METHODS OF TREATING HEART FAILURE BY ADMINISTERING OMECAMTIV MECARBIL

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and benefit of U.S. Provisional Patent Application No. 63/112,995, filed November 12, 2020, U.S. Provisional Patent Application No. 63/154,077, filed February 26, 2021, U.S. Provisional Patent Application No. 63/187,084, filed May 11, 2021, U.S. Provisional Patent Application No. 63/202,873, filed June 28, 2021, and U.S. Provisional Patent Application No. 63/203,436, filed July 22, 2021, the disclosures of which are hereby incorporated herein by reference in their entireties.

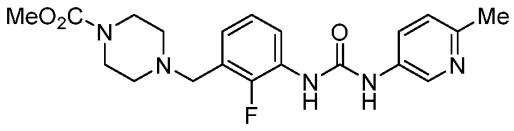
BACKGROUND

[0002] The cardiac sarcomere is the basic unit of muscle contraction in the heart. The cardiac sarcomere is a highly ordered cytoskeletal structure composed of cardiac muscle myosin, actin and a set of regulatory proteins. The discovery and development of small molecule cardiac muscle myosin activators would lead to promising treatments for acute and chronic heart failure. Cardiac muscle myosin is the cytoskeletal motor protein in the cardiac muscle cell. It is directly responsible for converting chemical energy into the mechanical force, resulting in cardiac muscle contraction.

[0003] Current positive inotropic agents, such as beta-adrenergic receptor agonists or inhibitors of phosphodiesterase activity, increase the concentration of intracellular calcium, thereby increasing cardiac sarcomere contractility. However, the increase in calcium levels increase the velocity of cardiac muscle contraction and shortens systolic ejection time, which has been linked to potentially life-threatening side effects. In contrast, cardiac muscle myosin activators work by a mechanism that directly stimulates the activity of the cardiac muscle myosin motor protein, without increasing the intracellular calcium concentration. They accelerate the rate-limiting step of the myosin enzymatic cycle and shift it in favor of the force-producing state. Rather than increasing the velocity of cardiac contraction, this mechanism instead lengthens the systolic ejection time, which results in increased cardiac muscle contractility and cardiac output in a potentially more oxygen-efficient manner.

[0004] A characteristic of heart failure with reduced ejection fraction is decreased systolic function leading to reduce cardiac output and increased filling pressures. To date, no drugs directly addressing systolic function have improved outcomes. Cardiac myosin activators are a class of myotropes that improve myocardial function by directly augmenting cardiac sarcomere function. Omecamtiv mecarbil, augments cardiac contractility by selectively binding to cardiac myosin increasing the number of force generators (myosin heads) that can bind to the actin filament and undergo a powerstroke once the cardiac cycle starts. In early clinical studies using short-term intravenous administration, omecamtiv mecarbil improved cardiac performance. In patients with chronic heart failure with reduced ejection fraction, treatment with omecamtiv mecarbil for 20 weeks increased left ventricular systolic function, decreased left ventricular systolic and diastolic volumes suggestive of beneficial reverse cardiac remodeling, and reduced natriuretic peptide concentrations and heart rate.

[0005] U.S. Patent No. 7,507,735, herein incorporated by reference, discloses a genus of compounds, including omecamtiv mecarbil (AMG 423, CK-1827452), having the structure:



[0006] Omecamtiv mecarbil (OM) is a first in class direct activator of cardiac myosin that directly targets the contractile mechanisms of cardiac myocytes intended to enhance efficiency of myocardial contraction in patients suffering from a cardiovascular condition, such as heart failure.

[0007] Many therapies have been developed that improve cardiovascular outcomes in patients with heart failure with reduced ejection fraction (HFrEF). However, none of the currently available drugs directly improve the central defect of HFrEF, reduced systolic function. Moreover, severe impairment of systolic function is often associated with lower blood pressure and greater difficulty tolerating target doses of guideline-directed medical therapies. Myotropes represent a new class of drugs that improve myocardial function by directly augmenting cardiac sarcomere function. The cardiac myosin activator, omecamtiv mecarbil, is the first of this class and it increases systolic function by selectively facilitating the actin-myosin interaction, increasing contractile force without altering the cardiomyocyte calcium transient.

[0008] Despite significant improvements in prognosis with contemporary medical therapy, HF with reduced ejection fraction (HFrEF) remains a progressive clinical syndrome and many patients develop worsening over time despite optimal guideline-based treatment. The nomenclature to describe such patients is varied and includes “advanced HF”, “severe HF”, “refractory HF”, or “Stage D HF”. Regardless of terminology, these patients have a high burden of symptoms, recurrent HF hospitalizations, high mortality, and account for a large proportion of the total costs of HF care. As HF progresses, many patients become progressively intolerant of neuro-hormonal blockade with beta-blockers or renin-angiotensin-aldosterone system (RAAS) modulators due to hypotension or renal dysfunction, limiting their options for medical therapy. Selected patients with advanced HF may be candidates for other therapies such as cardiac transplantation or mechanical cardiac support, but these therapies are costly, highly invasive, and have limited availability. Intravenous inotropic therapy can be used for palliation of symptoms in selected patients but may be associated with increased mortality. Thus, there is a clear unmet need for effective and safe chronic medical therapies for patients with more advanced stages of HF.

[0009] The identification of safe drugs that increase cardiac performance has been a goal of heart failure therapeutics for more than a century, yet those that have been developed have consistently increased the incidence of myocardial ischemia, ventricular arrhythmias, or death due to their mechanism increasing intracellular calcium transients. As a selective cardiac myosin activator, omecamtiv mecarbil has been shown to have no effect on these transients.

[0010] Despite prior developments in this area, there remains a need for treating heart failure in patients.

SUMMARY

[0011] Provided herein are methods of treating heart failure in a patient having a left ventricular ejection fraction (LVEF) of less than 35% (such as less than 30%, less than 28%, less than 25%, or less than 22%) comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil as described herein.

[0012] Also provided herein are methods of treating heart failure in a patient who does not exhibit atrial fibrillation or atrial flutter comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil as described herein.

[0013] Also provided herein are methods of treating heart failure in a patient having heart failure classified as Class III or IV as determined using the New York Heart Association (NYHA) classification comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil as described herein.

[0014] Also provided herein are methods of treating heart failure in a patient having advanced heart failure comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil as described herein.

[0015] The disclosure further provides methods of treating ischemic heart failure in a patient comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil as described herein.

[0016] Also provided herein are methods of treating heart failure in a patient who has had a myocardial infarction comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil as described herein.

[0017] Also provided herein are methods of treating heart failure in a patient having a NT-proBNP level of at least 2,000 pg/mL prior to start of omecamtiv mecarbil treatment comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil as described herein.

[0018] Also provided herein are methods of treating heart failure in a patient who has low blood pressure, symptomatic hypotension, impaired renal function, or bradycardia comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil as described herein.

[0019] Also provided herein are methods of treating heart failure in a patient who is unable to tolerate one or more of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, diuretics, aldosterone antagonists, inotropes, neprilysin inhibitors, digitalis, and digoxin comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil as described herein.

[0020] Also provided herein is a method of preventing stroke in a patient suffering from heart failure with reduced ejection fraction (HFrEF) comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil as described herein.

BRIEF DESCRIPTION OF THE FIGURES

[0021] Figure 1A shows the primary endpoint in the patient population evaluated, wherein the primary endpoint was the composite of time to a heart failure event or cardiovascular death, whichever occurred first.

[0022] Figure 1B shows the incidence of cardiovascular death in the patient population evaluated.

[0023] Figure 1C shows the incidence of heart failure events in the patient population evaluated.

[0024] Figure 1D shows the incidence of all deaths in the patient population evaluated.

[0025] Figure 2A, 2B, and 2C show the primary outcome of the trial as a composite of heart failure event or cardiovascular death, according to subgroups that were prespecified in the protocol. Race was self-reported by patients. Baseline NT-proBNP subgroups exclude subjects in atrial fibrillation/flutter at screening.

[0026] Figure 3 shows a multiplicity testing propagation approach.

[0027] Figure 4 shows a design of a clinical trial of omecamtiv mecarbil.

[0028] Figure 5 shows a X-ray powder diffraction pattern (XRPD) for Form A of omecamtiv mecarbil dihydrochloride monohydrate.

[0029] Figure 6 shows a XRPD of a omecamtiv mecarbil dihydrochloride hydrate salt form, including Form B, at varying temperatures.

[0030] Figure 7 shows a XRPD of a omecamtiv mecarbil dihydrochloride hydrate salt form, including Form C, at varying relative humidity conditions.

[0031] Figure 8A shows progressively greater improvement in the primary composite endpoint (PCE) with decreasing left ventricular ejection fraction (LVEF) as indicated by the continuously improving hazard ratio.

[0032] Figure 8B shows the incidence of the primary composite endpoint (PCE) increased with decreasing ejection fraction (EF) and omecamtiv mecarbil (circles) producing increasing greater absolute reductions in the PCE with decreasing EF as compared to placebo (stars).

[0033] Figure 9 shows **a**nalysis of ejection fraction as a continuous variable (interaction effect, p = 0.004) demonstrated a progressively larger treatment effect of omecamtiv mecarbil with decreasing ejection fraction (EF).

[0034] Figure 10A shows The difference in the incidence of the primary composite endpoint increased disproportionately between the placebo (stars) and omecamtiv mecarbil (circles) treatment groups with lower ejection fractions.

[0035] Figure 10B shows that absolute risk reduction by omecamtiv mecarbil progressively increased with decreasing ejection fraction (EF).

[0036] Figure 11A shows The beneficial effect of treatment with omecamtiv mecarbil on the primary outcome was driven predominantly by the significant reduction in heart failure events.

[0037] Figure 11B shows the incidence rate of heart failure hospitalizations increases with decreasing ejection fraction in both the placebo (stars) and omecamtiv mecarbil (circles) treated patients, but was significantly impacted by treatment with omecamtiv mecarbil, and showed a progressively greater reduction in the absolute difference with decreasing ejection fraction.

