I'd love to see that. My belief is yes, we will show a difference in terms of the effect of pirfenidone, even in patients with more severe disease. These patients have typically been neglected and ignored in the context of clinical trials.

With that I must mention a presentation that I went to at the European Respiratory Society meeting last month that was held in Paris. The presentation was looking at nintedanib versus nintedanib plus sildenafil and the inclusion criteria of the study were based on the prior STEP-IPF study, where patients were enriched for having pulmonary hypertension, with the major inclusion criteria being a diffusing capacity less than 35% of predicted. And we know the majority of patients who have IPF with DLs less than 35% will have an element of pulmonary hypertension.

In the context of this study that was published simultaneously in the *New England Journal of Medicine* the end point, I believe it was at 12 weeks, was change in the St. George's Respiratory Questionnaire. And this was a negative study based on the primary endpoint, but what was very interesting in the study were various secondary endpoints. Including the UCSD Shortness of Breath Questionnaire, which favored the combination therapy of nintedanib plus sildenafil, verus nintedanib alone.

And what was even more intriguing is change in the FVC over 12 weeks where there was, virtually no change in the dual therapy arm, nintedanib plus sildenafil, versus some change in the nintedanib arm alone. And this was statistically significant. We traced the whole concept of whether or not there's some kind of antifibrotic synergy between nintedanib and sildenafil. With that said, there's an ongoing study of pirfenidone plus sildenafil, and hopefully we'll see some results from that in the not too distant future.