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Evaluation of Mavacamten in Symptomatic Patients with Nonobstructive Hypertrophic Cardiomyopathy

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Abstract

Background:

Patients with nonobstructive hypertrophic cardiomyopathy (nHCM) often experience a high burden of symptoms; however, there are no proven pharmacological therapies. By altering the contractile mechanics of the cardiomyocyte, myosin inhibitors have the potential to modify pathophysiology and improve symptoms associated with HCM.

Objectives:

MAVERICK-HCM (Mavacamten in Adults with Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy) explored the safety and efficacy of mavacamten, a first-in-class reversible inhibitor of cardiac-specific myosin, in nHCM.

Methods:

The MAVERICK-HCM trial was a multicenter, double-blind, placebo-controlled, dose-ranging phase II study in adults with symptomatic nHCM (New York Heart Association functional class II/III), left ventricular ejection fraction (LVEF) ≥55%, and N-terminal pro−B-type natriuretic peptide (NT-proBNP) ≥300 pg/ml. Participants were randomized 1:1:1 to

mavacamten at a pharmacokinetic-adjusted dose (targeting plasma levels of 200 or 500 ng/ml), or placebo for 16 weeks, followed by an 8-week washout. Initial dose was 5 mg daily with 1 dose titration at week 6.

Results:

Fifty-nine participants were randomized (19, 21, 19 patients to 200 ng/ml, 500 ng/ml, placebo, respectively). Their mean age was 54 years, and 58% were women. Serious adverse events occurred in 10% of participants on mavacamten and in 21% participants on placebo. Five participants on mavacamten had reversible reduction in LVEF ≤45%. NT-proBNP geometric mean decreased by 53% in the pooled mavacamten group versus 1% in the placebo group, with geometric mean differences of −435 and −6 pg/ml, respectively ($p = 0.0005$). Cardiac troponin I (cTnI) geometric mean decreased by 34% in the pooled mavacamten group versus a 4% increase in the placebo group, with geometric mean differences of −0.008 and 0.001 ng/ml, respectively ($p = 0.009$).

Conclusions:

Mavacamten, a novel myosin inhibitor, was well tolerated in most subjects with symptomatic nHCM. Furthermore, treatment was associated with a significant reduction in NT-proBNP and cTnI, suggesting improvement in myocardial wall stress. These results set the stage for future studies of mavacamten in this patient population using clinical parameters, including LVEF, to guide dosing. (A Phase 2 Study of Mavacamten in Adults with Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy [MAVERICK-HCM]; NCT03442764)