[0038] Figure 12A shows OM had no overall effect on cardiovascular death, neither in the overall population, nor as a function of baseline ejection fraction (EF).

[0039] Figure 12B shows OM the incidence of cardiovascular death increased comparably in both the placebo (stars) and omecamtiv mecarbil (circles) arms with decreasing ejection fraction (EF).

[0040] Figure 13A shows the distribution of baseline ejection fractions in GALACTIC-HF.

[0041] Figure 13B shows the distribution of ejection fractions in GALACTIC-HF.

[0042] Figure 14A shows Kaplan-Meier curves comparing patients with and without more advanced heart failure (HF) for each endpoint (CV Death or HF event)

[0043] Figure 14B shows Kaplan-Meier curves comparing patients with and without more advanced heart failure (HF) for each endpoint (CV Death).

[0044] Figure 15A shows event rates for primary endpoints by treatment assignment and advanced heart failure (HF) criteria met (specific advanced HF criteria).

[0045] Figure 15B shows shows event rates for primary endpoints by treatment assignment and advanced heart failure (HF) criteria met (total number of advanced HF criteria met).

[0046] Figure 16A shows outcomes according to baseline NT-proBNP in the prespecified analysis population (no atrial fibrillation/flutter at baseline) randomized (primary composite outcome) (placebo - stars; omecamtiv mecarbil – circles).

[0047] Figure 16B shows outcomes according to baseline NT-proBNP in the prespecified analysis population (no atrial fibrillation/flutter at baseline) randomized (HF hospitalization) (placebo - stars; omecamtiv mecarbil – circles).

[0048] Figure 16C shows outcomes according to baseline NT-proBNP in the prespecified analysis population (no atrial fibrillation/flutter at baseline) randomized (CV death) (placebo - stars; omecamtiv mecarbil – circles).

[0049] Figure 16D shows outcomes according to baseline NT-proBNP in the prespecified analysis population (no atrial fibrillation/flutter at baseline) randomized (all-cause mortality) (placebo - stars; omecamtiv mecarbil – circles).

[0050] Figure 17A shows outcomes according to baseline NT-proBNP in the prespecified analysis population in all patients randomized (primary composite outcome) (placebo - stars; omecamtiv mecarbil – circles).

[0051] Figure 17B shows outcomes according to baseline NT-proBNP in the prespecified analysis population in all patients randomized (HF hospitalization) (placebo - stars; omecamtiv mecarbil – circles).

[0052] Figure 17C shows outcomes according to baseline NT-proBNP in the prespecified analysis population in all patients randomized (CV death) (placebo - stars; omecamtiv mecarbil – circles).

[0053] Figure 17D shows outcomes according to baseline NT-proBNP in the prespecified analysis population in all patients randomized (all-cause mortality) (placebo - stars; omecamtiv mecarbil – circles).

[0054] Figure 18A shows effect of randomized treatment on outcomes according to baseline NT-proBNP concentration (shown as a continuous measure) in the prespecified analysis population (no atrial fibrillation/flutter at baseline) randomized (primary composite outcome).

[0055] Figure 18B shows effect of randomized treatment on outcomes according to baseline NT-proBNP concentration (shown as a continuous measure) in the prespecified analysis population (no atrial fibrillation/flutter at baseline) randomized (HF hospitalization).

[0056] Figure 18C shows effect of randomized treatment on outcomes according to baseline NT-proBNP concentration (shown as a continuous measure) in the prespecified analysis population (no atrial fibrillation/flutter at baseline) randomized (CV death).

[0057] Figure 18D shows effect of randomized treatment on outcomes according to baseline NT-proBNP concentration (shown as a continuous measure) in the prespecified analysis population (no atrial fibrillation/flutter at baseline) randomized (all cause mortality).

[0058] Figure 19A shows effect of randomized treatment on outcomes according to baseline NT-proBNP concentration (shown as a continuous measure) in the prespecified analysis population in all patients randomized (primary composite outcome).

[0059] Figure 19B shows effect of randomized treatment on outcomes according to baseline NT-proBNP concentration (shown as a continuous measure) in the prespecified analysis population in all patients randomized (HF hospitalization).

[0060] Figure 19C shows effect of randomized treatment on outcomes according to baseline NT-proBNP concentration (shown as a continuous measure) in the prespecified analysis population in all patients randomized (CV death).

[0061] Figure 19D shows effect of randomized treatment on outcomes according to baseline NT-proBNP concentration (shown as a continuous measure) in the prespecified analysis population in all patients randomized (all cause mortality).

[0062] Figure 20A shows effect of omecamtiv mecarbil, compared with placebo, on NT-proBNP after randomization in the prespecified analysis population (no atrial fibrillation/flutter at baseline and all NT-proBNP concentrations).

[0063] Figure 20B shows effect of omecamtiv mecarbil, compared with placebo, on NT-proBNP after randomization in the prespecified analysis population (no atrial fibrillation/flutter at baseline, NT-proBNP > median).

[0064] Figure 20C shows effect of omecamtiv mecarbil, compared with placebo, on NT-proBNP after randomization in the prespecified analysis population (no atrial fibrillation/flutter at baseline, NT-proBNP ≤ median).

[0065] Figure 20D shows effect of omecamtiv mecarbil, compared with placebo, on NT-proBNP in all patients randomized (all NT-proBNP concentrations).

[0066] Figure 20E shows effect of omecamtiv mecarbil, compared with placebo, on NT-proBNP in all patients randomized (NT-proBNP > median).

[0067] Figure 20F shows effect of omecamtiv mecarbil, compared with placebo, on NT-proBNP in all patients randomized (NT-proBNP ≤ median).

[0068] Figure 21A shows the proportion of patients having AFF as a function of the percentage of LVEF.

[0069] Figure 21B shows effect of omecamtiv mecarbil in patients with or without AFF who were or were not receiving digoxin.

[0070] Figure 21C shows the effect of omecamtiv mecarbil in patients with or without AFF on mortality, for cardiovascular death or all-cause death, and heart failure hospitalization.

[0071] Figure 21D shows the effect of omecamtiv mecarbil in patients with or without AFF who were or were not receiving digoxin on mortality, for cardiovascular death or all-cause death, and heart failure hospitalization.

[0072] Figure 21E shows the effect of omecamtiv mecarbil in patients with AFF as compared to placebo on the occurrence of serious adverse events.

[0073] Figure 21F shows arithmetic mean pharmacokinetic concentration-time profiles for digoxin administration alone and digoxin administration with omecamtiv mecarbil.

[0074] Figure 21G shows geometric mean pharmacokinetic parameters for digoxin administration alone and digoxin administration with omecamtiv mecarbil.

[0075] Figure 22 shows Kaplan-Meier curves for primary composite endpoint by EF quartile.

[0076] Figure 23A shows outcomes according to baseline systolic blood pressure (SBP) in all patients randomized (primary composite outcome) (placebo – stars; omecamtiv mecarbil – circles).

[0077] Figure 23B shows the treatment effect of omecamtiv mecarbil on primary composite outcomes according to baseline systolic blood pressure (SBP).

[0078] Figure 24 shows the incidence of stroke (fatal and non-fatal stroke events) in all patients randomized.

[0079] Figure 25 shows the treatment effect of omecamtiv mecarbil in patients with or without a history of stroke as compared to placebo on the occurrence of stroke (fatal and non-fatal stroke events) (placebo - stars; omecamtiv mecarbil – circles).

[0080] Figure 26 shows the treatment effect of omecamtiv mecarbil in patients with or without a history of atrial fibrillation as compared to placebo on the occurrence of stroke (fatal and non-fatal stroke events) (placebo - stars; omecamtiv mecarbil – circles).

[0081] Figure 27 shows the treatment effect of omecamtiv mecarbil in patients without an atrial fibrillation / atrial flutter (AFF) at screening and those without a history of AFF as compared to placebo on the occurrence of new-onset AFF (placebo - stars; omecamtiv mecarbil – circles).

DETAILED DESCRIPTION

[0082] The present disclosure provides methods of treating heart failure in a patient comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil as described herein. In various cases, the methods disclosed herein include, e.g., treating heart failure in patients having other cardiovascular conditions, such as patients having left ventricular ejection fraction (LVEF) of less than 28%, patients who do not exhibit atrial fibrillation or atrial flutter, patients having heart failure classified as Class III or IV as determined by New York Heart Association classification, patients having ischemic heart failure, patients who have had a myocardial infarction, patients having a NT-proBNP level greater than median, or patients having reduced ejection fraction (HFrEF).

[0083] The present disclosure provides methods of treating patients with heart failure and reduced ejection fraction receiving guideline-based medical and device therapy. In addition, the disclosed methods provide a statistically significant reduction in the risk of the primary composite outcome of a heart failure event or death from cardiovascular causes. This effect is evident after approximately 3 months of treatment and persists for a period of time (e.g., 3 years post treatment) without evidence of an increase in the risk of myocardial ischemic events, ventricular arrhythmias or death from cardiovascular or all causes. As described herein, a patient undergoing a method as disclosed herein can exhibit a reduction in NT-proBNP levels, compared to placebo.

[0084] The patients treated by the disclosed methods exhibit approximately the same rates of myocardial ischemia, ventricular arrhythmias and death between treatment groups through almost 7,500 patient-years of follow-up, which suggests that treatment with omecamtiv mecarbil does not increase the risk of these clinical adverse effects. Combined with a lack of detrimental effects on blood pressure, heart rate, creatinine or potassium concentrations, this supports the finding that the mechanism of selectively targeting the cardiac sarcomere with omecamtiv mecarbil is a safe approach to improving cardiac function.

