FEATURED STATE-OF-THE-ART REVIEW

Omecamtiv Mecarbil in Chronic Heart Failure With Reduced Ejection Fraction
Rationale and Design of GALACTIC-HF

John R. Teerlink, MD,[a] Rafael Diaz, MD,[b] G. Michael Felker, MD, MHS,[c] John J.V. McMurray, MD,[d] Marco Metra, MD,[e]
Scott D. Solomon, MD,[f] Jason C. Legg, PHD,[g] Gustavo Büchele, MD,[g] Claire Varin, MD,[h] Christopher E. Kurtz, MD,[g]
Fady I. Malik, MD, PHD,[i] Narimon Honarpour, MD, PHD[g]

HIGHLIGHTS

- Decreased systolic function is a central factor in HFrEF.

- Current and investigational inotropic calcitropic drugs have uniformly resulted in signals of increased mortality.

- OM is a myotrope and a selective cardiac myosin activator that improves cardiac function.

- The GALACTIC-HF trial evaluates the effect of OM on outcomes in patients with chronic HF.

ABSTRACT

A central factor in the pathogenesis of heart failure (HF) with reduced ejection fraction is the initial decrease in systolic function. Prior attempts at increasing cardiac contractility with oral drugs have uniformly resulted in signals of increased mortality at pharmacologically effective doses. Omecamtiv mecarbil is a novel, selective cardiac myosin activator that has been shown to improve cardiac function and to decrease ventricular volumes, heart rate, and N-terminal pro–B-type natriuretic peptide in patients with chronic HF. The GALACTIC-HF (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure) trial tests the hypotheses that omecamtiv mecarbil can safely improve symptoms, prevent clinical HF events, and delay CV death in patients with chronic HF. The GALACTIC-HF trial is an international, multicenter, randomized, double-blind, placebo-controlled, event-driven cardiovascular outcomes trial. More than 8,000 patients with chronic symptomatic (New York Heart Association functional class II to IV) HF, left ventricular ejection fraction ≤35%, elevated natriuretic peptides, and either current hospitalization for HF or history of hospitalization or emergency department visit for HF within a year of screening will be randomized to either oral placebo or omecamtiv mecarbil employing a pharmacokinetic-guided dose titration strategy using doses of 25, 37.5, or 50 mg twice daily. The primary efficacy outcome is the time to cardiovascular death or first HF event. The study has 90% power to assess a final hazard ratio of approximately 0.80 in cardiovascular death, the first secondary outcome. The GALACTIC-HF trial is the first trial examining whether selectively increasing cardiac contractility in patients with HF with reduced ejection fraction will result in improved clinical outcomes. (Registrational Study With Omecamtiv Mecarbil/AMG 423 to Treat Chronic Heart Failure With Reduced Ejection Fraction [GALACTIC-HF]; NCT02929329) (J Am Coll Cardiol HF 2020;8:329–40) Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ABBREVIATIONS AND ACRONYMS

ATP = adenosine triphosphate

CI = confidence interval

CV = cardiovascular

ETT = exercise treadmill test

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

OM = omecamtiv mecarbil

PK = pharmacokinetic

SET = systolic ejection time

Of the millions of patients with heart failure (HF) worldwide, at least one-half have HF with reduced ejection fraction (HFrEF). A central factor in the pathogenesis of HFrEF is the initial decrease in cardiac systolic function, yet for more than a century scientists and physicians have been unsuccessful in developing effective and safe oral therapies to directly improve systolic function. Omecamtiv mecarbil (OM) is a novel selective cardiac myosin activator that improves cardiac function in patients with chronic HFrEF [1]. The GALACTIC-HF (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure) trial will test the hypothesis that OM can safely improve clinical outcomes in patients with HFrEF.

HFrEF AND APPROACHES TO INCREASING CARDIAC CONTRACTILITY

THERAPEUTIC HYPOTHESIS. HFrEF is an insidious disorder resulting from loss or dysfunction of cardiomyocytes [2]. The consequent reduction in contractile function and increase in cardiac wall stress triggers multiple interrelated compensatory mechanisms, including neurohormonal activation and ventricular remodeling. This ventricular remodeling results in increased myocardial oxygen demand and reduced contractile efficiency, eventually promoting additional myocardial injury and cardiomyocyte death, perpetuating a negative feedback cycle that results in symptomatic HF and eventually death. Multiple life-saving therapies, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid antagonists, beta-blockers, and most recently, angiotensin receptor-neprilysin inhibitors, have been developed to address the neurohormonal activation in HFrEF. However, these therapies do not address the central driver in the pathogenesis of HFrEF, the initial decrease in systolic function. The hypothesis that improving systolic function will prevent or attenuate deleterious neurohormonal activation and ventricular remodeling, and consequently improve symptoms and reduce the incidence of subsequent clinical events such as HF hospitalizations and death has been pursued since the discovery of epinephrine in 1895.

FAILURE OF INOTROPES THAT INCREASE INTRACELLULAR CALCIUM (CALCITROPES). Many clinical programs have developed oral inotropic drugs in chronic HFrEF, all of which have failed to reduce mortality (**Table 1**). These drugs shared the common mechanism of increasing intracellular calcium to affect an increase

