Aficamten: A Cardiac Myosin Inhibitor for Obstructive Hypertrophic Cardiomyopathy

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Interview Summary

Cardiac myosin inhibitors (CMI) are the first medications specifically targeting the underlying pathophysiology of hypertrophic cardiomyopathy (HCM). Phase II results with the newest entrant into this class of drugs, aficamten, have been reported in three cohorts of obstructive HCM (oHCM), the most recent of which examined aficamten treatment in patients with oHCM treated with disopyramide.[1,2] The launch of SEQUOIA-HCM (Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM), the Phase III trial of aficamten in patients with symptomatic oHCM has been announced.[3]

In this interview with the EMJ, Perry Elliott, Director of the University College London (UCL) Institute for Cardiovascular Science, and specialist in cardiomyopathy at Bart's Heart Centre, London, UK, provided his perspectives on the Phase II data, and the design of the Phase III trial for aficamten.

REDWOOD-HCM PHASE 2 TRIAL

REDWOOD-HCM is a multicentre, dose-finding, clinical trial of aficamten in patients with symptomatic HCM on background medical therapy. Cohorts 1 and 2 included patients with symptomatic oHCM taking background therapy exclusive of disopyramide; they were randomly allocated 2:1 to aficamten or placebo. Patients allocated to aficamten received up to three escalating doses once daily: 5, 10, and 15 mg in cohort 1 (n=21); and 10, 20, and 30 mg in cohort 2 (n=20). The distinguishing feature of patients in cohort 3 (n=13), an open-label study for symptomatic oHCM, was that the background medical therapy included disopyramide. These patients received the same escalating dose schedule as cohort 1. For all three cohorts, echocardiography was performed at Weeks 2, 4, and 6 of treatment at each dose to assess eligibility to up-titrate to the next dose. The overall treatment duration was 10 weeks, with a 4 week follow-up period after the last dose. The target goal of treatment was a resting left ventricular outflow tract (LVOT) gradient <30 mmHg, and Valsalva LVOT gradient <50 mmHg at Week 10.

In all three cohorts, treatment with aficamten was well tolerated, and no interruptions or discontinuations of aficamten therapy were required in any patient. Coadministration of aficamten with disopyramide and β-blockers or

calcium channel blockers in cohort 3 did not lead to any adverse electrocardiographic changes, for example in the QT interval, or in blood pressure or heart rate.

Patients treated with aficamten achieved clinically meaningful reductions in LVOT gradients. For example, the average Valsalva LVOT gradient in cohort 1 (n=14) changed from 74 mmHg at baseline to 38 mmHg at 10 weeks; while in cohort 2 (n=14) it changed from 82 mmHg to 30 mmHg. The corresponding reduction for patients in the combined placebo group (n=13) was from 85 mmHg at baseline to 76 mmHg at 10 weeks ($p=0.001$ for cohort 1; $p<0.0001$ for cohort 2 versus placebo). In cohort 3, the average Valsalva LVOT gradient changed from 78 mmHg at baseline to 50 mmHg at Week 10. Substantial reductions in resting LVOT gradient were also observed in all three groups receiving aficamten.

REDWOOD-HCM cohort 4 will include patients with non-obstructive HCM receiving background standard of care medical therapy and is currently ongoing.[4]

"REDWOOD-HCM adds to existing data for the myosin inhibitors, suggesting that this is a potentially very promising group of drugs for HCM, a disease in which we've had no therapeutic innovation in terms of pharmacology for decades," said Elliott.

He noted that the dose response reduction in LVOT gradient demonstrated in the REDWOOD-HCM Phase II studies has been associated with improvements in functional class and biomarkers. In cohort 3, for example, 11 of 13 patients (85%) experienced improvement in New York Heart Association (NYHA) by $\geq$1 class. In addition, patients experienced a significant improvement in N-terminal pro B-type natriuretic peptide, and trended to lower high-sensitivity troponin I.

"This suggests that the drug is also influencing myocardial strain and reducing myocardial injury," said Elliott. "Another promising aspect from the REDWOOD series is that aficamten appears to be safe and well tolerated. One of the worries about the drug is that it is a negative inotrope, so it reduces ejection fraction, but there were no serious adverse events related to impaired systolic function in the studies conducted so far.

"The cohort 3 study now brings additional data on the interaction between aficamten and disopyramide," he continued. "This is important to the clinical community because disopyramide, along with β-blockers and calcium antagonists, is the current standard of care for symptomatic outflow tract obstruction,[5] so physicians will be reassured that the combination appears to be safe."

Elliott pointed out that the response in cohort 3 was somewhat different to cohorts 1 and 2. He said: "The proportion of cohort 3 that achieved complete improvement in LVOT gradients using the predefined criteria was less than in cohorts 1 and 2. Paradoxically, however, the NYHA functional class response was still very good. This is probably because aficamten has a beneficial effect on diastolic function as well as LVOT obstruction, but that is yet to be proven."