[0085] As used herein, “treatment” or “treating” means any treatment of a disease in a patient, including: a) preventing the disease, that is, causing the clinical symptoms of the disease not to develop; b) inhibiting the disease; c) slowing or arresting the development of clinical symptoms; and/or d) relieving the disease, that is, causing the regression of clinical symptoms. Treatment of diseases and disorders herein is intended to also include the prophylactic administration of a pharmaceutical formulation described herein to a subject (i.e., an

animal, preferably a mammal, most preferably a human) believed to be in need of preventative treatment, such as, for example, chronic heart failure.

[0086] As used herein, the term "therapeutically effective amount" means an amount effective, when administered to a human or non-human patient, to treat a disease, e.g., a therapeutically effective amount may be an amount sufficient to treat a disease or disorder responsive to myosin activation. The therapeutically effective amount may be ascertained experimentally, for example by assaying blood concentration of the chemical entity, or theoretically, by calculating bioavailability.

Patient Populations

[0087] The present disclosure provides methods of treating heart failure in patients in need thereof. The disclosed methods provide a reduction in the composite of heart failure events or cardiovascular deaths without evidence of adverse safety signals in a broad range of patients, including patients with moderate to severe heart failure symptoms and lower ejection fraction, systolic blood pressure and renal function. In various cases, a patient with heart failure exhibits an 8% overall risk reduction when administered omecamtiv mecarbil as disclosed herein, compared to placebo control.

[0088] In some embodiments, treatment of heart failure in patients in need thereof may result in reduction of risk of heart failure hospitalization and/or cardiovascular death as well as other benefits, including reduction in heart rate, stroke, and/or natriuretic peptide concentrations.

[0089] In another aspect, the present disclosure also provides methods for reducing heart rate, reducing risk of stroke, reducing risk of heart failure hospitalization, reducing risk of cardiovascular death, and/or reducing/decreasing natriuretic peptide concentrations (*e.g.*, NT-proBNP levels) in patients having heart failure.

[0090] While multiple drugs have been developed to improve inotropy, omecamtiv mecarbil is the first drug to specifically increase systolic function by targeting the sarcomere without any direct vascular, electrophysiologic, or neurohormonal effects and without increasing mortality. It exerts this effect by selectively binding to myosin, stabilizing its lever arm in a primed position resulting in accumulation of cardiac myosin heads in the pre-powerstroke state prior to onset of cardiac contraction. This mechanism increases the number of force generators (myosin heads) that can bind to the actin filament and undergo a powerstroke once the cardiac cycle starts without altering the cardiomyocyte calcium transient.

[0091] Furthermore, treatment with omecamtiv mecarbil was associated with greater reductions in heart failure events in patients with lower baseline ejection fraction. Combined with the high risk of heart failure events in these patients, patients treated with omecamtiv mecarbil displayed an even greater relative treatment effect and a progressively larger absolute risk reduction for the primary composite endpoint of heart failure events and cardiovascular death with lower baseline ejection fraction. These findings support the concept that certain subpopulations of heart failure patients, such as patients with more severe heart failure, may derive greater clinical benefit from cardiac myosin activator therapy.

[0092] *Patients with left ventricular ejection fraction (LVEF) of less than 35%:* In some cases, the patient with heart failure is one that also exhibits lower ejection fraction (ejection fraction ≤ 35%), prior to start of omecamtiv mecarbil therapy as described herein. In some embodiments, in conjunction with embodiments above or below, the patients have left ventricular ejection of less than or equal to (e.g., less than) 35%, less than or equal to (e.g., less than) 30%, less than or equal to (e.g., less than) 28%, less than or equal to (e.g., less than) 25%, or less than or equal to (e.g., less than) 22% (e.g., 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%, or less than any of 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%). In some embodiments, in conjunction with embodiments above or below, the patients have left ventricular ejection of less than or equal to 22%, less than or equal to 28%, or between 23% and 28%..

[0093] Lower ejection fraction may be correlated with other patient characteristics. In a large clinical trial, when assessed by quartiles, patients with lower ejection fractions were younger, more likely to be male and non-white, and less likely to be enrolled in Eastern Europe or Russia and more likely to be enrolled in the United States, Canada, Western Europe, South Africa, or Australasia. Patients with lower ejection fraction were more likely to have a non-ischemic etiology of heart failure, NYHA III/IV functional class, lower body mass index, lower systolic blood pressure, higher heart rate, higher NT-proBNP, higher cardiac troponin I, and were less likely to have coronary artery disease, hypertension, type 2 diabetes mellitus, or atrial fibrillation/ flutter. Lower ejection fraction was associated with greater symptom burden in patients enrolled as inpatients (lower KCCQ-TSS), but there was no meaningful difference in the outpatients. Patients with lower ejection fractions had higher use of ARNi, ivabradine, digitalis glycosides, cardiac resynchronization therapy and implantable cardioverter defibrillators compared to patients with higher ejection fractions. Accordingly, in any of the embodiments provided herein, the patients may have one or more of the aforementioned characteristics.

[0094] In one aspect, provided herein is a method of treating heart failure in a patient having heart failure who also exhibits lower ejection fraction. In some embodiments, provided herein is a method of treating heart failure in a patient having heart failure who also exhibits lower ejection fraction by administering omecamtiv mecarbil, wherein administration results in a risk reduction, for example, in occurrence or time to heart failure event or cardiovascular death. In a large clinical trial, selectively increasing systolic function in patients with HFrEF improved cardiovascular outcomes (primary composite endpoint: HR, 0.92; p = 0.025), predominantly through reducing heart failure events. Omecamtiv mecarbil provided progressively greater benefit by reducing heart failure events in patients with lower baseline ejection fraction such that patients with an ejection fraction below the median (≤28%) had a 16% reduction in the primary endpoint. Patients with ejection fraction in the lowest quartile had a relative risk reduction of 17% and an absolute risk reduction of 7.4 events per 100 patient-years (NNT for 3 years = 11.8) for the primary composite endpoint.

[0095] In some embodiments, treatment in patients with lower ejection fraction is effective to provide risk reduction compared to placebo. The risk reduction may be relative risk reduction and/or absolute risk reduction. In some embodiments, risk reduction is measured as event rates per 100 patient years. An event may be a first

heart failure event or cardiovascular death. In various cases, patients with LVEF of less than or equal to 28% had a 16% reduction in time-to-first heart failure event or cardiovascular death. In some embodiments, the risk reduction may be an absolute risk reduction and/or relative risk reduction, in patients with EF of less than about 28% or less than about 22%. In some embodiments, the absolute risk reduction is at least about 5 events per 100-patient years (*e.g.*, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5 events per 100 patient years). In some embodiments, the absolute risk reduction is about 7.4 events per 100 patient years. In some embodiments, the treatment is effective to provide a relative risk reduction of at least 10% (*e.g.*, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, etc.) In some embodiments, the relative risk reduction is 15%.

[0096] In some embodiments, the relative risk reduction is 17%. In some embodiments, provided is a method of reducing the time-to-first heart failure event in a patient having left ventricular ejection of less than or equal to (e.g., less than) 35%, less than or equal to (e.g., less than) 30%, less than or equal to (e.g., less than) 28%, less than or equal to (e.g., less than) 25%, or less than or equal to (e.g., less than) 22% (e.g., 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%, or less than any of 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%) by administering omecamtiv mecarbil as described herein. In particular embodiments, the patient has LVEF of less than or equal to (e.g., less than) 28%. In particular embodiments, the patient has LVEF of less than or equal to (e.g., less than) 22%.

[0097] In some embodiments, provided is a method of reducing the number or frequency of heart failure events (e.g., heart failure hospitalizations) in a patient having left ventricular ejection of less than or equal to (e.g., less than) 35%, less than or equal to (e.g., less than) 30%, less than or equal to (e.g., less than) 28%, less than or equal to (e.g., less than) 25%, or less than or equal to (e.g., less than) 22% (e.g., 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%, or less than any of 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%) by administering omecamtiv mecarbil as described herein. In particular embodiments, the patient has LVEF of less than or equal to (e.g., less than) 28%. In particular embodiments, the patient has LVEF of less than or equal to (e.g., less than) 22%. In some embodiments, provided is a method of reducing risk of cardiovascular death in a patient having left ventricular ejection of less than or equal to (e.g., less than) 35%, less than or equal to (e.g., less than) 30%, less than or equal to (e.g., less than) 28%, less than or equal to (e.g., less than) 25%, or less than or equal to (e.g., less than) 22% (e.g., 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%, or less than any of 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%) by administering omecamtiv mecarbil as described herein. In particular embodiments, the patient has LVEF of less than or equal to (e.g., less than) 28%. In particular embodiments, the patient has LVEF of less than or equal to (e.g., less than) 22%.

[0098] It was also observed that patients with a lower ejection fraction exhibited a greater reduction in NT-proBNP upon treatment with omecamtiv mecarbil. In a large clinical trial, administration of omecamtiv mecarbil

resulted in greater reductions in NT-proBNP with decreasing ejection fraction, with a 22% reduction of NT-proBNP at week 24 in the lowest EF quartile (≤22%). Accordingly, provided herein are methods of treating heart failure in patients, having LVEF of less than or equal to (e.g., less than) 35%, less than or equal to (e.g., less than) 30%, less than or equal to (e.g., less than) 28%, less than or equal to (e.g., less than) 25%, or less than or equal to (e.g., less than) 22% (e.g., 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%, or less than any of 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%), wherein administration of omecamtiv mecarbil reduces the patient's NT-proBNP level as compared to baseline. In particular embodiments, the patient has LVEF of less than or equal to (e.g., less than) 28%. In particular embodiments, the patient has LVEF of less than or equal to (e.g., less than) 22%. In some such embodiments the patient's NT-proBNP level is reduced by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%. In some embodiments, the NT-proBNP level is reduced to less than 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, or 1500 pg/ml in a patient having left ventricular ejection of less than or equal to (e.g., less than) 35%, less than or equal to (e.g., less than) 30%, less than or equal to (e.g., less than) 28%, less than or equal to (e.g., less than) 25%, or less than or equal to (e.g., less than) 22% (e.g., 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%, or less than any of 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%). In some embodiments, the reduction in NT-proBNP occurs over a period of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 36, or 48 weeks.