TABLE 1 Clinical Trials With Oral Calcitropic Drugs in Chronic Heart Failure
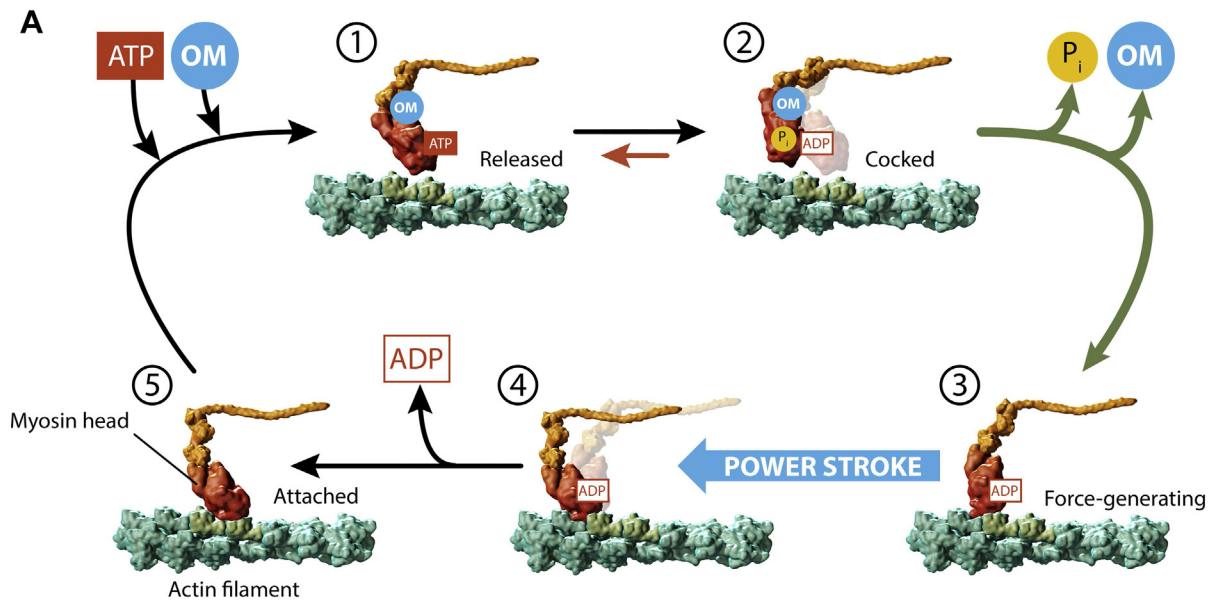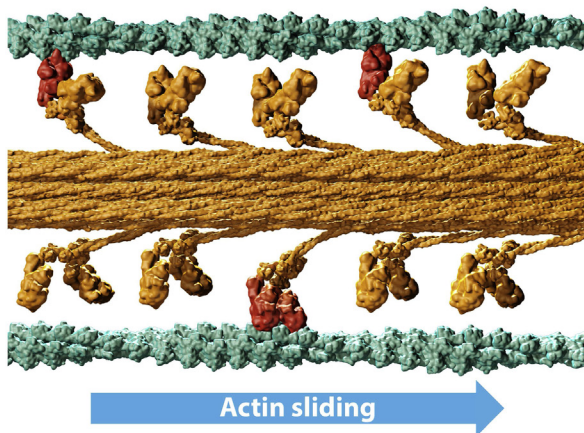
Clinical Trial (Ref. #)	Calcitrope	Year	N	Key Inclusion Criteria	Effects on Mortality
Xamoterol (Supplemental Ref. 1)	Xamoterol	1990	516	LVEF <35%, NYHA functional class III-IV	Xamoterol: 32 deaths/n = 352 (9.1%) Placebo: 6 deaths/n = 164 (3.7%) Within 100 days of randomization (p = 0.02)
PROMISE (Supplemental Ref. 2)	Milrinone	1991	1,088	LVEF ≤35%, NYHA functional class III-IV	Milrinone: 168 deaths/n = 561 (30%) Placebo: 127 deaths/n = 527 (24%) Log-rank test: 28% increase mortality; 95% CI: 1%-61%; p = 0.038
PROFILE (Supplemental Ref. 3)	Flosequinan	1993	2,345	LVEF ≤35%, NYHA functional class III-IV	Flosequinan: 255 deaths/n = 1,170 Placebo: 192 deaths/n = 1,175 HR: 1.39; 95% CI: 1.15-1.67; p = 0.0006
PICO (Supplemental Ref. 4)	Pimobendan	1996	317	LVEF ≤45%, NYHA functional class II-III	Pimobendan (2.5 mg): 13 deaths/n = 106; HR: 1.5; 95% CI: 0.9-2.5 Pimobendan (5.0 mg): 11 deaths/n = 103 HR: 1.2; 95% CI: 0.7-2.1 Placebo: 6 deaths/n = 108
PRIME II (Supplemental Ref. 5)	Ibopamine	1997	1,906	LVEF <35%, NYHA functional class III-IV	Ibopamine: 232 deaths/n = 953 (25%) Placebo: 193 deaths/n = 953 (20%) Relative risk: 1.26; 95% CI: 1.04-1.53; p = 0.017
VEST (Supplemental Ref. 6)	Vesnarinone	1998	3,833	LVEF ≤30, NYHA functional class III-IV	Vesnarinone (60 mg): 292 deaths/n = 1,275 (22.9%) p = 0.02 vs. placebo Vesnarinone (30 mg): 268 deaths/n = 1,275 (21.0%) p = 0.21 vs. placebo Placebo: 242 deaths/n = 1,283 (18.9%)
Enoximone Multicenter Trial (Supplemental Ref. 7)	Enoximone	1990	102	LVEF ≤40%, NYHA functional class II-III	Enoximone: 10 deaths/n = 50 Placebo: 3 deaths/n = 52 p < 0.05
EMOTE Trial (Supplemental Ref. 8)	Enoximone	2007	201	LVEF ≤25%, NYHA functional class IV, inotrope dependence	Enoximone: 38 deaths/n = 101 Placebo: 31 deaths/n = 100 p = 0.37
ESSENTIAL Trials Program (Supplemental Ref. 9)	Enoximone	2009	1,854	LVEF ≤35%, NYHA functional class III-IV (2 trials)	Enoximone: 196 deaths/n = 926 (21.2%) Placebo: 203 deaths/n = 928 (21.9%) HR: 0.97; 95% CI: 0.80-1.17; p = 0.73 (Note: No improvement in major clinical outcomes)

CI = confidence interval; EMOTE = EnoxiMone in intravenous inOTropE-dependent subjects; ESSENTIAL = Studies of Oral Enoximone Therapy in Advanced HF; HR = hazard ratio; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PICO = Pimobendan in Congestive Heart Failure; PRIME = Prospective Randomised Study of Ibopamine on Mortality and Efficacy; PROFILE = Prospective Randomized Flosequinan Longevity Evaluation; PROMISE = Prospective Randomized Milrinone Survival Evaluation; VEST = Vesnarinone Trial.

in cardiac function and most also had confounding vasoactive or electrophysiologic properties. A recent proposal classifies these drugs that increase myocardial force production by altering the concentration of intracellular Ca^{2+} as calcitropes (3).

