Trial name: CIRRUS-HCM: An Open-label Study to Evaluate the Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Effects of EDG-7500 in Adults with Hypertrophic Cardiomyopathy

Trial Sponsor: Edgewise Therapeutics

Company Providing Support

Trial Acronym: CIRRUS-HCM

Clinical Trial Category (Industry, Non-Profit, or NIH-funded): Industry

Christopher Dufton[1], Marc Evanchik[1], Laura Emery[1], Alan Russel[1], and Marc Semigran[1]

[1]Edgewise Therapeutics

Hypertrophic cardiomyopathy (HCM) is a chronic, progressive disease of the sarcomere. A significant portion of affected individuals have at least one identifiable mutation in a gene that encodes sarcomere proteins. Regardless of the genetic variant present, excess myosin-actin crossbridge formation in systole and diastole leads to hyperdynamic contraction and impaired relaxation. Over time these abnormalities lead to tissue remodeling characterized histologically by myocyte hypertrophy, myofilament disarray, microvascular remodeling, and fibrosis. Clinically, patients experience fatigue, exertional dyspnea, and an increased risk of sudden cardiac death.

EDG-7500 is a novel, orally bioavailable, cardiac sarcomere modulator (CSM) designed to slow the rate of myocardial force generation in early systole and speed the rate of myocardial relaxation during early diastole. This molecule is being developed for the treatment of obstructive HCM (oHCM) and nonobstructive HCM (nHCM). Preclinical models demonstrate improved left ventricular (LV) compliance and distensibility and ameliorate LV outflow tract obstruction. In a Phase 1 healthy volunteer study, once-daily dosing of EDG-7500 was well tolerated for 14 days, and at plasma concentrations that exceed those demonstrating efficacy in nonclinical oHCM models, decreases in LVEF below normal were not observed.

The CIRRUS-HCM study is a first-in-patient, open-label study that will evaluate safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) in patients with oHCM or nHCM. A dose range of EDG-7500 will be evaluated in cohorts of patients with oHCM (single dose, once-daily for 28d) and nHCM patients (once-daily for 28d). Echocardiography will be used to assess the PD effects of EDG-7500 on myocardial systolic and diastolic function. Dose and exposure response relationships of the resulting echocardiography parameters along with safety and tolerability will be used to select doses for subsequent HCM patient studies. It is anticipated that participants in CIRRUS-HCM will be eligible for chronic administration of EDG-7500 in an open-label extension study.