[0099] In other embodiments, provided herein is a method of reducing NT-proBNP in a patient having left ventricular ejection of less than or equal to (e.g., less than) 35%, less than or equal to (e.g., less than) 30%, less than or equal to (e.g., less than) 28%, less than or equal to (e.g., less than) 25%, or less than or equal to (e.g., less than) 22% (e.g., 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%, or less than any of 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%) by administering omecamtiv mecarbil as described herein, In some embodiments, the NT-proBNP level is reduced by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% in a patient having left ventricular ejection of less than or equal to (e.g., less than) 35%, less than or equal to (e.g., less than) 30%, less than or equal to (e.g., less than) 28%, less than or equal to (e.g., less than) 25%, or less than or equal to (e.g., less than) 22% (e.g., 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%, or less than any of 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%). In some embodiments, the NT-proBNP level is reduced to less than 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, or 1500 pg/ml in a patient having left ventricular ejection of less than or equal to (e.g., less than) 35%, less than or equal to (e.g., less than) 30%, less than or equal to (e.g., less than) 28%, less than or equal to (e.g., less than) 25%, or less than or equal to (e.g., less than) 22% (e.g., 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%, or less than

any of 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%). In some embodiments, the reduction in NT-proBNP occurs over a period of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 36, or 48 weeks. In some embodiments, provided is a method of decreasing NT-proBNP in a patient having left ventricular ejection of less than or equal to (e.g., less than) 35%, less than or equal to (e.g., less than) 30%, less than or equal to (e.g., less than) 28%, less than or equal to (e.g., less than) 25%, or less than or equal to (e.g., less than) 22% (e.g., 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%, or less than any of 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%) by administering omecamtiv mecarbil as described herein.

[0100] In a large clinical trial, there was no significant effect on systolic blood pressure, serum potassium or creatine across ejection fraction quartiles observed with administration of omecamtiv mecarbil as compared to placebo. There were also no significant differences noted in the incidence of most adverse events between the omecamtiv mecarbil and placebo treated groups. However, notably there was an apparent reduction in the incidence of adjudicated stroke for patients treated with omecamtiv mecarbil. Thus, in some embodiments, provided is a method for reducing risk of stroke in a patient with heart failure (e.g., HFrEF) comprising administering omecamtiv mecarbil as described herein.

[0101] In some embodiments, provided herein is a method of treating heart failure in a patient having left ventricular ejection of less than or equal to (e.g., less than) 35%, less than or equal to (e.g., less than) 30%, less than or equal to (e.g., less than) 28%, less than or equal to (e.g., less than) 25%, or less than or equal to (e.g., less than) 22% (e.g., 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%, or less than any of 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%) by administering omecamtiv mecarbil as described herein, wherein the administration of omecamtiv mecarbil reduces the patient's risk of stroke as compared to placebo. In some embodiments, provided is a method of preventing or reducing risk of stroke in a patient with heart failure (e.g., HFrEF). In some embodiments, the patient has LVEF of less than or equal to (e.g., less than) 35%. In certain embodiments, the patient has LVEF of less than or equal to (e.g., less than) 28%. In particular embodiments, the patient has LVEF of less than or equal to (e.g., less than) 22%. In some embodiments, the risk reduction may be an absolute risk reduction and/or relative risk reduction. In some embodiments, the risk reduction is a relative reduction of the risk of stroke as compared to placebo. In some such embodiments the patient's relative risk of stroke is reduced by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%. In some embodiments wherein the patient has LVEF of less than or equal to (e.g., less than) 35%, the patient's relative risk of stroke is reduced by at least 5%, 10%, 15%, 20%, or 25%. In other embodiments wherein the patient has LVEF of less than or equal to (e.g., less than) 28%, the patient's relative risk of stroke is reduced by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, or 45%. In some embodiments wherein the patient has LVEF of less than or equal to (e.g., less than) 22%, the patient's relative risk of stroke is reduced by at least 5%, 10%, 15%, 20%, 25%, 30%, or 35%. In some embodiments, in conjunction with embodiments above or below, the stroke is fatal. In some embodiments, in

conjunction with embodiments above or below, the stroke is nonfatal. In some embodiments, in conjunction with embodiments above or below, the stroke is ischemic or nonhemorrhagic. In some embodiments, in conjunction with embodiments above or below, the stroke is ischemic with hemorrhagic transformation. In some embodiments, in conjunction with embodiments above or below, the stroke is hemorrhagic. In some embodiments, in conjunction with embodiments above or below, the patient has no history of stroke. In some embodiments, in conjunction with embodiments above or below, the patient has a history of stroke. In some embodiments, in conjunction with embodiments above or below, the patient has no history of atrial fibrillation. In some embodiments, in conjunction with embodiments above or below, the patient has a history of atrial fibrillation. In some embodiments, in conjunction with embodiments above or below, the patient has no atrial fibrillation/flutter at the time of initial administration of omecamtiv mecarbil. In some embodiments, in conjunction with embodiments above or below, the patient has no history of atrial fibrillation/flutter.

[0102] In a large clinical trial, omecamtiv mecarbil had no adverse effect on blood pressure, heart rate, potassium homeostasis or renal function when assessed by ejection fraction quartile. A small reduction in heart rate, believed to be due to the secondary effect of sympathetic withdrawal, was consistently observed across the ejection fraction groups.

[0103] In some embodiments, provided herein is a method of treating heart failure in a heart failure patient having left ventricular ejection of less than or equal to (e.g., less than) 35%, less than or equal to (e.g., less than) 30%, less than or equal to (e.g., less than) 28%, less than or equal to (e.g., less than) 25%, or less than or equal to (e.g., less than) 22% (e.g., 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%, or less than any of 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%) by administering omecamtiv mecarbil as described herein, wherein administration results in a reduction of heart rate. In some embodiments, provided herein is a method of reducing heart rate in a heart failure patient having left ventricular ejection of less than or equal to (e.g., less than) 35%, less than or equal to (e.g., less than) 30%, less than or equal to (e.g., less than) 28%, less than or equal to (e.g., less than) 25%, or less than or equal to (e.g., less than) 22% (e.g., 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%, or less than any of 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%) by administering omecamtiv mecarbil as described herein, as compared to placebo. In some embodiments, the patient has LVEF of less than or equal to (e.g., less than) 35%. In certain embodiments, the patient has LVEF of less than or equal to (e.g., less than) 28%. In particular embodiments, the patient has LVEF of less than or equal to (e.g., less than) 22%. In some embodiments, the reduction in heart rate is a reduction of about 1, 2, 3, 4 or 5 beats per minute (bpm), In certain embodiments, the reduction in heart rate is a reduction of about 1-5, 1-4, 1-3, 1-2, 2-5, 2-4, 2-4, 3-5, 3-4 or 4-5 bpm. In still other embodiments, the reduction in heart rate is a reduction of about 1-2 bpm.

[0104] In some embodiments, provided herein is a method of treating heart failure in a heart failure patient having left ventricular ejection of less than or equal to (e.g., less than) 35%, less than or equal to (e.g., less than) 30%, less than or equal to (e.g., less than) 28%, less than or equal to (e.g., less than) 25%, or less than or equal to (e.g., less than) 22% (e.g., 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%, or less than any of 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%) by administering omecamtiv mecarbil as described herein, wherein administration results in a reduction in the risk of stroke. In certain embodiments, provided herein is a method of reducing risk of stroke in a heart failure patient having left ventricular ejection of less than or equal to (e.g., less than) 35%, less than or equal to (e.g., less than) 30%, less than or equal to (e.g., less than) 28%, less than or equal to (e.g., less than) 25%, or less than or equal to (e.g., less than) 22% (e.g., 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%, or less than any of 34%, 33%, 32%, 31%, 30%, 29%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, or 10%) by administering omecamtiv mecarbil as described herein, as compared to placebo. In some embodiments, the patient has LVEF of less than or equal to (e.g., less than) 35%. In certain embodiments, the patient has LVEF of less than or equal to (e.g., less than) 28%. In particular embodiments, the patient has LVEF of less than or equal to (e.g., less than) 22%. In some embodiments, the risk reduction may be an absolute risk reduction and/or relative risk reduction. In some embodiments, the risk reduction is a relative reduction of the risk of stroke as compared to placebo. In some such embodiments the patient's relative risk of stroke is reduced by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%. In some embodiments wherein the patient has LVEF of less than or equal to (e.g., less than) 35%, the patient's relative risk of stroke is reduced by at least 5%, 10%, 15%, 20%, or 25%. In other embodiments wherein the patient has LVEF of less than or equal to (e.g., less than) 28%, the patient's relative risk of stroke is reduced by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, or 45%. In some embodiments wherein the patient has LVEF of less than or equal to (e.g., less than) 22%, the patient's relative risk of stroke is reduced by at least 5%, 10%, 15%, 20%, 25%, 30%, or 35%.

[0105] *Patients who do not exhibit atrial fibrillation or atrial flutter (AFF):* As is understood, atrial fibrillation and atrial flutter are types of tachyarrhythmias, wherein atrial fibrillation presents as a rapid and chaotic beating of the atria and atrial flutter results in a rapid but regular heartbeat. Atrial fibrillation and atrial flutter can be diagnosed using any suitable method (e.g., electrocardiogram echocardiogram, transesophageal echocardiogram, chest X-rays, MRI scans, CT scans, exercise stress test, etc.). In some embodiments, in conjunction with embodiments above or below, the patient with heart failure does not exhibit atrial fibrillation or atrial flutter, prior to start of omecamtiv mecarbil therapy as described herein.

