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Long-Term Effects of Inhaled Treprostinil in Patients with Pulmonary Hypertension Due to Interstitial Lung Disease: The INCREASE Study Open-Label Extension

Announcer:
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Dr. Nathan:
Hi, I'm Doctor Steve Nathan, talking to you from Inova Fairfax Hospital in Falls Church, Virginia. I was privileged to be a part of the INCREASE study and equally privileged to present the open-label extension data that was presented for the first time at the American Thoracic Society meeting in May of 2022 in San Francisco. So, the title of this presentation is, "Long-Term Effects of Inhaled Treprostinil in Patients with Pulmonary Hypertension Due to Interstitial Lung Disease." And as mentioned, this is the open-label extension of the original INCREASE Study.

Inhaled treprostinil was shown to improve exercise capacity as measured by the 6-minute walk in the INCREASE study. This was a 16-week study, a placebo control trial in patients with various forms of interstitial lung disease, but all of them had to have pulmonary hypertension documented by right heart cath based on the old definition of an mPAP 25 or more. There were numerous secondary endpoints which were also positive including our biomarker of the NT-proBNP. And then, probably our most important secondary endpoint, which was time to clinical worsening, was also statistically favorable for the inhaled treprostinil arm versus the placebo arm. Interestingly, lung function was looked at as a safety endpoint, but in actual fact, the FVC was shown to be better, or improved, for the inhaled treprostinil group compared to the placebo arm, which was somewhat of a surprise finding, but a very pleasant surprise, I have to say.

Patients completing the randomized phase of INCREASE study were then eligible for the open-label extension. In the context of this patients were assessed at week four, week 12, and then every 12 weeks up to week 108 for safety and efficacy parameters. The INCREASE open-label extension was discontinued once approval was obtained from the FDA for inhaled treprostinil for patients with PH due to their interstitial lung disease. At that time, all patients had been enrolled in the open-label extension for at least 60 weeks at the time of FDA approval. The current analysis includes the 6-minute walk test data that was obtained in the open extension as well as the FVC. And then of course, adverse events as well were captured in the open-label extension.

This is the demographic table of patients who were included in the study. As you can see, there were 119 who were in the original inhaled treprostinil arm versus 121 in the original placebo arm. And so the total number of patients entering open label extension was 247. In the initial INCREASE study, there were approximately 347 patients who enrolled at time zero. If you look at the demographics it kind of replicates what was seen in the original INCREASE data set. The groups were pretty much matched for most demographics including the underlying primary disease. Most of this was constituted by one of the idiopathic interstitial pneumonias, mostly idiopathic pulmonary fibrosis. There were some connective tissue disease patients as well as some CPFE patients. And you can see the breakdown of all the different disease conditions in the table. This was a sick population, 72 and 75% of them were on supplemental

oxygen. And the patients who had been on inhaled treprostinil could walk approximately 282 meters at the time of the open-label extension. So that was 16 weeks after the start of the increased study, versus 267 meters in the group who had been assigned to placebo previously. You can see quite a big difference in actual fact in the NT-proBNP, which was positive on the primary analysis. So significantly lower, at least it looks numerically lower in the inhaled treprostinil arm versus the former placebo arm, at 1300 plus versus 3,100 plus.

Moving on to the results. The primary endpoint was the 6-minute walk, you can see at 16 weeks, the difference between the two arms. Now what's different at 16 weeks is that this only includes patients who rolled over to open-label extension. Not all the patients were included in the first 16 weeks, as was reported from the original INCREASE study. If you look at the blue line, which is the former inhaled treprostinil arm, now getting inhaled treprostinil open-label, it looks like the 6-minute walk is maintained through the course of the open-label extension after week 52. When one looks at the former placebo arm there is no real discernible improvement although it does look like their lowest 6-minute walk distance is pretty much maintained through the course of the 52 weeks. Of course, what we'd like to have seen was in some kind of improvement, and maybe buried in these numbers there were some patients who did improve but for the group as a whole, it looked like they remained low, and they continued to remain low. What was very interesting, and supportive of the FVC data that was seen from the original INCREASE study, was what happened to the FVC in the placebo arm once they got rolled over to open-label inhaled treprostinil and it's quite evident that the placebo arm then had an increase in their FVC and actually looked like they overtook the FVC change in the original inhaled treprostinil arm. So that's kind of gratifying to see, perhaps reinforces what we think might be an antifibrotic effect of inhaled treprostinil that's currently being tested in the randomized control clinical trial called TETON which is looking at inhaled treprostinil purely for its antifibrotic properties. If one looks at the FVC for the IPF subgroup you can see similar data over here. What's interesting about this is, for the IPF subgroup, the former inhaled treprostinil arm in blue continues to do well and remains numerically above where they started at time zero, which was when they enrolled initially in the INCREASE study. But once again, the placebo arm had a decrement and now have increased beyond where they were when they enrolled in the original INCREASE study.

In terms of adverse events. I'm not going to read these all, but there were no surprises that weren't seen in the original INCREASE study. Cough was a little bit of an issue. Dyspnea was reported as an AE, and then you can see the typical side effects that we see with inhaled treprostinil as well, but nothing new, really, which we didn't know about inhaled treprostinil in terms of adverse events in patients with PH-ILD.

So, in conclusion, the 6-minute walk distance improvements were maintained through 52 weeks for patients assigned to active treatment originally. The differential response in the 6-minute walk distance between the former placebo group and the active group suggests a benefit to early initiation of therapy with inhaled treprostinil. The sustained improvement in the FVC both in patients who received inhaled treprostinil in the parent study, as well as patients who in the former placebo arm really supports the notion that inhaled treprostinil might have independent antifibrotic properties and provides further rationale for the TETON study which is looking at the antifibrotic effects of inhaled treprostinil agnostic to the presence of pulmonary hypertension. There are, of course, limitations to the study any open-label study lacks a placebo control, and so, therefore, this data should be interpreted with some caution in the context of it being an open-label design. Thank you very much.

Announcer:
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