Beta-adrenergic agonists increase cardiac contractility by stimulating the beta-adrenergic receptor, resulting in generation of cAMP. As a second messenger, cAMP promotes phosphorylation of L-type calcium channels to increase calcium influx as well as ryanodine receptor-mediated sarcoplasmic reticulum calcium release. These agents also increase heart rate and may have mild vasodilatory actions. Xamoterol, a β_1-selective partial adrenergic agonist, increased mortality within 100 days of randomization in a study of 516 patients with chronic HF. Ibopamine, a dopamine-1, dopamine-2, and alpha-adrenergic receptor agonist with mild beta-1 and beta-2 adrenergic agonist activity demonstrated a 26% excess of deaths in patients with HFrEF. Phosphodiesterase-3 inhibitors increase cardiac contractility by reducing the degradation of cAMP, resulting in prolonged and increased signaling with significant increases in intracellular calcium. These agents are also potent vasodilators. All of the oral phosphodiesterase-3 inhibitor drugs, including milrinone, pimobendan, and enoximone, have demonstrated signals of increased mortality in chronic HF outcome studies. The largest of these trials investigated the role of 2 doses of the phosphodiesterase-3 inhibitor vesnarinone compared with placebo in 3,833 patients with symptomatic HF and left ventricular ejection fraction (LVEF) ≤30%. There were significantly more deaths in the 60-mg vesnarinone group (292 deaths, or 22.9%) than in the placebo group (242 deaths, or 18.9%) (p = 0.02). Another calcium-based mechanism for increasing cardiac contractility is to reduce Na^+/Ca^{2+} exchange, thereby increasing intracellular calcium, and it is a putative mechanism of action of flosequinan, which also has marked vasodilating activity. Despite symptomatic improvements, flosequinan-treated patients had increases in heart rate and norepinephrine plasma concentrations, and the PROFILE (Prospective Randomized Flosequinan Longevity Evaluation) trial was terminated due to a 39% increase in mortality. Of note, the excess mortality signal was readily evident

CENTRAL ILLUSTRATION Mechanism of Action of Omecamtiv Mecarbil
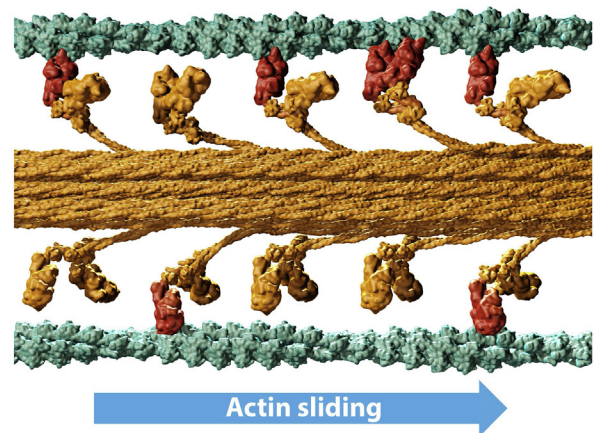
Teerlink, J.R. et al. J Am Coll Cardiol HF. 2020;8(4):329–40.

Omecamtiv mecarbil (OM) stabilizes the pre-powerstroke state of myosin enabling more myosin heads to undergo a powerstroke during systole. **(A)** During diastole, myosin exists in an equilibrium between an adenosine triphosphate (ATP) state **(1)** and an adenosine diphosphate (ADP)-P_i state **(2)**; the forward and backward arrows between **(1)** and **(2)**, denoting the forward and backward transition rates of ATP hydrolysis, are usually of roughly equal length. State **(2)** is the "pre-powerstroke" state and capable of binding to actin. During systole, a subset of myosin heads (10% to 15%) in the pre-powerstroke conformation engage binding sites on actin **(3)**, release P_i, and undergo a powerstroke to generate force **(4)**, shortening the sarcomere. The loss of ADP **(5)** and subsequent binding of ATP releases the myosin from the actin filament. The duration of systole is long enough, in general, for myosin to undergo this cycle only once. OM binds with highest affinity to the pre-powerstroke state **(2)** by more than 6-fold compared with the other states, stabilizing the myosin head in that conformation and shifting the equilibrium in diastole toward state **(2)** by reducing the transition rate back to state **(1) (shorter red arrow)**. With more myosin heads in state **(2)**, the number of myosin heads ready to bind to the actin filaments and undergo a powerstroke also increases **(thicker green arrow)**, thus producing more force during each cycle of cardiac contraction. A simple analogy is that there are multiple hands available to pull on a rope; the more hands (the myosin heads) that can grasp the rope (the actin filament) to pull, the more force is produced during each contractile cycle. This principle is illustrated in **B and C**. OM = omecamtiv mecarbil; ADP = adenosine diphosphate; ATP = adenosine triphosphate.

TABLE 2 Selected Clinical Studies With Omecamtiv Mecarbil

Trial (Phase), Year(s) (Ref. #)	Subjects	Dose (Route)	Design	Endpoints	Major Outcomes
NCT01380223 (I), 2005–2006 (10)	Young, healthy, 85% white, male subjects in 4 successive cohorts of 8 (n = 34)	0.005–1.0 mg/kg/h for 6 h (IV)	Double-blind, placebo-controlled, dose-escalating, crossover, single-center trial	1. Maximum infusion dose tolerated in ≥8 subjects for 6 h. 2. Safety, tolerability, pharmacokinetics, pharmacodynamics.	1. Maximum tolerated infusion 0.5 mg/kg/h. 2. Dose-dependent linear increase in SET ($r^2 = 0.99$), with increased LVEF, FS, and SV. $t_{1/2}$ = 17.1–21.0 h. Cardiac ischemia in some participants at plasma concentrations >1,200 ng/ml.
NCT00624442 (II), 2007–2009 (11)	Stable HF, 87% male, 64% ischemic, HFrEF, LVEF ≤40% or LVEF ≤30% in cohort 4 (n = 45)	Loading 0.125–1.0 mg/kg/h; Maintenance 0.0625–0.5 mg/kg/h (IV)	Double-blind, placebo-escalating, crossover, multicenter international trial	1. Safety and tolerability for 2, 24, and 72 h. 2. Establish tolerated range of pharmacologically active plasma concentrations.	1. Cardiac ischemia at plasma concentrations >1,300 ng/ml. 2. Dose-dependent increases in SET, FS, LVEF, SV, and CO; decreased HR, QTc, LVESV, LVEDV, and standing SBP and DBP.
NCT00682565 (II), 2008 (13)	Stable HF, 80% male, ischemic HFrEF with LVEF ≤35% and angina (n = 94)	Loading 24–48 mg/h for 2 h, then maintenance 6–11 mg/h for 18 h (IV)	Double-blind, placebo-controlled, randomized, multicenter study	1. Safety and tolerability exercise during infusion; proportion stopping ETT due to angina at earlier stage than baseline. 2. Duration of exercise, angina, ECG changes.	1. Only 1 patient (receiving placebo) stopped ETT early due to angina. 2. No statistical difference in time to angina, exercise duration, or ischemic ECG changes.
NCT01786512 ATOMIC-AHF (IIb), 2013–2015 (14)	Acute HFrEF, 77% male, 88% white, 62% ischemic, with LVEF ≤40%, dyspnea and elevated BNP (n = 613)	Loading 7.5–20 mg/h for 4 h, then maintenance 1.5–4 mg/h for 44 h (IV)	Double-blind, placebo-controlled, dose-escalating, randomized international multicenter trial	1. Dyspnea relief by 7-point Likert-type scale at 6, 24, and 48 h without worsening HF or death. 2. Safety and tolerability, biomarkers, hospital length of stay, 30-day morbidity, and mortality.	1. No benefit for dyspnea relief at 6, 24, or 48 h vs. pooled placebo; improved dyspnea in third cohort vs. paired placebo. 2. No benefit for 30-day death or worsening HF, length of stay, or NT-proBNP; increased SET and SBP; decreased HR and LVESD.
NCT01300013 COSMIC-HF (IIb), 2011–2015 (15)	Expansion phase: stable HF, 83% male, >90% white, HFrEF with LVEF ≤40% and elevated NT-proBNP (n = 448)	25 mg twice-daily or PK-guided titration to 50 mg twice daily (oral)	Double-blind, placebo-controlled, dose-escalating, randomized, multicenter, international trial	1. Pharmacokinetics of modified release dosing over 20 weeks. 2. Safety and tolerability, echocardiographic, and biomarker changes over 20 weeks.	1. Modified release allowed titration to 50 mg twice daily in 60% of patients. 2. Increased SET and SV and decreased HR, LVESV, LVEDV, and NT-proBNP; asymptomatic small increased troponin at 20 weeks: 0.001 ng/ml with 25 mg and 0.006 ng/ml with 25–50 mg twice daily.