[0106] In one aspect, provided herein is a method of treating heart failure in a patient having heart failure who does not exhibit AFF. In some embodiments, the patient with heart failure does not exhibit AFF. In some embodiments, the patient without AFF is receiving digoxin. In some embodiments, the patient without AFF is not receiving digoxin. In some embodiments, treatment in patients without AFF by administering omecamtiv mecarbil is effective to provide risk reduction compared to placebo. The risk reduction may be relative risk reduction

and/or absolute risk reduction. In some embodiments, risk reduction is measured as event rates per 100 patient years. An event may be a first heart failure event or cardiovascular death. In some embodiments, the risk reduction may be an absolute risk reduction and/or relative risk reduction, in patients having heart failure who do not exhibit AFF. In some embodiments, the treatment is effective to provide a relative risk reduction of at least 10% (*e.g.*, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, etc.). In some embodiments, the relative risk reduction is 12%. In some embodiments, the relative risk reduction is 15%. In some embodiments, the relative risk reduction is 17%. In some embodiments, treatment with omecamtiv mecarbil results in a reduction in the risk of cardiovascular death and/or heart failure events (e.g., heart failure hospitalization) in patients without AFF. In some embodiments, provided is a method of reducing the time-to-first heart failure event in a patient without AFF by administering omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing the number or frequency of heart failure events (e.g., heart failure hospitalizations) in a patient without AFF by administering omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing risk of cardiovascular death in a patient without AFF by administering omecamtiv mecarbil as described herein.

[0107] In some embodiments, provided is a method of reducing the time-to-first heart failure event in a heart failure patient who does not exhibit AFF by administering omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing the number or frequency of heart failure events (e.g., heart failure hospitalizations) in a heart failure patient who does not exhibit AFF by administering omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing risk of cardiovascular death in a heart failure patient who does not exhibit AFF by administering omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing risk of all-cause death in a heart failure patient who does not exhibit AFF by administering omecamtiv mecarbil as described herein. In some embodiments, the relative risk reduction is at least 10% (*e.g.*, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, etc.). In some embodiments, the relative risk reduction is 12%. In some embodiments, the relative risk reduction is 15%. In some embodiments, the relative risk reduction is 17%.

[0108] In some embodiments, provided is a method of reducing the time-to-first heart failure event in a heart failure patient without AFF, wherein the patient is not receiving digoxin, by administering omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing the number or frequency of heart failure events (e.g., heart failure hospitalizations) in a heart failure patient who does not exhibit AFF, wherein the patient is not receiving digoxin, by administering omecamtiv mecarbil as described herein. In other embodiments, provided herein is a method of reducing risk of cardiovascular death in a heart failure patient having without AFF, wherein the patient is not receiving digoxin, by administering omecamtiv mecarbil as described herein. In other embodiments, provided herein is a method of reducing risk of all-cause death in a heart failure patient having without AFF, wherein the patient is not receiving digoxin, by administering omecamtiv mecarbil as described herein. In some embodiments, the relative risk reduction for the heart failure patient without AFF who is not receiving digoxin is at least 10% (*e.g.*, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, etc.). In some

embodiments, the relative risk reduction is 12%. In some embodiments, the relative risk reduction is 15%. In some embodiments, the relative risk reduction is 17%.

[0109] In other embodiments, provided is a method of reducing the time-to-first heart failure event in a heart failure patient without AFF, wherein the patient is receiving digoxin, by administering omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing the number or frequency of heart failure events (e.g., heart failure hospitalizations) in a heart failure patient who does not exhibit AFF, wherein the patient is receiving digoxin, by administering omecamtiv mecarbil as described herein. In other embodiments, provided herein is a method of reducing risk of cardiovascular death in a heart failure patient having without AFF, wherein the patient is receiving digoxin, by administering omecamtiv mecarbil as described herein. In other embodiments, provided herein is a method of reducing risk of all-cause death in a heart failure patient having without AFF, wherein the patient is receiving digoxin, by administering omecamtiv mecarbil as described herein. In some embodiments, the relative risk reduction for the heart failure patient without AFF who is not receiving digoxin is at least 10% (*e.g.*, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, or 25%, etc.). In some embodiments, the relative risk reduction is 12%. In some embodiments, the relative risk reduction is 15%. In some embodiments, the relative risk reduction is 17%. In still other embodiments, 20%. In some embodiments, the relative risk reduction is 22%. In yet other embodiments, the relative risk reduction is 25%.

[0110] *Patients who exhibit atrial fibrillation or atrial flutter (AFF):* Treatment with omecamtiv mecarbil may reduce the occurrence of serious adverse events in patients with AFF. In some aspects, provided herein is a method of reducing the risk of serious adverse events in heart failure patients with AFF, wherein the patient is receiving digoxin, by administering omecamtiv mecarbil as described herein. In some embodiments, the treatment is effective to provide a relative risk reduction of at least 10% (*e.g.*, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, etc.) In some embodiments, the relative risk reduction is 15%.

[0111] *Patients having heart failure classified as Class III or IV:* The New York Heart Association (NYHA) classification is a paradigm describing patients suffering from heart failure, wherein patients are placed into one of four categories based on the extent the patient is limited during physical activity. Class I patients are not limited during physical activity, that is, ordinary physical activity does not cause undue fatigue, palpitation, or shortness of breath. Class II patients are slightly limited during physical activity such that ordinary physical activity results in fatigue, palpitation, or shortness of breath. Class III patients suffer from marked limitation during physical activity, wherein less than ordinary activity causes fatigue, palpitation, or shortness of breath. The Class IV heart failure patient experiences symptoms of heart failure at rest and is unable to carry on any physical activity without increasing discomfort. In some embodiments, in conjunction with embodiments above or below, the patient with heart failure is classified as Class III or IV as determined using the New York Heart Association (NYHA) classification.

[0112] *Patients having more advanced heart failure (HF):* In some aspects, provided is a method of treating a patient having more advanced HF by administering omecamtiv mecarbil as described herein. More advanced

HF, also referred to as severe HF, refractory HF, or Stage D HF, can be determined based on a number of criteria recognized in the medical field. In some embodiments, more advanced HF refers to the published criteria from the 2018 ESC-HFA position statement (*European journal of heart failure*. 2018;20:1505-1535). For the ESC-HFA criteria, patients were required to have all of 1) NYHA class III-IV symptoms, 2) a left ventricular ejection fraction ≤ 30%, 3) 2 or more hospitalizations for HF within the prior 12 months, and 4) evidence of severe functional impairment as defined by cardiopulmonary exercise testing or 6-minute walk test. In some embodiments, the hospitalization criteria is modified to one HF hospitalization within the prior 6 months In some embodiments, more advanced HF refers to patients having all of 1) NYHA class III-IV symptoms, 2) a left ventricular ejection fraction ≤ 30%, and 3) 1 or more hospitalizations for HF within the prior 6 months.

[0113] On the other hand, patients with true end-stage HF who may require mechanical support, cardiac transplant, or hospice care, referred to as Stage D patients in the AHA/ACC guidelines, represents a very small proportion of the HF population (approximately 2 % in an unselected community cohort). In some embodiments, patients having advanced HF as described herein do not include patients with true end-stage HF who may require mechanical support, cardiac transplant, or hospice care, referred to as Stage D patients in the AHA/ACC guidelines. In still other embodiments, patients having advanced HF do not include patients requiring IV inotropic therapy or mechanical ventilatory or circulatory support. A much larger population of ambulatory HF patients have significant symptoms, severely impaired cardiac performance, and frequent hospitalizations, but do not yet require advanced HF therapies such mechanical support or cardiac transplant. In some embodiments, patients having advanced heart failure include patients who have significant symptoms, severely impaired cardiac performance, and frequent hospitalizations, but do not yet require advanced HF therapies such mechanical support or cardiac transplant. In some embodiments, patients having advanced HF as described herein may include patients having NYHA class III-IV, ejection fraction ≤ 30%, and HF hospitalization within the prior 6 months.

[0114] In some embodiments, the patient receiving treatment has heart failure classified as Class III or IV as determined using the NYHA classification. In some embodiments, the patient has a LVEF of less than 30% (*e.g.*, 29%, 28%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, and 1%). In some embodiments, the patient is hospitalized for heart failure or one or more (*e.g.*, 1, 2, 3, 4, 5, etc.) hospitalization for heart failure within 6 months prior to treatment. In some embodiments, the patient has severe functional impairment as defined by cardiopulmonary exercise testing or 6-minute walk test. In some embodiments, the patient meets one or more of the following: 1) NYHA class III-IV symptoms, 2) a left ventricular ejection fraction ≤ 30%, 3) one or more hospitalizations for HF within the prior 6 months (including those hospitalized at the time of study enrollment), and 4) evidence of severe functional impairment as defined by cardiopulmonary exercise testing or 6-minute walk test. In some embodiments, the patient meets all of the following: 1) NYHA class III-IV symptoms, 2) a left ventricular ejection fraction ≤ 30%, 3) one or more hospitalizations for HF within the prior 6 months (including those hospitalized at the time of study enrollment), and 4) evidence of severe functional impairment as defined by cardiopulmonary exercise testing or 6-minute walk test. In some embodiments, the patient meets one or more of the following: 1)

NYHA class III-IV symptoms, 2) a left ventricular ejection fraction ≤ 30%, and 3) 1 or more hospitalizations for HF within the prior 6 months. In some embodiments, the patient meets all of the following: 1) NYHA class III-IV symptoms, 2) a left ventricular ejection fraction ≤ 30%, and 3) 1 or more hospitalizations for HF within the prior 6 months.

[0115] Despite substantial improvements in medical therapy for HFrEF, patients with more advanced HF continue to experience a high burden of symptoms, frequent HF hospitalizations, and high mortality. As HF worsens, the economic costs of care increase dramatically, and these patients account for disproportionate share of HF costs. With the progression of HF, the pathologic manifestations of severely impaired systolic function and low cardiac output often begin to predominate, including hypotension and progressive renal insufficiency. These features progressively limit the ability to tolerate guideline recommended HF therapy such as beta-blockers, RAAS modulators, or mineralocorticoid receptor antagonists, creating a mismatch between patient risk and intensity of medical therapy. Omecamtiv mecarbil differs from other HF therapies in that it directly targets systolic performance rather than modulating associated neuro-hormonal perturbations. Unlike other HFrEF treatments, omecamtiv mecarbil does not lower blood pressure, affect renal function, or alter potassium homeostasis, allowing its use even in patients with cardio-renal limitations to other HF therapies. In a large clinical trial, in patients classified as advanced HF, there was no significant difference in systolic blood pressure, serum creatinine, or serum potassium at 24 weeks between patients treated with omecamtiv mecarbil or placebo. These data support both the efficacy and tolerability of omecamtiv mecarbil in a patient population that is difficult to treat effectively with other HF drugs.

