Introduction and Background

Heart failure (HF) affects at least 6 million people in the United States, and its prevalence is projected to rise to 8 million by 2030.[1] Approximately half these cases consist of heart failure with reduced ejection fraction (HFrEF), a condition in which systolic function is decreased, leading to a decrease in cardiac output and a rise in filling pressures. Therapy for HFrEF depends on its severity, underlying cause(s), and patient comorbidities. Evidence-based options for management include angiotensin-converting enzyme inhibitors, β-blockers, angiotensin II receptor blockers, diuretics, aldosterone antagonists, positive inotropes, sodium glucose co-transporter 2 inhibitors [SGLT2i], and other medications; procedures and surgeries such as coronary bypass, valve repair or replacement, implantable cardioverter-defibrillators, biventricular pacing, ventricular assist devices, and heart transplantation; and dietary and lifestyle changes.

The number and diversity of these interventions underscores the complexity of managing HFrEF in both inpatient and outpatient settings. Guideline-directed medical therapy (GDMT) improves survival and readmissions,[2,3] but optimizing and adhering to GDMT is challenging. Omecamtiv mecarbil (OM), an investigational, first-in-class, selective small molecule cardiac myosin activator, enhances the ability of cardiac myosin to bind the actin filament and initiate a power stroke at the start of systole.[4] Unlike prior agents developed to improve cardiac function, OM does not increase calcium transients inside cardiomyocytes and thus does not increase risk for myocardial ischemia or ventricular arrhythmias.

Adding intravenous OM to standard HF therapy significantly improved the composite primary outcome of HF event or death from cardiovascular causes in a randomized, placebo-controlled, phase 3 trial of 8,256 inpatients and outpatients with HFrEF and LVEF $\leq$35% (GALACTIC-HF).[4] However, OM did not demonstrate effects on secondary or exploratory outcomes in this trial. In a subgroup analysis of patients with severe HFrEF (defined as NYHA symptom class III to IV, LVEF $\leq$30%, and hospitalization for HF within the past 6 months), OM significantly improved both the primary composite endpoint and cardiovascular mortality. Upon investigation, researchers determined that the benefits of OM were restricted to this GALACTIC-HF subgroup, for which OM also showed a good safety profile. Even though only about one-third of patients with HFrEF resemble this subgroup (i.e., they have LVEF ≤ 30%),[5] these patients account for about half of all HF hospitalizations and the majority of HF treatment costs.