Transcript Details

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https://reachmd.com/programs/cme/multicenter-randomized-active-comparator-controlled-double-blind-double-dummy-parallel-group-dose-finding-phase-2-study-comparing-the-safety-of-the-oral-fxia-inhibitor-asundexian-with-apixaban-in-patients-with-atrial-fibrillation-pacific-af/14053/

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Multicenter, Randomized, Active Comparator-controlled, Double-blind, Double-dummy, Parallel Group, Dose-finding Phase 2 Study Comparing the Safety of the Oral FXIa Inhibitor Asundexian With Apixaban in Patients With Atrial Fibrillation: PACIFIC AF

Dr. Patel:
Hello, this is Manesh Patel from Duke University. I'm the chief of cardiology and I'm presenting the results of the Pacific AF trial which was a late-breaking clinical trial presented at the American College of Cardiology 2022 and simultaneously published in Lancet. It's my honor to present the results on behalf of the investigators, the steering committee. And most importantly the patients.

We know that atrial fibrillation is an important condition that leads to stroke and thromboembolism worldwide. Unfortunately, 30 to 40% of patients do not get therapy often before and because of considerations around bleeding.

We're also aware that in normal physiology we have two processes. One process that is called hemostasis by which when there's a disruption in the blood vessel through tissue factor we activate thrombin generation that activates platelets and leads to a clot thrombin then is amplified and can lead to a biologic process called thrombosis that can be pathologic leading to clots in heart arteries, brain arteries, or leg arteries, leading to the downstream effects, To date we have had anticoagulants that have interrupted this pathway in numerous ways. Specifically, we've had anticoagulants that have interrupted this pathway like warfarin through vitamin K antagonism through multiple different spots in this pathway. We've found that to be not specific enough and often led to bleeding.

Over the last 12 years we've had an improvement in some of the possibilities with direct-acting oral anticoagulants, like apixaban and rivaroxaban that interrupt factor 10A, important in the thrombin generation and propagation. So that we have the improvement in preventing thrombus but we still sometimes have some bleeding. Factor 11 inhibitors then have the biologic hypothesis that they can uncouple hemostasis from thrombosis by preventing the amplification phase of the thrombin that leads to the thrombus. It is therefore postulated that factor 11s may lead to interruption of thrombosis but continuation of hemostasis and less bleeding.

It's under that background that we have Asundexian which is a small molecule, a factor 11 inhibitor that is anticipated to hopefully help us with our patients with atrial fibrillation. Asundexian has as a half life of 14 to 17 hours. It is 15% renally cleared. It doesn't have many food or drug interactions and it doesn't have any pH interactions. It was studied in patients with atrial fibrillation in 750 such patients in the Pacific AF study, randomized to 20 milligrams once daily of Asundexian, 50 milligrams once daily of Asundexian, or apixaban based on standard dosing.

Pacific AF then aimed to identify 750 patients in a phase two study to show if Asundexian had less bleeding compared to apixaban. The atrial fibrillation patients enrolled in the study were those that we commonly see with a CHADS2-VASc of four. Many of the patients had hypertension, diabetes and cardiovascular disease in the history of a MI or other such disorders. These patients were followed for 12 weeks and then we had a closeout period of 30 days for which we followed the patients.

We also did a factor 11 assay to see if we had inhibition of patients. Factor 11 activity in vivo as they were taking the therapy. The primary results of Pacific AF show that the factor 11 assay was inhibited both at peak and trough, both at the 20 and 50-milligram dose near 90%. In fact, at the 50-milligram dose, it's over 90% inhibition as shown in the publication and in the slides with the activity assay.

The primary bleeding endpoint of ISTH major or non-major clinically relevant bleeding was present in apixaban at a rate of 2.4%. When the pooled Asundexian rates were looked at, they were less than 50% those incident ratio of apixaban and the 50-milligram dose itself had a significant reduced bleeding ratio compared to apixaban, as did the pooled ratio.

The efficacy outcomes were not aimed or anticipated to be different. And in fact, there were less than 10 events. So we did not see any interpretable efficacy events for this study.

So in summary, Pacific AF showed that Asundexian is a promising new potential therapy for patients with atrial fibrillation that has to be studied in phase three to demonstrate efficacy. But in this phase two dose finding study in patients with atrial fibrillation, we're able to demonstrate and see significantly less bleeding than apixaban. These data warrant further investigation as a possible new therapy for many patients that remain untreated in clinical practice. We ask investigators, patients and others to join us as we aim to study Asundexian in a phase three study called OCEANIC AF. Thank you for listening to this presentation of the Pacific AF results from ACC 2022.