SPEAKER 1: --about the development of liposomal amikacin actually, this drug had its early interests as a potential therapy for treating pseudomonas in cystic fibrosis patients. But honestly, that didn't really attract me, because in treating pseudomonas you want high concentrations in the space. It's not about just trying to keep drug in the airway for a longer period of time, it's about getting high-high concentrations. So packing the drug in liposomes didn't seem to make a lot of sense for me for pseudomonas. But dealing with intracellular organisms, like micro bacteria that actually had some appeal. And then based upon some earlier work, published by Ken Olivier about the benefits of inhaled amikacin became a very attractive approach.

And so, the phase study done with liposomal amikacin looked at patients who had treatment refractory NTM lung disease. So they could have MAC, they could have abscesses. They could have cystic fibrosis or they could not have cystic fibrosis. They essentially took all comers, who had refractory NTM lung disease and then randomized them to remain on their therapy, plus the inhaled liposome amikacin or empty liposomes. So, there was a blinded study there, and there weren't a lot of patients with cystic fibrosis so it was a smaller subset, and as they began to sort of tease out the data, what became evident to them was, that the population who had MAC, were the ones that seem to have this evidence of culture conversion. And culture conversion and that study was defined as three consecutive months of negative cultures. And that's what ultimately led to the phase three design which was, to randomize people to a guideline based therapy. They are on their standard regimen plus inhaled liposomal amikacin.

In this case, the control was to not be on empty liposomes. Because in part, what's the risk or advantage of empty liposomes but also, how well can you actually blind people to the study? Can they really tell the difference? And so, another key observation from the phase two study, was looking at functional status of patients and looking at six minute walk data. And in the treated group, there seemed to be an improvement in six minute walk not appreciated by those patients in the placebo controlled group. So that too, was another key secondary endpoint in the phase 3 design.

So there were, roughly, 330 patients enrolled into the phase three study at the 2-1 randomization ratio. So there's twice as many people who were given the opportunity to be on inhaled liposomal product in addition to their therapy from the get go. And they were treated for six months. And then after six months, those patients who were in the control group were allowed to now enroll into an open label addition of liposomal amikacin and so they were guaranteed to get, opportunity to get, drug at any time. And, in those patients who were already randomized to it, they too could remain on product. But those patients who achieved culture conversion were required to stay in it to complete a full year of treatment. Because another question one has is, is what's the durability of the response?

The data that were presented to the FDA were focused on that six month comparator trial. Now, aside from the fact that you're taking patient population, which is extremely difficult to treat and to get a clinical benefit, meaning a microbiological benefit on because they've already defined themselves as treatment refractory disease. Another key element to this, is that by definition to be culture conversion, to have three consecutive negative cultures, meant that that culture by month four had to be negative in order for them to meet the definition. If they didn't meet it until month five they would have failed that. So it was a pretty high bar.

Another feature of this study that I think demonstrates its rigor is that these patients were seen monthly, they had sputum cultures done three times every month. So, they would obtain these specimens, bring them to the clinic in which we would culture. So, if anything, you're increasing your ascertainment bias of identifying a bug. So there was a very, very rigorous approach to assess the response to therapy and in the end nearly 30%, 29% of those patients who had out the liposomal amikacin added to their regimen, achieved that definition of culture conversion. Now keep in mind, there may be others who still yet achieve culture conversion, because they're on for a longer period of time. But those data had not been analyzed yet and presented to the FDA for that approval process. In the control group, those patients who just stayed on their usual regimen, only 9% of those met the definition of culture conversion. So, that was the big difference and it was actually greater than had been expected and powered for and so ultimate that's what led to the conditional approval.

Now a comment about the functional status. So in the phase two study, where we had looked at six minute walk data and there was a treatment benefit in the treated group compared to the placebo, that actually wasn't seen in the phase three study. What I mean by that, is those patients who were randomized to receive liposomal amikacin, in addition to their usual therapy, their six minute walk distance wasn't different from that in the other group. If however, you looked at those patients who achieved culture conversion. Whichever group, in the liposomal amikacin group or the just guideline based therapy group, if you look at those patients, they did actually improve their six minute walk distance and by a meaningful amount, meaning, greater than what we have learned to be the minimal important difference.

Now, I would argue that you have no reason to suspect that taking an inhaled antibiotic is going to improve your cardiac pulmonary status. So, by itself, it shouldn't be expected to improve your functional status. But, if you achieve the desired goal, meaning you have that antibiological effect, so you reduce the burden of organism or you get culture conversion, then you might expect a clinical benefit and that actually is what you see. So, my interpretation of that, is that if you can achieve culture conversion then you should expect to see that functional benefit. And, since the population on that inhaled liposomal amikacin have a greater proportion of patients achieving culture conversion. That actually to me is a compelling finding.

There are still data to be analyzed from that study. The data that were presented in front of the FDA represent only the first six months of data. But, what you will then also have, is all of those patients who remained on therapy, who achieve culture conversion, to talk about their durability of response. Those patients who did not start the inhaled episode limit case in until six months into the study, did they achieve a similar response in terms of culture conversion? Of those patients, who had not yet achieved culture conversion, were there more who had success if you gave them a longer period of therapy? Those are all very interesting questions to which we look forward to the answer.