Background

• Heart failure (HF) is a progressive disorder with a natural history punctuated by frequent recurrent hospitalizations and ultimately death.
• HF is a condition most commonly marked by cardiac systolic dysfunction.
• While several interventions have been shown to reduce the rate of HF hospitalizations and improve morbidity, including angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, aldosterone antagonists, coronary revascularization, and biventricular pacing, mortality and morbidity still remain high.
• Another target for treatment of HF is to improve myocardial contractility. 2
• Omecamtiv mecarbil (OM) is a novel therapy to increase cardiac contractility. It increases stroke volume, decreases filling pressures, and improves ventricular volumes by increasing the left ventricular systolic ejection time, without increasing the rate of left ventricular pressure development or heart rate, and without noticeable effect upon myocardial oxygen uptake, blood pressure, or coronary blood flow. 3

KEY Eligibility Criteria – Inclusion

• Male/female ≥ 18 and ≤ 85 years of age
• History of chronic stable HF and left ventricular systolic dysfunction (defined as requiring treatment for HF for a minimum of 4 weeks prior to screening)
• Treated for HF with stable, optimal pharmacological therapy
• Optimal therapy will include a beta-blocker and an ACE inhibitor and/or an angiotensin receptor blocker at doses shown to be efficacious in HF trials, unless not tolerated:
  - Stable therapy is defined as having no new HF drug class introduced or uptitrated ≤ 4 weeks prior to randomization.
• LVEF ≥ 40%
• At screening, NT-proBNP ≥ 200 pg/mL, ≥ 1200 pg/mL, or ≥ 1416 pg/mL if the subject has atrial fibrillation at presentation
• Subjects enrolled in expansion phase must have NYHA class II or III symptoms and an acceptable image quality of screening echocardiogram per central echo core laboratory

Cosmic-Hf: primary objectives

• To select an oral modified release (MR) formulation and dose of OM for chronic twice daily (BID) dosing in subjects with HF and left-ventricular systolic dysfunction.
• To characterize its pharmacokinetics (PK) over 20 weeks of treatment.

Cosmic-Hf: Secondary objectives

• To evaluate the safety and tolerability of oral OM
• To measure changes in systolic ejection time (SET), stroke volume, left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), and heart rate over 20 weeks of oral dosing with OM
• To evaluate the effect over 20 weeks of oral dosing with OM on N-terminal pro-B-type natriuretic peptide (NT-proBNP)
• To evaluate the PK of OM metabolites with oral OM dosing

Cosmic-HF: Trial: Study Design

• Multicenter, randomized, double-blind, placebo-controlled, dose escalation
• Dose escalation phase to select 1 of 3 OM oral formulations in 2 dose escalation cohorts, compared with placebo BID, for 7 days each.
  - Cohort 1: 25 mg BID
  - Cohort 2: 50 mg BID
  - Cohort 3 (contingent of) 75 mg BID was determined not to be necessary based on preclinical profiling data from cohorts 1 and 2
• Following completion of the escalation phase, an expansion phase to evaluate 20 weeks of administration of the selected formulation at 3 target dose levels
  - Approximately up to 550 subjects with HF and left ventricular systolic dysfunction
  - 40 subjects in each dose escalation cohort randomized 1:1:1 to receive 1 of 3 OM formulations (A, B, or C) or placebo
  - Approximately 450 subjects in expansion phase randomized 1:1:1 to receive the selected OM formulation at 1 of 2 target dose levels or placebo