Modified with permission from Psotka et al. (1).

BNP = B-type natriuretic peptide; CO = cardiac output; COSMIC-HF = Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure; DBP = diastolic blood pressure; ECG = electrocardiogram; ETT = exercise tolerance test; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; IV = intravenous; LVEDD = left ventricular end diastolic dimension; LVEDV = left ventricular end diastolic volume; LVESD = left ventricular end systolic dimension; LVESV = left ventricular end systolic volume; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PK = pharmacokinetic; QTc = corrected QT interval; SBP = systolic blood pressure; SET = systolic ejection time; SV = stroke volume; $t_{1/2}$ = plasma half-life; other abbreviations as in **Table 1**.

in most of these trials with approximately 400 death events. Attempts at increasing cardiac contractility with oral calcitropes have uniformly resulted in signals of increased mortality at pharmacologically effective doses. The challenge for these agents is that their adverse effects, including increased mortality, are inextricably linked to their mechanism of benefit.

OM, A NOVEL CARDIAC MYOSIN ACTIVATOR

MECHANISM OF ACTION AND PRECLINICAL STUDIES. OM was developed to address the hypothesis that direct activation of the human sarcomere could augment cardiac performance without the adverse effects of conventional inotropic agents. To pursue this

hypothesis, a high-throughput screen of approximately 400,000 small-molecule compounds in a biochemically reconstituted sarcomere was performed and identified small-molecule activators of cardiac myosin. An initial lead compound was further optimized for potency, physical properties, and pharmacokinetics, culminating in the synthesis of OM (4-6).

OM is a selective cardiac myosin activator that increases cardiac contractility by specifically binding to myosin at an allosteric site (**Central Illustration**) that stabilizes its lever arm in a primed position, resulting in accumulation of cardiac myosin heads in the primed pre-powerstroke state prior to onset of cardiac contraction (7). This has the effect of increasing the number of "force generators" (myosin heads) that can

bind to the actin filament and undergo a powerstroke once the cardiac cycle starts. By stabilizing the pre-powerstroke state, OM also decreases the turnover of adenosine triphosphate (ATP) in the absence of an interaction with the actin filament, potentially increasing the overall energetic efficiency of the system by diminishing ATP use not associated with mechanical work. OM increases the contraction of isolated cardiomyocytes by direct action on the myofilament, as a myotrope (3), in the absence of changes in the cardiomyocyte calcium transient (4,8). The lack of change in the calcium transient differentiates OM from the mechanism of current calcitropes such as β-adrenergic receptor agonists or phosphodiesterase inhibitors.

In preclinical models, OM produced dose- and concentration-dependent increases in cardiac function as assessed by echocardiography in both Sprague Dawley rats and beagle dogs (4). In a conscious dog model of HF produced through a combination of myocardial infarction followed by continuous rapid ventricular pacing, OM increased fractional shortening, myocardial wall thickening, systolic ejection time, stroke volume, and cardiac output measured by implanted hemodynamic and ultrasonographic sensors. OM decreased heart rate and left atrial pressure without accompanying changes in mean arterial pressure or change in pressure with respect to time (dP/dt). No statistically significant changes in myocardial blood flow and oxygen consumption were observed (9).

Altogether, OM increased cardiac performance in the absence of adverse changes in heart rate, blood pressure, and myocardial oxygen consumption in preclinical studies at clinically relevant concentrations, supporting its advancement into clinical studies.

PHASE 1 AND PHASE 2 CLINICAL EXPERIENCE. Prior to the initiation of the GALACTIC-HF trial, OM was administered to more than 1,000 participants in 16 completed clinical studies (Table 2). The overall objective of the phase 1 and phase 2 development program was to carefully characterize the safety and tolerability, pharmacokinetics, and effect on cardiac function in relation to dose and exposure of OM prior to the conduct of more sizable trials in patients with acutely decompensated HF and with chronic HF. The latter trials served to inform the design of a cardiovascular (CV) phase 3 outcomes study, the GALACTIC-HF trial.

Intravenous OM was initially studied in 34 healthy young men (10) and subsequently in 45 stable patients with chronic HF and LVEF ≤40% (11). In both studies, OM produced dose-dependent increases in systolic ejection time (SET), fractional shortening, stroke volume, and LVEF, and decreases in ventricular volumes. A risk of symptomatic myocardial ischemia was associated with plasma concentrations >1,200 ng/ml. Additional phase 1 studies defined the pharmacokinetic profile of orally administered OM and demonstrated low potential for clinically significant drug-drug interactions (10-12).

The safety and tolerability of OM in the presence of exercise and elevated heart rates were assessed in 95 patients with chronic stable ischemic HFrEF, LVEF ≤35%, and exercise-induced angina (Table 2) (13). After 2 baseline, symptom-limited exercise treadmill tests (ETTs), patients were later randomized to blinded 20-h infusions of placebo or OM. On the repeat ETT performed prior to completion of the study drug infusion, there was no difference in the primary endpoint (proportion of patients stopping the ETT during infusion at a stage earlier than baseline due to angina) between the groups (only 1 patient in the placebo group stopped their on-treatment ETT a stage early due to angina), supporting the safety of OM in a population prone to inducible ischemia.

