Title: HFA 23: REDWOOD-HCM-Cohort 4: Aficamten in Non-obstructive Hypertrophic Cardiomyopathy
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What is currently understood about the pathophysiology of nHCM and what treatment options are available in 2023?

"So, the pathophysiology of non-obstructive HCM is pretty distinct, where we have hypercontractility as well as abnormal relaxation. And the combination of those two can lead to progressive stiffness at the myocardial level, as well as progressive syndrome of clinical heart failure with symptoms and exercise intolerance. Currently, there are no evidence-based therapies that are available to help us treat these patients. While we use beta blockers and calcium channel blockers in certain patients, there are no proven therapies that can help these patients feel better or improve the function of the heart.

How does Aficamten, a selective inhibitor of cardiac myosin, work?

Aficamten is the next in class cardiac myosin inhibitor. It works by decreasing the excessive myosin actin interactions. And so, what it does eventually is counteracting this hypercontractility and promoting active relaxation. And so ultimately, at least what we see in the obstructive group of patients is that you relieve obstruction. In the non-obstructive group of patients, what we are hoping to achieve is to improve or decrease the hypercontractility, improve cardiac function, but also improve relaxation.

What was the study design, patient population, and outcome measures of REDWOOD-HCM-Cohort 4?

Redwood HCM Cohort Four is an open-label study. It's a ten week on treatment study with four weeks of washout. Patients would start on Aficamten at day one, patients had to have non-obstructive HCM already diagnosed, symptomatic NYHA class two or

three, and they had to have an EF 60% and above and NT-proBNP 300 and more. So symptomatic patients with disease burden and they got started on aficamten, five milligrams. And over the study period, we titrated them to the maximum available dose, which is 15 milligrams if they're eligible. And we use a simple criterion for eligibility, which is LVEF. So, if their LVEF is above 55%, we up titrate the reason behind that. This was a phase two study in non-obstructive HCM, and we wanted to show what is the effect of the maximumly tolerated dose of the drug in these patients.

What data was presented at the HFA and what conclusions can be drawn from the findings?

So, we presented a lot of data in this meeting at the European Society of Cardiology Heart Failure meeting. The first set was related to safety, that aficamten was well tolerated in this patient population and we didn't have any surprising findings in relationship to safety. There were three patients who had ejection fraction decreased below 50%. Part of the mechanism of action of the drug is to reduce ejection fraction a little bit. On average, in the study it was 5.5%. But in those three patients, by the end of week ten dropped below 50% and within the washout period recovered. Those patients had atrial fibrillation, which is known to interfere with our ability to quantify ejection fraction, as well as our ability to understand what's happening at the patient level sometimes. So, there were a couple of SAEs in the study. None of them were related to aficamten. Now, in terms of the efficacy portion, which is exploratory as part of this study is when we looked at KCCQ Kansas City Cardiomyopathy questionnaire and we showed that there was a 10.6-point increase in KCCQ from baseline by week ten. That is statistically significant from baseline but also is well beyond what you would have expected from a placebo effect in this population. We also showed that 56% of the patients had improvement in NYHA class. A third of them became totally asymptomatic. So, NYHA class one, which is in my opinion is an important finding. As well as patients who had angina at baseline had significant improvement in their Seattle Angina questionnaire and so decrease in the frequency of angina. On top of that. All of this was mirrored by improvements in troponin NT-proBNP, as well as - we looked at multiple subgroups within the patient population at BMI, beta-blocker use, being gene positive or having family history of HCM and a subgroup. That is typically historically considered

a high-risk subgroup by having elevated Troponin or E over E Prime to be elevated. And we saw consistent effect across all subgroups.

What safety considerations and adverse events were observed?

So, as I mentioned, this was a phase two trial, so we wanted to push the dose as high as possibly tolerated. So, 85% of the patients achieved a 15-milligram dose, which is the highest dose in the trial, and the rest were on ten milligrams, so no one stayed at the lowest dose which is five milligrams. And in terms of safety, we had a mean reduction of LVF of 5.5%. Three patients had LVF reduction to below 50% and all three of them had either permanent atrial fibrillation or they had worsening of their atrial fibrillation during the study and all of them had recovery of their ejection fraction during the washout period by two weeks of follow-up. So, they had a reduction in LVEF at ten weeks which is the end of treatment period and then recovery of their ejection fraction by two weeks of follow-up. There were four SAEs as part of the study, none of them were related to aficamten.

What are the next steps in research or clinical development?

So, it's really an exciting time to be taking care of patients with hypertrophic cardiomyopathy. We now can offer them more options, including those options as part of clinical research. In terms of Redwood HCM Cohort Four, the data are supportive for our progression to phase three which is going to be larger, longer and have more efficacy endpoints in relationship to the drug use versus placebo and we are looking at this to be starting towards the end of this year or the second half of 2023.Now we also have other treatments that are being investigated in non-obstructive HCM. Mavacamten is another cardiac myosin inhibitor that is being currently investigated in the Odyssey HCM trial, so a phase three trial as well for non-obstructive HCM. And we also have an energy modulator by a sponsor named Embrya which is looking at trying to improve the energetics at the myocardial level. And finally, there are a couple of sponsors looking at the use of gene therapy to correct the deficiency in MYBPC3 which is one of the most common causes, genetically proven common causes, of hypertrophic cardiomyopathy. So many trials are coming up in non-obstructive hypertrophic cardiomyopathy."