Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): Final Results from a Double-blind, Randomized, Placebo-controlled, Multicenter Study


**Background:** Improving myocardial contractile function remains an attractive therapeutic target in patients with heart failure and reduced ejection fraction (HFrEF). Omecamtiv mecarbil (OM) is a novel selective cardiac myosin activator which when administered intravenously increases stroke volume by prolonging LV systolic ejection time (SET) without increasing heart rate or decreasing blood pressure. COSMIC-HF (NCT 01786512) was a Phase 2 study designed to select an oral modified-release formulation and dose of OM in patients with chronic HFrEF, and to characterize its pharmacokinetics (PK) and effects on cardiac function, as well as its safety and tolerability during 20 weeks of treatment.

**Methods:** COSMIC-HF was a two-phase, multicenter, randomized, double-blind, placebo-controlled trial in outpatients with a history of optimally-treated chronic HF, LVEF ≤40%, and NT-proBNP ≥200 pg/mL (≥1200 pg/mL in patients with atrial fibrillation). Two cohorts were studied during the initial dose escalation phase; Cohort 1 was randomized 1:1:1:1 to 25 mg BID of one of three OM oral formulations or placebo for 7 days. Cohort 2 was randomized in the same manner to 50 mg BID. Based on PK, safety and tolerability, one formulation was advanced into the expansion phase, where patients were randomized 1:1:1 to receive the selected OM formulation in one of two treatment groups (25 mg BID or PK-based dose escalation to 50 mg BID) or placebo for 20 weeks. PK, echocardiographic and other clinical variables were assessed.

**Results:** An oral formulation of OM was selected based on data from Cohorts 1 (n=49) and 2 (n=47) of the dose escalation phase (mean age 65 years, 21% female). The expansion phase completed enrollment and follow-up of 448 patients (mean age 63 years, 17% female). For the first time, the main results of COSMIC-HF, including Cmax/Ctrough (ng/ml), SET (msec), LV end-systolic dimension (mm), and adverse events will be presented.

**Conclusion:** In addition to providing information on the PK of the selected oral formulation, COSMIC-HF will furnish some data addressing the hypothesis that oral administration of OM can increase SET and provide a sustained effect on cardiac performance in patients with chronic HFrEF.

**Disclosure:**

**J.R. Teerlink:** Research Grant; Modest; Cytokinetics, Bayer, Trevena. Research Grant; Significant; Amgen and Novartis. Consultant/Advisory Board; Modest; Cytokinetics, Bayer, Travena. Consultant/Advisory Board; Significant; Amgen and Novartis. **G. Felker:** Research Grant; Significant; Amgen, Roche Diagnostics, Novartis, Otuska and NHLBI. Consultant/Advisory Board; Significant; served as a consultant for Amgen, Novartis, Roche Diagnostics, Singulex, Trevena, Celladon, Bristol Meyers Squibb, Merck and Medtronic. **J.J. McMurray:** Employment; Significant; Glasgow University has been paid by Cytokinetics/Amgen for his ime spent working on the clinical trial program with omecamtiv mecarbil.
Other; Modest; Travel accommodations costs paid by Cytokinetics/Amgen in relation to advisory board and clinical trial meetings about omecamtiv-mecarbil. **S.D. Solomon:** Other Research Support; Modest; Amgen. Consultant/Advisory Board; Modest; Amgen. **M. Monsalvo:** Employment; Significant; employee and stockholder of Amgen. **J. Legg:** Employment; Significant; employee and stockholder of Amgen. **F.I. Malik:** Employment; Significant; Stockholder of Cytokinetics. **N. Honarpour:** Employment; Significant; employee and stockholder of Amgen.