The ATOMIC-AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure) study (Table 2) (14) randomized 606 patients hospitalized for acute HF with LVEF ≤40%, dyspnea, and elevated natriuretic peptides in 3 ascending-dose cohorts to 48-h infusions of placebo or OM. Concentration-dependent increases in SET and systolic blood pressure, and decreases in heart rate and left ventricular end-systolic dimensions were observed. The ATOMIC-AHF trial did not demonstrate a statistically significant difference in its primary outcome of improvement in dyspnea at 48 h in the individual OM treatment groups when compared with the pooled placebo groups, but a prespecified sensitivity analysis demonstrated a 41% relative increase in dyspnea relief with the highest OM dose compared with its matched placebo group, a finding supported by a nominally significant dose- and concentration-dependent effect on dyspnea relief. Plasma troponin concentrations were slightly higher in OM-treated patients compared with placebo-treated patients (median difference at 48 h, 0.004 ng/ml) but with no relationship with OM concentration (p = 0.95). Adverse events were similar, with numerically fewer patients on OM than on placebo developing supraventricular tachycardias (1.0% vs. 8.0%) or renal failure (11.9% vs. 17.2%) during the infusions. Thus, ATOMIC-AHF trial provided evidence for the safety and tolerability of OM in an acutely decompensated HF population and suggested increased dyspnea relief.

FIGURE 1 Prespecified Efficacy Variables in the COSMIC-HF Study
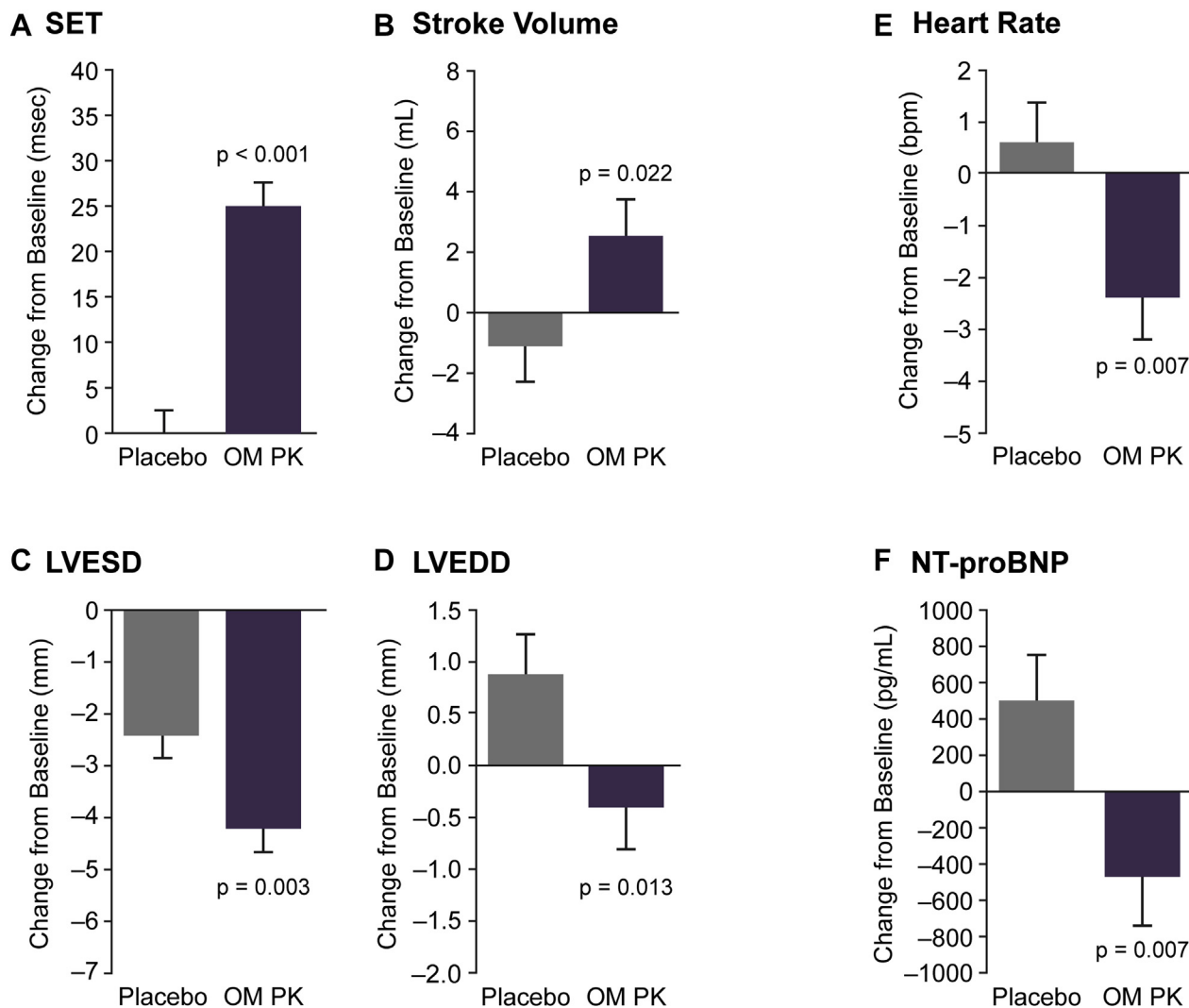
The COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) study had 6 prespecified efficacy variables: **(A)** systolic ejection time (SET), **(B)** stroke volume, **(C)** left ventricular end-systolic dimension (LVESD), **(D)** left ventricular end-diastolic dimension (LVEDD), **(E)** heart rate, and **(F)** N-terminal pro-B-type natriuretic peptide (NT-proBNP). The least-squares mean ± SEM changes from baseline at week 20 are shown by treatment group: placebo and omecamtiv mecarbil (OM) pharmacokinetic-guided dose titration (PK) group. The p values represent comparisons to placebo group using a repeated-measures model. The model was fitted separately for each variable and included the stratification factor of presence or absence of atrial fibrillation or flutter at randomization, baseline value, treatment group, visit, and the treatment group by visit interaction. Modified with permission from Teerlink et al. (15).

The COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) trial evaluated the role of 20 weeks of OM in patients with stable HF (15). The expansion phase in the COSMIC-HF trial enrolled 448 outpatients with chronic symptomatic HFrEF (New York Heart Association functional class II or III), LVEF ≤40%, and elevated natriuretic peptides. Patients were randomized 1:1:1 to placebo or 25 mg of oral OM twice daily, or an oral OM pharmacokinetic (PK)-guided dose titration group (initial 25 mg twice daily dose increased to 50 mg twice daily depending on a trough plasma concentration of OM after 2 weeks of initial therapy) for a total duration of 20 weeks. In addition to achieving its primary objective of demonstrating stable pharmacokinetics of the selected formulation, all of the prespecified secondary efficacy endpoints were significantly improved in the OM PK-guided

FIGURE 2 Schematic of Study Design for the GALACTIC-HF Trial
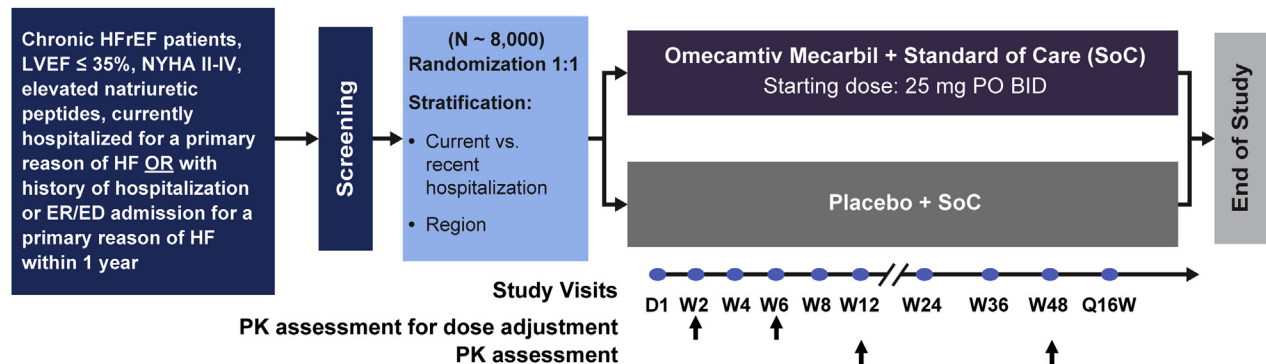
Overview of study design including summary patient inclusion criteria, randomization stratification variables, and visit schedule for GALACTIC-HF. BID = twice daily; D = day; ED = emergency department; ER = emergency room; GALACTIC-HF = Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PK = pharmacokinetic; PO = orally; Q16W = every 16 weeks; SoC = standard of care; W = week.

dose titration group (**Figure 1**). In a community cohort study, a shorter left ventricular ejection time was predictive of incident HF (16), and SET has been shown to be decreased by 10 to 70 ms in patients with HF (17). SET is also a pharmacodynamic marker of OM action, and was significantly increased in the OM PK-guided dose titration group by 25 ms (95% confidence interval [CI]: 18 to 32 ms; p < 0.0001), suggesting that OM shifts patients toward a normal ejection duration. Improved cardiac function was reflected in the increased stroke volume and reduced end-systolic dimensions, while reverse cardiac remodeling was suggested by a decrease in end-diastolic dimensions. The improvement in cardiac performance also appeared to result in reduced ventricular wall stress, as reflected in the decreased N-terminal pro-B-type natriuretic peptide (NT-proBNP), and sympathetic withdrawal, supported by the decreased heart rate. Treatment with OM for 20 weeks was associated with asymptomatic increases in median plasma troponin of 0.006 ng/ml (95% CI: 0 to 0.024 ng/ml) in the PK-guided dose titration group. In epidemiologic studies, increased troponin is typically associated with worsened clinical outcomes; however, for this therapeutic intervention, the clinical significance of the increase in troponin remains unclear. In the COSMIC-HF trial, the increase in troponin occurred in the context of decreased NT-proBNP, reduced heart rate and improved ventricular volumes, generally markers of patient improvement and reduced risk. There was no correlation of the troponin increases with peak plasma concentrations of OM and no asymptomatic troponin elevation events were

positive for myocardial ischemia or infarction after review by independent adjudicators. This magnitude of change in troponin is evident during diurnal variation (18) or after vigorous endurance exercise (19). Additionally, there are examples of therapeutically beneficial drugs that can cause unfavorable biomarker changes (e.g., angiotensin-converting enzyme inhibitors or angiotensin receptor blockers: increased creatinine; angiotensin receptor neprilysin inhibitors: increased microalbuminuria). In the COSMIC-HF trial, OM had a tolerability and adverse event profile that was similar to placebo, and there were no differences in atrial or ventricular arrhythmias, myocardial ischemia, or hypotension. Overall, the results of the COSMIC-HF trial supported the progression of OM into a CV outcomes trial to definitively assess the balance of benefit and risk for this novel therapeutic approach.

THE GALACTIC-HF TRIAL: STUDY DESIGN AND METHODS

The GALACTIC-HF trial (NCT02929329) (**Figure 2**) trial is a multicenter, randomized, double-blind, placebo-controlled CV outcomes trial to evaluate the efficacy, safety, and tolerability of OM in patients with chronic HFrEF. The primary outcome of the trial is the time to the first occurrence of CV death or an HF event. More than 8,000 patients receiving standard-of-care background HF therapy recruited from both the hospital and outpatient settings were randomized in a 1:1 fashion to OM or placebo. Patients were to receive study treatment from the time of their randomization