[0116] In patients with more advanced HF defined by NYHA class, EF, and recent HF hospitalization, omecamtiv mecarbil therapy provided a clinically significant reduction in the composite of HF hospitalizations and cardiovascular death. These data support the possible role of omecamtiv mecarbil in patients for whom current treatment options are limited.

[0117] In a large clinical trial, it was found that treatment with omecamtiv mecarbil provided a clinically important improvement in outcomes in the patients meeting an accepted definition of advanced HF, *e.g.*, one or more of the following: 1) NYHA class III-IV symptoms, 2) a left ventricular ejection fraction ≤ 30%, 3) one or more hospitalizations for HF within the prior 6 months (including those hospitalized at the time of study enrollment), and 4) evidence of severe functional impairment as defined by cardiopulmonary exercise testing or 6-minute walk test. Given that patients with more advanced HF have higher baseline risk, the 20% relative risk reduction translated into a significant absolute risk reduction of 8.3 events/100-patient-years (NNT = 12) for the primary endpoint of time to first HF event or death from cardiovascular causes.

[0118] In some embodiments, treatment in patients with more advanced HF with omecamtiv mecarbil is effective to provide risk reduction as compared to placebo. In some embodiments, the risk reduction is an absolute risk reduction. In some embodiments, the risk reduction is a relative risk reduction of about 20% (*e.g.*, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, etc.). For example, absolute risk reduction may be at least 2 events per 100 patient years (*e.g.*, 3, 4, 5, 6, 7, 8, 9, 10 events/100-

patient-years). In some embodiments, absolute risk reduction is about 8 events per 100 patient years (*e.g.*, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9 events/100-patient-years). In some embodiments, treatment in patients with more advanced HF shows no significant increase in treatment emergent serious adverse events. In some embodiments, treatment in patients with more advanced HF shows no significant increase in serious adverse events related to ventricular tachyarrhythmia. In some embodiments, treatment with omecamtiv mecarbil results in a reduction in the risk of cardiovascular death and/or heart failure events (e.g., heart failure hospitalization) in patients with more advanced HF. In some embodiments, provided is a method of reducing the time-to-first heart failure event in a patient with advanced HF by administering omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing the number or frequency of heart failure events (e.g., heart failure hospitalizations) in a patient with more advanced HF by administering omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing risk of cardiovascular death in a patient with more advanced HF by administering omecamtiv mecarbil as described herein.

[0119] In the more advanced HF population, treatment with omecamtiv mecarbil has been observed to be associated with a significant decrease in NT-proBNP. In some embodiments, the NT-proBNP level is reduced by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% in a patient with more advanced HF. In some embodiments, the NT-proBNP level is reduced to less than 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, or 1500 pg/ml in a patient with more advanced HF. IN some embodiments, the reduction in NT-proBNP occurs over a period of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 36, or 48 weeks. In some embodiments, provided is a method of decreasing NT-proBNP in a patient with more advanced HF by administering omecamtiv mecarbil as described herein.

[0120] *Patients having Ischemic Heart Failure:* In some embodiments, in conjunction with embodiments above or below, the patient with heart failure exhibits ischemic heart failure. As is understood, ischemic heart failure refers to heart failure characterized by inadequate blood supply and oxygen delivery in tissues due to, for example, narrowing of arteries from a blood clot or vessel constriction (e.g., plaque buildup). Ischemic heart disease, also known as coronary heart disease (CHD) can be diagnosed in several ways. For example, patients with documented (prior) myocardial infarction or coronary artery revascularization (either with percutaneous coronary interventions (PCI) or coronary artery bypass (CABG) surgery have CHD. Moreover, the presence of typical angina suggests a clinical diagnosis of CHD, but most often requires confirmation by additional diagnostic tests, such as coronary angiography.

[0121] *Patients having myocardial infarction:* As is understood, myocardial infarction or heart attack, occurs when blood flow to the heart is blocked. Typically, the blockage is due to arterial plaques in coronary arteries. A myocardial infarction, or damage therefrom, can be diagnosed using any suitable method (e.g., electrocardiogram, blood tests, chest x-rays, echocardiogram, angiogram, cardiac CT or MRI, etc.). In some embodiments, in conjunction with embodiments above or below, the patient with heart failure also has had a myocardial infarction.

[0122] *Patients having reduced ejection fraction:* In some embodiments, in conjunction with embodiments above or below, the patient with heart failure also has reduced ejection fraction (HFrEF). As is understood, HFrEF is characterized by diminished ability of the left ventricle to pump, such that the ejection fraction is 40% or less, wherein normal ejection fraction is more than 55%. In some cases of HFrEF, the left ventricle is enlarged, and thus cannot pump normally. In other cases, HFrEF can be caused by coronary heart disease, heart attack, cardiomyopathy, high blood pressure, aortic stenosis, mitral regurgitation, viral myocarditis, and/or arrhythmia.

[0123] In addition, it is understood that the risk of stroke in a patient increases with decreasing ejection fraction. Accordingly, the disclosed method provides a method of preventing or reducing the risk of stroke in a patient suffering from HFrEF comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, as described herein.

[0124] *Patients having a pretreatment level of NT-proBNP of at least 2000 pg/mL:* In some aspects, provided is a method of treating a patient having heart failure with elevated NT-proBNP levels, by administering omecamtiv mecarbil as described herein. NT-proBNP levels are understood to be a marker for heart failure (e.g., higher levels indicate a progression of heart failure). Patients with very high natriuretic peptide levels are at especially high risk and often have other clinical features such as low blood pressure and poor renal function causing intolerance of some recommended therapies. Any additional therapeutic option is attractive for these individuals and it is often in these patients that inotropic therapy is resorted to, or even use of mechanical support or transplantation. Omecamtiv mecarbil may one such treatment possibility. Omecamtiv mecarbil was found to result in higher treatment efficacy in populations having higher NT-proBNP levels at baseline. In contrast, for another new therapy, vericiguat, treatment efficacy declined at higher NT-proBNP concentrations. Plasma natriuretic peptide concentrations reflect cardiac chamber wall stress, blood volume, heart rhythm and kidney function. Therefore, in patients with HFrEF, natriuretic peptides provide an integrated measure of cardiac preload and afterload, chamber size, wall thickness and systolic function, as well as the systemic consequences of pump dysfunction. Moreover, by reflecting multiple aspects of cardiac structure and physiology, natriuretic peptides give a more complete assessment of cardiac performance than left ventricular ejection fraction, the most widely used measure of contractile function. It is not surprising, therefore, that selectively targeting the cardiac sarcomere to improve pump function might have most benefit in those with elevated NT-proBNP levels, by identifying the individuals with greatest cardiac dysfunction.

[0125] In some embodiments, in conjunction with embodiments above or below, the patient with heart failure has an N-terminal-pro hormone B-type natriuretic peptide (BNP) (NT-proBNP) of at least 2000 pg/mL prior to start of omecamtiv mecarbil treatment as described herein. In some cases, the patient exhibits a NT-proBNP level of at least 2000 pg/mL. In some embodiments, the patient as a pretreatment level of NT-proBNP of 2000 to 150,000 pg/mL. For example, in some cases, the patient has a NT-proBNP level of 1,700, 1,800, 1,900, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 21,000, 22,000, 23,000, 24,000, 25,000, 26,000, 27,000,

28,000, 29,000, 30,000, 31,000, 32,000, 33,000, 34,000, 35,000, 36,000, 37,000, 38,000, 39,000, 40,000, 41,000, 42,000, 43,000, 44,000, 45,000, 46,000, 47,000, 48,000, 49,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, 100,000, 105,000, 110,000, 115,000, 120,000, 125,000, 130,000, 135,000, 140,000, 145,000, or 150,000 pg/mL, prior to omecamtiv mecarbil therapy as described herein. Thus, the patient prior to treatment can exhibit a NT-proBNP level bounded by, and including any of the aforementioned values. For example, in some cases, the patient has a NT-proBNP level of 2000 to 150,000 pg/mL prior to omecamtiv mecarbil therapy as described herein, e.g., 2000 to 125,000 pg/mL, or 2500 to 150,000 pg/mL, or 3000 to 125,000 pg/mL, or 3000 to 100,000 pg/mL. In various cases, the disclosed methods reduce NT-proBNP levels in a patient upon omecamtiv mecarbil therapy as described herein. The levels of NT-proBNP can be measured using any suitable method. In various cases, the patient's NT-proBNP levels decrease by at least 5%, or at least 10%, e.g., 5% to 15%, upon treatment with omecamtiv mecarbil as disclosed herein.

[0126] It was observed that omecamtiv mecarbil reduced the risk of the primary endpoint to a greater extent in patients without AF/F who had higher NT-proBNP levels, compared to lower NT-proBNP levels, at baseline. Omecamtiv mecarbil reduced the risk of both components of the primary endpoint in patients with higher NT-proBNP levels. Omecamtiv mecarbil also reduced the risk of the primary endpoint in the overall patient population, but to a lesser extent compared to participants without AF/F.