"REDWOOD-HCM shows that there is an incremental benefit of dose escalation but the therapeutic effect is still seen at really quite a low dose, which improves the safety margin," he added. "The sustainability during the observation period is important, but the long-term extension studies and real-life use of the drugs will show the durability of the treatment effect. Another reassuring finding is the rapid washout effect which should mitigate concerns about significant reductions in left ventricular ejection fraction should they occur during treatment."

Aficamten has a plasma half-life of 3.4 days with a steady state achieved after 2 weeks of dosing. The shallow exposure response relationship and steady state at 2 weeks informed the broad dose range and short titration schedule studied in REDWOOD-HCM. The half-life impacts functional reversibility, which was observed after a 2-week washout (Cytokinetics, unpublished data).[6]

Elliott highlighted the consistent results across all endpoints as a real strength of the REDWOOD-HCM data. He said: "The fact that patients who are already receiving standard of care treatments have objective improvements in LVOT obstruction, symptoms, quality of life, and biomarkers is going to be really important in any future approvals process, because the target is a functional endpoint."

USE OF CARDIAC MYOSIN INHIBITORS IN CLINICAL PRACTICE

The therapeutic goal for symptomatic patients with moderate-to-severe outflow tract obstruction is to improve symptoms and quality of life. "Of course, treatment aims to reduce the LVOT gradient, but the somewhat more important thing is whether patients feel better and can do more in daily life," explained Elliott. In the short term, that means improvements in NYHA class, exercise tolerance, and Kansas City Cardiomyopathy Questionnaire (KCCQ) scores. Criteria for medium- and long-term responses could include reductions in left ventricular hypertrophy, incident heart failure, sudden death, atrial fibrillation, and stroke.

"It would be good to understand the effect of this drug on diastolic function," added Elliott. "I think there's also the potential to look at other biomarkers, for example fibrosis. In addition, these patients are often young, employed people with families, and the disease affects day-to-day functioning, so there is a big scope here for patient-reported outcome measures."

Adopting CMIs in clinical practice comes with some challenges. Frequent echocardiography is needed to enable safe up-titration, which could prove difficult in some clinical settings. "We may need to modify or create new systems of care for patients with oHCM in order to improve their access and monitoring of CMI drugs in real clinical practice," said Elliott.

STUDY DESIGN OF SEQUOIA-HCM

SEQUOIA-HCM is a Phase III randomised, placebo-controlled, clinical trial designed to evaluate aficamten in patients with symptomatic oHCM on background medical therapy for 24 weeks.[3] Patients whose background therapy includes disopyramide are eligible for enrolment. The primary endpoint is the change in peak oxygen uptake measured by cardiopulmonary exercise testing from baseline to Week 24. Previous studies have correlated this objective assessment with morbidity and mortality in patients with heart failure.[7] Secondary endpoints include the change from baseline to Week 12 and Week 24 in KCCQ score; the proportion of patients with ≥1 class improvement in NYHA; change in Valsalva LVOT gradient; and the proportion of patients with Valsalva LVOT gradient <30 mmHg. Each patient will receive up to four escalating doses (5, 10, 15, and 20 mg once daily) of aficamten or placebo, based on echocardiography performed after 2 weeks of treatment at each dose.

Elliott said that if the trial meets the primary endpoint and achieves consistent improvement across the secondary endpoints "that would be pretty powerful evidence that this drug is doing something important." He added: "There is a slight jeopardy related to the paradox in cohort 3 of the Phase II study, where big reductions in NYHA class occurred without dramatic changes in obstruction. Could we foresee the same being true for reductions in NYHA class, but failure to reach the peak maximal oxygen consumption endpoint? We will have to wait and see."

REMAINING DATA GAPS FOR CARDIAC MYOSIN INHIBITORS

Elliott highlighted that the impact of underlying genotype on CMI treatment effect needs to be resolved. He explained: "There may be some genotypes where giving a myosin inhibitor could be associated with adverse outcomes. For example, some mutations are associated with hypocontractility rather than hypercontractility, the main target of this drug. As we start to use CMIs in large, genotyped populations, we will find out whether genotype influences the response."

He added that more data are needed about safety in children with oHCM. Another open question is whether CMIs might be given prophylactically, given the experimental data suggesting that they could help to prevent the disease from developing.

"Obviously, the big question is whether these drugs have a place in non-obstructive disease; there I think the target is the effect on diastolic function," said Elliott. REDWOOD-HCM is currently enrolling cohort 4, which focuses on patients with non-obstructive HCM, a group with functional limitations and symptoms, but few treatment options.

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