TABLE 3 Selected Inclusion And Exclusion Criteria In The GALACTIC-HF Trial

Key Inclusion Criteria	Key Exclusion Criteria
Male or female, ≥18 to ≤85 yrs of age	Receiving mechanical hemodynamic support (e.g., intra-aortic balloon pump counterpulsation), or invasive mechanical ventilation ≤7 days prior to randomization
History of chronic HF (defined as requiring treatment for HF for a minimum of 30 days before randomization)	Receiving IV inotropes (e.g., dobutamine, milrinone, levosimendan) or IV vasopressors (e.g., epinephrine, norepinephrine, dopamine, or vasopressin) ≤3 days prior to randomization
LVEF ≤35%, per subject's most recent medical record, within 12 months prior to screening. The most recent qualifying LVEF must be at least 30 days after any of the following, if applicable: 1) an event likely to decrease EF (e.g., myocardial infarction, sepsis); 2) an intervention likely to increase EF (e.g., cardiac resynchronization therapy, coronary revascularization); or 3) the first ever presentation for HF	Receiving IV diuretic agents or IV vasodilators, supplemental oxygen therapy, or noninvasive mechanical ventilation (e.g., BiPAP or CPAP) ≤12 h prior to randomization (Note: the use of noninvasive ventilation for sleep disordered breathing is permitted)
NYHA functional class II to IV at most recent screening assessment	Acute coronary syndrome (ST-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction, unstable angina), stroke, or transient ischemic attack, major cardiac surgery or cardiac intervention (i.e., implantation of cardiac closure devices, cardiac resynchronization therapy, or catheter ablation), percutaneous coronary intervention, or valvuloplasty/other cardiac valve repair or implantation within the 3 months prior to randomization
Managed with HF SoC therapies consistent with regional clinical practice guidelines according to investigator judgment of subject's clinical status. Oral SoC therapies for chronic HF (e.g., beta-blockers, renin-angiotensin-aldosterone system inhibitors) should be present, if not contraindicated. Subjects enrolled during either HF hospitalization or early after HF hospitalization discharge can be reinitiating or titrating oral SoC chronic HF therapies at the same time of randomization with the goal of achieving optimized therapy on study	Insertion of other cardiac devices (e.g., implantable cardioverter-defibrillator, permanent pacemaker, monitoring devices) within 30 days prior to randomization
Currently hospitalized with primary reason of HF *OR* 1 of the following events within 1 yr to screening: 1) hospitalization with primary reason of HF; 2) urgent visit to ED with primary reason of HF	Severe uncorrected valvular heart disease, hypertrophic or infiltrative cardiomyopathy, active myocarditis, constrictive pericarditis, or clinically significant congenital heart disease
BNP level ≥125 pg/ml or an NT-proBNP level ≥400 pg/ml at most recent screening assessment (subjects receiving ARNi must use NT-proBNP assessment; for subjects in atrial fibrillation/flutter at screening, the cutoff levels are: BNP ≥375 pg/ml or NT-proBNP ≥1,200 pg/ml)	Untreated severe ventricular arrhythmia (e.g., ventricular tachycardia or ventricular fibrillation)
	Routinely scheduled outpatient intravenous infusions for HF (e.g., inotropes, vasodilators [e.g., nesiritide], diuretics) or routinely scheduled ultrafiltration
	Systolic blood pressure >140 mm Hg or <85 mm Hg, or diastolic blood pressure >90 mm Hg, or heart rate >110 beats/min, or <50 beats/min at screening
	Estimated glomerular filtration rate <20 ml/min/1.73 m^2 or receiving dialysis at screening
	Severe, concomitant non-CV disease that is expected to reduce life expectancy to <2 yrs
	Recipient of any major organ transplant (e.g., lung, liver, heart, bone marrow, renal) or anticipated to receive chronic mechanical circulatory support or heart transplantation within 12 months from randomization
	Planned to be discharged from the hospital to long term care facility (e.g., skilled nursing facility) or hospice.
	History or evidence of any other clinically significant disorder (including cardiac arrhythmia), condition or disease (with the exception of those outlined previously) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion

See the Supplemental Appendix for a full listing.

ARNi = angiotensin receptor-neprilysin inhibitor; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CV = cardiovascular; ED = emergency department; GALACTIC-HF = Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure; SoC = standard of care; other abbreviations as in Tables 1 and 2.

until 1,590 CV deaths, the secondary outcome on which the trial is powered, had occurred.

The GALACTIC-HF trial Executive Committee (Supplemental Appendix) designed the trial and wrote the study protocol in collaboration with the clinical team from Amgen, Cytokinetics, and Servier. The protocol was approved by the Ethics Review Committee/Institutional Review Board affiliated with each center and the trial is being conducted in accordance with Good Clinical Practice and the Declaration of Helsinki 2002. All participants provided written informed consent. The trial is internationally registered (EU Clinical Trials Register 2016-002299-28).

STUDY POPULATION. The inclusion and exclusion criteria of the GALACTIC-HF trial (summarized in Table 3; see Supplemental Table 1 for full listing) were designed to enroll patients with symptomatic HF due to reduced ejection fraction and at an increased risk for HF events, including CV death. In addition to selecting patients most likely to benefit from the cardiac performance enhancing effects of OM, the higher expected event rate with lower ejection fraction informed the selection of the upper limit for ejection fraction of 35%. Increased concentrations of natriuretic peptides provide objective evidence of HF and are associated with increased rates of HF

hospitalizations and CV death. Given that atrial fibrillation independently increases natriuretic peptide concentrations and to avoid disproportionate enrichment of atrial fibrillation in the enrolled population, a higher threshold for natriuretic peptides was selected for patients in atrial fibrillation. Prior hospitalization for HF is a recognized risk factor for rehospitalization, but recent data demonstrate that visits to emergency departments for HF also confer a substantial risk for rehospitalization (20).

Predischarge initiation of new therapies improves medication adherence and clinical outcomes (21–23), yet clinical trials of chronic HF therapies have traditionally excluded these patients. One of the goals of the GALACTIC-HF trial was to establish the safety and efficacy of OM in these patients. The absence of any known adverse effects of OM on renal function, serum potassium, blood pressure, or heart rate suggested that in-hospital initiation would not interfere with initiation or up-titration of guideline-directed medical therapies. Thus, the entry criteria were designed to enable inclusion of a substantial proportion (approximately 25%) of patients currently hospitalized for HF.

Given the lack of adverse effects on blood pressure, heart rate, and renal function observed in the phase 2 program, inclusive thresholds were designed for these parameters. Patients with a systolic blood pressure of >85 mm Hg were eligible; however, patients with moderate hypertension defined as systolic blood pressure of >140 mm Hg or diastolic blood pressure >90 mm Hg were excluded on the assumption that medical therapy for the patient had not been optimized. Similarly, patients with a heart rate >110 beats/min or <50 beats/min at screening were excluded. With respect to renal function, the cutoff for estimated glomerular filtration rate was <20 ml/min/1.73 m^2.

STUDY TREATMENT. The formulation of OM administered in GALACTIC-HF trial was selected on the basis of the pharmacokinetic and efficacy results from the COSMIC-HF trial (15). Study drug was supplied as identical OM tablets or matching placebo, and was administered twice daily in the morning and evening under fasted or fed conditions, beginning at 25 mg twice daily. If a dose was missed, the next dose was taken without replacement.

To enhance the proportion of patients randomized to OM achieving plasma concentrations of at least 200 ng/ml, while avoiding concentrations >1,000 ng/ml, a guided dose titration strategy was adopted (Supplemental Appendix). After 2 weeks of 25 mg twice daily, a trough plasma concentration of OM was measured and at week 4 with the patient and

investigator blinded to the plasma concentrations and dispensed dose, the dispensed study drug was adjusted (25 mg twice daily maintained for plasma concentration ≥300 and <1,000 ng/ml; 37.5 mg twice daily for ≥200 and <300 ng/ml; 50 mg twice daily for <200 ng/ml). Another trough plasma concentration of OM was measured at week 6, and depending on this plasma concentration, a new study drug supply was dispensed at week 8. OM levels were then measured at week 12, week 48, and every 48 weeks thereafter in a blinded fashion but were not used to adjust dose. After week 8, visits occurred at weeks 12, 24, 36, and 48, and every 16 weeks thereafter, with study drug dispensed at each visit. Assessment of study drug adherence is checked by pill counts at all study drug dispensation visits and at end of study, and encouraged at all visits.