[0127] In the population of patients without AF/F, treatment with omecamtiv mecarbil led to a relative risk reduction of 18% (95%CI 10-27%) in the primary endpoint, with a somewhat larger reduction in heart failure hospitalization (21, 11-30%) than in cardiovascular mortality (13, 0-25%), in patients with a baseline NT-proBNP >median, with no benefit in patients with NT-proBNP ≤median. Analyses examining the effect of omecamtiv mecarbil using NT-proBNP as a continuous measure suggested a linear interaction, with a steadily increasing benefit of omecamtiv mecarbil as NT-proBNP level increased. The favorable effect of omecamtiv mecarbil emerged at a NT-proBNP threshold of around 2,000 pg/mL and increased in size with increasing NT-proBNP level across the remaining range of baseline values (up to approximately 20,000 pg/mL). The benefits of omecamtiv mecarbil were consistent in both inpatients and outpatients.

[0128] The benefits of omecamtiv mecarbil in the overall trial population were smaller than seen in participants without AF/F. This reflected an attenuation, or absence, of the effect of omecamtiv mecarbil in patients with AF/F, who accounted for 37% of the patients with a NT-proBNP level greater than the median. The reasons for this lack of benefit of omecamtiv mecarbil in patients with AF/F are not yet clear. However, atrial arrhythmias themselves elevate natriuretic peptides and, for a given natriuretic peptide level, the degree of left ventricular systolic dysfunction is less in patients with AF/F than in patients in sinus rhythm. Consequently, patients with AF/F may have "diluted" the prevalence of significant left ventricular systolic dysfunction in the overall trial population with a NT-proBNP greater than the median, compared to participants without AF/F with a NT-proBNP greater than the median. Just as natriuretic peptides increase with cardiac chamber dilatation, elevated wall stress and reduced systolic function, reversal of these abnormalities with effective therapy results in a decrease in natriuretic peptides.

[0129] In some embodiments, the patient receiving treatment has a pretreatment level of NT-proBNP of at least about 2,000 pg/ml (*e.g.*, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 7000, 8000, 9000, 10,000, 15,000, and 20,000 pg/ml). In some embodiments, the patient has a pretreatment level of NT-proBNP of below about 20,000 pg/ml. In some embodiments, the patient is without AF/F. In some embodiments, treatment in patients without AF/F is effective to achieve a risk reduction, wherein the risk reduction is a relative risk reduction of about 18% (*e.g.*, about 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, etc.). In some embodiments, the patient receiving treatment has a pretreatment level of NT-proBNP of at least about 2,000 pg/ml (*e.g.*, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 7000, 8000, 9000,10,000, 15,000, and 20,000 pg/ml). In some embodiments, the patient has a pretreatment level of NT-proBNP of below about 20,000 pg/ml. In some embodiments, the patient is without AF/F. In some embodiments, treatment in patients without AF/F is effective to achieve a risk reduction, wherein the risk reduction is a relative risk reduction of about 18% (*e.g.*, about 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, etc.).

[0130] In one aspect, provided herein is a method of treating heart failure in a patient with heart failure having no atrial fibrillation or flutter (without AFF) and who exhibits a NT-proBNP level of at least 2000 pg/mL, by administering omecamtiv mecarbil. In some embodiments, treatment in patients without AFF by administering omecamtiv mecarbil is effective to provide risk reduction compared to placebo. The risk reduction may be relative risk reduction and/or absolute risk reduction. In some embodiments, risk reduction is measured as event rates per 100 patient years. An event may be a first heart failure event or cardiovascular death. In some embodiments, the risk reduction may be an absolute risk reduction and/or relative risk reduction, in patients having heart failure who do not exhibit AFF. In some embodiments, the treatment is effective to provide a relative risk reduction of at least 10% (*e.g.*, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, etc.). In some embodiments, the relative risk reduction is 12%. In some embodiments, the relative risk reduction is 15%. In some embodiments, the relative risk reduction is 17%. In some embodiments, treatment with omecamtiv mecarbil results in a reduction in the risk of cardiovascular death and/or heart failure events (e.g., heart failure hospitalization) in patients without AFF and who exhibit a NT-proBNP level of at least 2000 pg/mL. In some embodiments, provided is a method of reducing the time-to-first heart failure event in a patient without AFF and who exhibits a NT-proBNP level of at least 2000 pg/mL by administering omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing the number or frequency of heart failure events (e.g., heart failure hospitalizations) in a patient without AFF and who exhibits a NT-proBNP level of at least 2000 pg/mL by administering omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing risk of cardiovascular death in a patient without AFF and who exhibits a NT-proBNP level of at least 2000 pg/mL by administering omecamtiv mecarbil as described herein.

[0131] In some embodiments, provided is a method of reducing the time-to-first heart failure event in a heart failure patient without AFF who exhibits a NT-proBNP level of at least 2000 pg/mL by administering omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing the number or frequency of heart failure events (e.g., heart failure hospitalizations) in a heart failure patient who does not exhibit AFF by administering omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing

risk of cardiovascular death in a heart failure patient without AFF who exhibits a NT-proBNP level of at least 2000 pg/mL by administering omecamtiv mecarbil as described herein. In some embodiments, the relative risk reduction is at least 10% (*e.g.*, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, etc.). In some embodiments, the relative risk reduction is 12%. In some embodiments, the relative risk reduction is 15%. In some embodiments, the relative risk reduction is 17%.

[0132] It was also observed that patients without AFF exhibited a greater reduction in NT-proBNP upon treatment with omecamtiv mecarbil. In a large clinical trial, omecamtiv mecarbil also reduced NT-proBNP to a significantly greater extent in those with a baseline concentration greater than the median, compared to those with a baseline NT-proBNP level less than or equal to the median. In other words, it appeared that NT-proBNP concentration at baseline identified patients likely to respond more favorably to omecamtiv mecarbil (i.e., those with a high baseline level) and reduction in NT-proBNP represented a surrogate for the efficacy of omecamtiv mecarbil, as seen with other treatments.

[0133] Accordingly, in one aspect, provided herein is a method of treating heart failure in a patient who does not exhibit AFF and who exhibits a higher NT-proBNP level at baseline (*e.g.* patient exhibits a NT-proBNP level of at least 2000 pg/mL), by administering omecamtiv mecarbil as described herein, wherein the administration results in a reduction of NT-proBNP levels relative to baseline. In another aspect, provided herein is a method of reducing NT-proBNP in a heart failure patient who does not exhibit AFF and who exhibits a higher NT-proBNP level at baseline (*e.g.* patient exhibits a NT-proBNP level of at least 2000 pg/mL) by administering omecamtiv mecarbil as described herein. In one aspect, provided herein is a method of reducing NT-proBNP levels in a heart failure patient without AFF who exhibits a higher NT-proBNP level at baseline (*e.g.* patient exhibits a NT-proBNP level of at least 2000 pg/mL at baseline).

[0134] In some embodiments, the NT-proBNP level is reduced by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% in a patient without AFF who exhibits a NT-proBNP level of at least 2000 pg/mL at baseline. In some embodiments, the NT-proBNP level is reduced to less than 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, or 1500 pg/ml in a patient without AFF who exhibits a NT-proBNP level of at least 2000 pg/mL at baseline. In some embodiments, the reduction in NT-proBNP occurs over a period of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 36, or 48 weeks. In some embodiments, provided is a method of decreasing NT-proBNP in a patient without AFF who exhibits a NT-proBNP level of at least 2000 pg/mL at baseline by administering omecamtiv mecarbil as described herein.

[0135] In patients with a NT-proBNP greater than the median at baseline, the proportional reduction in NT-proBNP in the omecamtiv mecarbil, compared with placebo, group was approximately 17%. In a prior analysis of 18 therapeutic interventions in heart failure, a 17% reduction in natriuretic peptide concentration was associated with an approximately 20% relative risk reduction in heart failure hospitalization and 13% reduction in mortality, estimates close to the actual reductions observed in a large clinical trial of omecamtiv mecarbil.

[0136] In yet another aspect, provided herein is a method of treating heart failure in a patient without AFF who exhibits a NT-proBNP level of at least 2000 pg/mL at baseline, by administering omecamtiv mecarbil as

described herein, wherein the administration results in a reduction of the risk of heart failure event or cardiovascular death and reduction in the level of NT-proBNP as compared to baseline. In still yet another aspect, provided herein is a method of reducing risk of heart failure event or cardiovascular death and reducing NT-proBNP level in a patient without AFF who exhibits a NT-proBNP level of at least 2000 pg/mL at baseline. In some embodiments, treatment with omecamtiv mecarbil results in a reduction in the risk of heart failure event or cardiovascular death, as well as a reduction in NT-proBNP levels. In some embodiments, the reduction in the risk of heart failure event or cardiovascular death is a relative risk reduction of about 20% (*e.g.*, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, etc.). In some embodiments, the reduction of NT-proBNP level is a reduction of at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%. In other embodiments, the NT-proBNP level is reduced to less than 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, or 1500 pg/mL. In certain embodiments, treatment with omecamtiv mecarbil results in a reduction in the risk of heart failure event or cardiovascular death is a relative risk reduction of about 20% (*e.g.*, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, etc.) and a reduction of NT-proBNP level at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%. In certain other embodiments, treatment with omecamtiv mecarbil results in a reduction in the risk of heart failure event or cardiovascular death is a relative risk reduction of about 20% (*e.g.*, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, etc.) and a reduction of NT-proBNP levels to less than 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, or 1500 pg/mL.

[0137] *Patients having a baseline systolic blood pressure (SBP):* In some aspects, provided is a method of treating a patient having heart failure with low systolic blood pressure (*e.g.*, less than or equal to 100 mmHg), by administering omecamtiv mecarbil as described herein. Typical HFrEF therapies may not be well-tolerated by patients having SBP less than or equal to 100 mmHg without increased incidence of adverse events or worsening renal function. Any additional therapeutic option is attractive for these individuals. Omecamtiv mecarbil may one such treatment possibility. Omecamtiv mecarbil was found to result in higher treatment efficacy in populations having lower baseline systolic blood pressure (*e.g.*, less than or equal to 100 mmHg) at baseline.

