Transcript Details
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/aficamten-in-patients-with-symptomatic-non-obstructive-hypertrophic-cardiomyopathy-redwood-hcm-cohort-4/15291/

Released: 03/27/2023
Valid until: 03/27/2024
Time needed to complete: 1h 18m

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Aficamten in Patients With Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy (REDWOOD-HCM Cohort 4)

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Masri:
Hello, my name is Ahmad Masri. I'm a Cardiologist at Oregon Health and Science University, and I direct the Hypertrophic Cardiomyopathy Center as well. Today I will be talking to you about our recent study of aficamten in patients with symptomatic non-obstructive hypertrophic cardiomyopathy. This is the REDWOOD-HCM Cohort 4 trial.

In terms of background, aficamten is a cardiac myosin inhibitor. It's a next-in-class, and we have been testing it primarily in obstructive hypertrophic cardiomyopathy, those were the REDWOOD-HCM cohorts 1 to 3. And those were a part of this phase 2 study. Then in Cohort 4, we moved on to investigate aficamten in non-obstructive HCM patients. As you're all well aware, non-obstructive HCM patients do not have proven therapies. And if they progress to burn-out stage, then they will need cardiac transplantation if they are eligible for it, but there are no other therapies. And so in this study, our goal was to assess the safety and efficacy of aficamten in patients with non-obstructive hypertrophic cardiomyopathy.

This is our eligibility criteria. So patients had to have symptoms as defined as NYHA class II or III, left ventricular ejection fraction about 60%, no LVOT gradients, even with provocation with Valsalva, the LVOT had to be less than 30, NT-proBNP had to be elevated to 300 or above, and no history of low ejection fraction below 45% in the past. And as I mentioned, safety NYHA class LVEF cardiac biomarkers were assessed.

So we enrolled 41 patients. I'm presenting the data on the study for 40 patients up to week 10. And then 35 patients up to week 12. Because the study just concluded a couple of weeks ago.

This is our study schema and titration schedule. So it is a 14-week study, 10 weeks on treatment and then 4 weeks of washout. Patients get screened, and then once they are eligible, they start day 1 with 5 milligrams of aficamten. Then at week 2, they go to 10 milligrams of aficamten. And then at week 4, they go to 15 milligrams of aficamten. This is a dose-finding study and safety evaluation. So we wanted to push aficamten for the whole range between 5 and 15 milligrams, it's safe to do so. So we used very simple titration schema, which is if the ejection fraction is above 55%, you up-titrate. If it's between 50 and 54, you maintain. And if it's below 50, you down-titrate. And you have up to week 6 to down-titrate. You can't up-titrate at week 6 again, even if you were on 10 milligrams. And then the rest is a follow-up phase. And so of course you discontinue if at any point it was below 40%.

And so with that in mind, we really didn't look at symptoms or biomarkers to titrate up or down. It was just simply left ventricular ejection fraction because we wanted to see what do patients do at these higher doses.

So these are our baseline characteristics and dose achieved. Mean age was 56. We had 59% women, and then our trial population was diverse 20% Black or African American and 5% Asians. In terms of NYHA class, half of the patients had NYHA class II, and the other half had NYHA class III. Left ventricular ejection fraction was 68% as you'd expect to from a non-obstructive HCM population. And NT-proBNP here the geometric mean was 1,254. This is the highest NP-proBNP mean that you've seen in any of the hypertrophic cardiomyopathy trials representative of the population who selected to enroll. And also high-sensitivity troponin was elevated at 28.7.

This is a representation of the doses used in the study; 85% of patients achieved 15 milligrams, so the highest dose offered to these patients. And then the rest achieved 10 milligrams, no patients stayed on 5 milligrams. This is important, because it shows us that any results you see going forward, that we were able to use the highest dose available for these patients. And this is part of the story in non-obstructive HCM, is that are you able to push these medications to derive the most benefits from them or not? And do that safely, obviously?

So aficamten was well tolerated. These are summary of the safety data. Treatment-emergent adverse events, 66% of patients, this is a summary of them, you can look at them, but I'm going to focus mainly on some other things.

So the first thing to focus on is the panel here on the right lower side where EF essentially just had a modest decrease from 70 to 66% on average. And in terms of EFs below 50%, there were three patients who EF of 50%, that's 7% essentially of the study population, two were in permanent a-fib and we all recognize how difficult it is to quantify LVEF patients with permanent atrial fibrillation. One only reported palpitations that required adjustment of their rate-control medications. I think what's more important is that these were numerical decreases, there were no AEs for heart failure reported. And so no clinical heart failure in any of these patients, and all of these decrements happened towards the end of the study. There wasn't an opportunity to down-titrate for these patients. So they just got off the drug by design at week 10. And their the EF returned to normal or baseline by week 12.

The other thing to mention is that there were three SAEs in this study. One was bronchitis, one was new-onset atrial fibrillation, and one was cardiac arrest; none were related aficamten. The cardiac arrest patient had already history of aborted sudden death, and had all the assessment throughout the study until they died. And there was no indication that this is related to aficamten. And you'll hear more about this in the future.

And then there were no drug discontinuations. And this is important because our patients tolerated aficamten throughout. And even despite the fact that they had some AEs, there were no drug discontinuations. One patient held the drug for 2 days in the setting of palpitations, and one patient had a dose reduction to 10 milligrams because they complained of fatigue, but none otherwise.

In terms of efficacy, we're excited to report that in terms of NYHA class, 55% or 54% of the patients had improvement in their NYHA class by at least one class. This is important. As you can see here at baseline, we started 50/50 in terms of NYHA class II and III. And then by the end, the majority of the patients were NYHA class I or II. The reason why this is important is that we also shifted a good number of patients to NYHA class I, so completely asymptomatic. And this is not an easy goal to achieve in non-obstructive HCM since patients have an overlap with heart failure syndrome as well.

And the other point is, this is an open-label study. So you'd expect there is some sort of placebo effect. But we know from multiple trials previously, that the placebo effect in HCM patients with NYHA class is about 30-35%. So this is way beyond what you'd expect from a placebo effect.

In terms of NT-proBNP, we started at around 1,200. And you can see over time how by week 10, we are – NT-proBNP was reduced by about 55-56% from baseline. So a robust reduction down to almost 5,500 range. And then troponin behaved in similar fashion, and those were statistically significant.

So in conclusion, REDWOOD-HCM Cohort 4 is the first study exploring dosing and tolerability of aficamten in patients with non-obstructive HCM. Aficamten was well tolerated with modest on-target reductions in LVEF in response to aficamten over 10 weeks while we were pushing the dose to the maximum tolerated by the patients and the ejection fraction. There were significant improvement in patient heart failure symptom burden as well as improvement in cardiac biomarkers during this open-label study. And we will be testing the 20-milligram dose in the open-label FOREST-HCM study.

So, in summary, these results do support our further study of aficamten in a larger, longer-term trial of patients with symptomatic non-obstructive HCM. Thank you.

Announcer:

You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, Inc. and is part of our MinuteCME curriculum.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.