STUDY ASSESSMENTS. Screening and randomization. All subjects signed informed consent prior to screening (Supplemental Appendix). OM was supplied as a modified release formulation requiring an intact pill, so a "placebo run-in" was done consisting of observed oral administration of a single placebo pill to ensure that participants could swallow pills whole without chewing, crushing or splitting. Central laboratories were measured to satisfy respective eligibility criteria. To facilitate enrollment of hospitalized participants, patients could qualify for enrollment using local lab values (including local BNP), but central values were drawn in all cases. Subjects meeting eligibility requirements were randomized 1:1 via an interactive web-based system to OM or placebo in a double-blind manner, stratified by randomization setting (inpatient or outpatient) and region. To be classified as inpatient, patients were randomized and received their first test dose of study drug prior to hospital discharge.

Events and endpoints. At every visit, adverse events and study endpoints were assessed. All deaths, HF events, major cardiac ischemic events (myocardial infarction or unstable angina hospitalization, and coronary revascularization), and strokes are adjudicated by an independent external Clinical Events Committee (Duke Clinical Research Institute) using standardized definitions (Supplemental Appendix) (24).

The primary outcome of the trial is the time to the first occurrence of CV death or an HF event. Given the importance of CV mortality, the sample size was chosen to power the GALACTIC-HF trial for CV death, which was also the first secondary endpoint in a hierarchical testing procedure (Supplemental Appendix, Supplemental Table 2). An HF event was defined as an

urgent, unscheduled clinic, office, or emergency department visit or hospital admission with a primary diagnosis of HF in which the patient exhibited new or worsening symptoms of HF on presentation, had objective evidence of new or worsening HF, and received initiation or intensification of treatment specifically for HF. This definition is consistent with recent standardized regulatory guidance (24) and accounts for the evolving treatment patterns for decompensated HF. A recent study has shown that the risk of death was similar in patients with outpatient intensification of HF therapy (hazard ratio: 4.8; 95% CI: 3.9 to 5.9), emergency department visit (hazard ratio: 4.5; 95% CI: 3.0 to 6.7), or hospitalizations (hazard ratio: 5.9; 95% CI: 5.2 to 6.6) for worsening HF (20), supporting the clinical relevance of these other HF events.

In the COSMIC-HF study, the total symptom score of the Kansas City Cardiomyopathy Questionnaire at 20 weeks was significantly improved in OM-treated patients, with the largest differences relative to placebo observed in the subgroup of moderately to severely symptomatic patients at baseline, with trends in improvements in both frequency and burden of symptoms (25). To evaluate the potential symptomatic benefit of OM, several validated patient-reported outcome instruments (Kansas City Cardiomyopathy Questionnaire, EuroQOL-5 Dimensions Questionnaire) were administered at day 1, every 12 weeks through week 48, and yearly thereafter. Subjects were asked to complete these questionnaires in a quiet place prior to the medical consultation and other tests and procedures to avoid biasing responses. Site staff checked the questionnaires for completeness before the end of the visit. Clinician Global Rating Severity and NYHA functional class were also assessed at screening and all study visits.

Laboratory values, electrocardiograms, and routine assessments. Specific assessments were obtained according to the study schedule (Supplemental Table 3). Electrocardiograms were performed and read locally at screening, at day 1, yearly, and at the end of study, except for approximately 200 sites in the United States with centralized electrocardiogram equipment. An electrocardiogram recorded at the screening visit was used to detect atrial fibrillation or flutter, which required a higher BNP or NT-proBNP level for eligibility than did sinus or other rhythms.

STATISTICAL CONSIDERATIONS. Efficacy analyses will be performed on the full analysis set, which includes all randomized patients who will be analyzed according to their randomized treatment group

assignment (intention to treat). To ensure there is no avoidable increased risk for harm to patients, accumulating data are formally reviewed quarterly for the first year and at least every 6 months thereafter by a Data Monitoring Committee comprising independent, external experts in HF and clinical trials supported by an independent statistical group.

Interim analyses. Two interim analyses for review by the Data Monitoring Committee were specified at approximately one-third and two-thirds of the target 1,590 CV deaths. The first interim analysis for futility alone was completed in March 2019 based on 534 CV deaths. The Data Monitoring Committee recommendation was to continue the trial without modification. The second interim analysis will assess for both futility and superiority, using a 1-sided alpha of 0.0005 (Haybittle-Peto approach) for superiority. The Data Monitoring Committee may recommend stopping the trial for superiority if the primary composite endpoint and the secondary endpoint of time to CV death both reach statistical significance. The remainder of the secondary endpoints will be assessed with an overall 1-sided alpha of 0.0005 following the testing diagram if the study is stopped early (Supplemental Appendix).

Sample size considerations. The study is endpoint-driven and will end after accumulation of approximately 1,590 CV deaths. A sample size of 8,000 patients was chosen to provide 90% power to detect a hazard ratio of 0.8 for CV death assuming the following: an annualized rate of CV death of 10% in the first year and 7% thereafter; a 24-month enrollment period; total study duration set to 48 months; a 3-month treatment lag with a treatment effect hazard ratio of 0.8 thereafter; 10% annual rate of study drug discontinuation; and 10% of subjects lost to endpoint determination either through non-CV death or study discontinuation over the course of the trial. The overall type I error is 0.05 for 2-sided testing. Assuming the rates for experiencing either an HF event or CV death are double those for CV death alone and the same other assumptions as for CV death alone, the primary composite endpoint is expected to have >99% power. The statistical analysis plan was approved prior to enrollment of the first patient and was developed with a special protocol assessment agreement with the Food and Drug Administration. Any changes to the statistical analysis plan will be finalized prior to the end of the study and treatment unblinding.

CONCLUSIONS

The GALACTIC-HF trial is the first trial designed to address the hypothesis that selectively increasing

cardiac contractility with the cardiac myosin activator OM in patients with HFrEF will result in improved clinical outcomes. The preclinical and clinical data suggest that OM can improve cardiac function, decrease ventricular wall stress, reverse ventricular remodeling, and promote sympathetic withdrawal. The changes in ventricular volumes and natriuretic peptides are supportive of a potential survival benefit of OM (26,27). Thus far, OM has not shown liabilities that typically limit use of current HF therapies, such as adverse effects on blood pressure, heart rate, potassium homeostasis, or renal function. If the GALACTIC-HF trial demonstrates favorable clinical outcomes in patients receiving OM, patients may be able to benefit from this therapy without interfering with initiation or up-titration of current guideline-directed medical therapy. Final results of the GALACTIC-HF trial should be available in 2021 if the trial runs to full term.

ADDRESS FOR CORRESPONDENCE: Dr. John R. Teerlink, San Francisco VA Medical Center, Cardiology, 111C, Building 203, Room 2A-49, 4150 Clement Street, San Francisco, California 94121-1545. E-mail: john.teerlink@ucsf.edu.

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