[0138] In some embodiments, the patient exhibits a systolic blood pressure at baseline of less than or equal to about 120 mmHg, less than or equal to about 115 mmHg, less than or equal to about 110 mmHg, less than or equal to about 105 mmHg, less than or equal to about 100 mmHg, less than or equal to about 95 mmHg, less than or equal to about 90 mmHg, between about 85 mmHg and about 120 mmHg, or between about 110mmHg and about 100 mmHg. In some embodiments, the patient with heart failure has a systolic blood pressure less than or equal to 100 mmHg prior to start of omecamtiv mecarbil treatment as described herein. In certain embodiments, the patient having heart failure exhibits a systolic blood pressure at baseline of between about 85 mmHg and about 100 mmHg, between about 85 mmHg and about 95 mmHg, between about 85 mmHg and about 90 mmHg, between about 90 mmHg and about 100 mmHg, between about 90 mmHg and about 95 mmHg, or between about 95 mmHg and about 100 mmHg.

[0139] It was observed that omecamtiv mecarbil reduced the risk of the primary endpoint to a greater extent in patients with lower SBP, demonstrating a linear inverse relation to baseline SBP. In some embodiments, patient receiving treatment exhibits a systolic blood pressure at baseline of less than or equal to about 100 mmHg, less than or equal to about 95 mmHg, less than or equal to about 90 mmHg, between about 85 mmHg and about 100 mmHg, between about 85 mmHg and about 95 mmHg, between about 85 mmHg and about 90 mmHg, between about 90 mmHg and about 100 mmHg, between about 90 mmHg and about 95 mmHg, or between about 95 mmHg and about 100 mmHg.

[0140] In some embodiments, treatment is effective to achieve a risk reduction, wherein the risk reduction is a relative risk reduction of about 18% (*e.g.*, about 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, etc.). In some embodiments, the patient receiving treatment exhibits a SBP at baseline of less than or equal to about 100 mmHg. In some embodiments, treatment in patients who exhibit a SBP at baseline of less than or equal to about 100 mmHg is effective to achieve a risk reduction, wherein the risk reduction is a relative risk reduction of about 18% (*e.g.*, about 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, etc.).

[0141] In one aspect, provided herein is a method of treating heart failure in a patient with heart failure who exhibits a SBP at baseline of less than or equal to about 100 mmHg, by administering omecamtiv mecarbil. In some embodiments, treatment in patients who exhibit a SBP at baseline of less than or equal to about 100 mmHg, by administering omecamtiv mecarbil is effective to provide risk reduction compared to placebo. The risk reduction may be relative risk reduction and/or absolute risk reduction. In some embodiments, risk reduction is measured as event rates per 100 patient years. An event may be a first heart failure event or cardiovascular death. In some embodiments, the risk reduction may be an absolute risk reduction and/or relative risk reduction, in patients having heart failure who exhibits a SBP at baseline of less than or equal to about 100 mmHg. In some embodiments, the treatment is effective to provide a relative risk reduction of at least 10% (*e.g.*, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, etc.). In some embodiments, the relative risk reduction is 12%. In some embodiments, the relative risk reduction is 15%. In some embodiments, the relative risk reduction is 17%. In some embodiments, treatment with omecamtiv mecarbil results in a reduction in the risk of cardiovascular death and/or heart failure events (e.g., heart failure hospitalization) in patients who exhibit a SBP at baseline of less than or equal to about 100 mmHg. In some embodiments, provided is a method of reducing the time-to-first heart failure event in a patient who exhibits a SBP at baseline of less than or equal to about 100 mmHg by administering omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing the number or frequency of heart failure events (e.g., heart failure hospitalizations) in a patient who exhibits a SBP at baseline of less than or equal to about 100 mmHg by administering omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing risk of cardiovascular death in a patient who exhibits a SBP at baseline of less than or equal to about 100 mmHg by administering omecamtiv mecarbil as described herein.

[0142] In some embodiments, provided is a method of reducing the time-to-first heart failure event in a heart failure patient who exhibits a SBP at baseline of less than or equal to about 100 mmHg by administering

omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing the number or frequency of heart failure events (e.g., heart failure hospitalizations) in a heart failure patient who exhibits a SBP at baseline of less than or equal to about 100 mmHg by administering omecamtiv mecarbil as described herein. In some embodiments, provided is a method of reducing risk of cardiovascular death in a heart failure patient who exhibits a SBP at baseline of less than or equal to about 100 mmHg by administering omecamtiv mecarbil as described herein. In some embodiments, the relative risk reduction is at least 10% (*e.g.*, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, etc.). In some embodiments, the relative risk reduction is 12%. In some embodiments, the relative risk reduction is 15%. In some embodiments, the relative risk reduction is 17%.

[0143] *Patients unable to tolerate other standard of care medications*: In some embodiments, in conjunction with embodiments above or below, the patient with heart failure is unable to tolerate other standard of care medications. Illustrative standard of care medications for treating heart failure include, for example, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, diuretics, aldosterone antagonists, inotropes, neprilysin inhibitors, digitalis, and/or digoxin. In some instances, these patients have an inability to tolerate other standard of care medications due to, for example, low blood pressure, symptomatic hypotension, impaired renal function, or bradycardia. In some embodiments, the disclosure provides a method for treating a patient with heart failure having symptomatic hypotension, impaired renal functions, or bradycardia comprising administering omecamtiv mecarbil, as disclosed herein. Further, in some embodiments, the treated patient has not been previously treated with one or more of an angiontensin-converting enzyme inhibitor, an angiotension II receptor blocker, a beta blocker, a diuretic, an aldosterone antagonist, an inotrope, neprilysin inhibitors, digitalis, and/or digoxin. Moreover, in some embodiments, in conjunction with embodiments above or below, the patient treated herein has low blood pressure, symptomatic hypotension, impaired renal function, and/or bradycardia.

[0144] In some instances, the patient with heart failure has undergone or is undergoing, at the time of omecamtiv mecarbil treatment, one or more additional therapies (e.g., antihypertensive) and/or intervention strategies (e.g., implantable device). In some embodiments, in conjunction with embodiments above or below, the patient has undergone cardiac resynchronization therapy (CRT) prior to treatment. In some embodiments, in conjunction with embodiments above or below, the patient has an implantable cardioverter defibrillator (ICD) device. In some instances, the patient is administered sacubitril/valsartan.

[0145] *Patients with chronic heart failure:* in some embodiments, provided is a method of reducing the risk of heart failure events or death from cardiovascular causes in a heart failure patient, such as a patient with chronic heart failure, by administering omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof, as described herein. A heart failure event includes, but is not limited to, urgent clinic visit, emergency department visit, and hospitalization for worsening heart failure. In some embodiments, in conjunction with embodiments above or below, a heart failure event is an urgent clinic visit, an emergency department visit, or hospitalization for worsening heart failure leading to treatment intensification beyond changed oral diuretic therapy.

[0146] In some embodiments, in conjunction with embodiments above or below, treatment is effective to reduce the risk of heart failure events in a heart failure patient, such as a patient with chronic heart failure. In

some embodiments, the patent with chronic heart failure also has one or more of the following: reduced ejection fraction, LVEF of less than 30%, LVEF of less than 28%, LVEF of less than 25%, LVEF of less than 22%, advanced heart failure, heart failure classified as Class III or IV as determined using the NYHA classification, or at least one heart failure hospitalization within 6 months prior to the treatment. In some embodiments, the heart failure patient, such as a patient with chronic heart failure, is an inpatient.

[0147] In some embodiments, in conjunction with embodiments above or below, treatment is effective to reduce the risk of death, such as fatal stroke in a heart failure patient. In some embodiments, treatment is effective to reduce the risk of fatal stroke or non-fatal stroke in a heart failure patient (*e.g.*, patient with chronic heart failure).

Administration Route and Dosing

[0148] The OM can be administered via any suitable route. In some embodiments, in conjunction with other above or below embodiments, omecamtiv mecarbil is administered orally. In some embodiments, in conjunction with other above or below embodiments, OM is administered as a tablet.

[0149] OM can be administered in any suitable amount. In some embodiments, in conjunction with other above or below embodiments, OM is administered at a dosage of 10 mg or more (e.g., 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, or 40 mg or more). Alternatively, or in addition, OM can be administered at a dosage of 75 mg or less (e.g., 70 mg, 65 mg, 60 mg, 55 mg, 50 mg, or 45 mg or less).

[0150] It will be understood that descriptions herein regarding the amount of omecamtiv mecarbil, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable hydrate of a pharmaceutically acceptable salt thereof, is relative to the salt or hydrate form of the active ingredient. The amount of omecamtiv mecarbil described herein refers to the amount (or the equivalent amount) of omecamtiv mecarbil free base. For example, when a tablet formulation is indicated to have 1 mg of omecamtiv mecarbil, the tablet formulation comprises 1.22 mg of omecamtiv mecarbil dihydrochloride monohydrate (molecular weight (MW) of 492.37 g/mol) which provides 1 mg of omecamtiv mecarbil (MW of 401.43 g/mol).

[0151] The disclosed method comprises administering OM using a suitable dosing schedule (e.g., once-a-day or twice daily). In some embodiments, in conjunction with other above or below embodiments, OM is administered twice daily.

[0152] In some embodiments, in conjunction with other above or below embodiments, OM is administered in a dosage of 25 mg twice daily, or 37.5 mg twice daily, or 50 mg twice daily. Plasma concentrations of omecamtiv mecarbil may be assessed after 2 weeks of treatment at a given dose and the dose adjusted so patients are in the target plasma concentration range according to the following: 1) if plasma concentration is < 300 ng/mL, then increase to next higher dose; 2) if plasma concentration is 300-750 ng/mL, no change; and 3) if plasma concentration is >750 ng/mL, then decrease to next lower dose (if >750 ng/mL on starting dose of 25 mg BID, then 25 mg QD may be appropriate). Plasma concentrations of omecamtiv mecarbil may be assessed

approximately 12 hours after the last dose of omecamtiv mecarbil. In some embodiments, the target plasma concentration range of omecamtiv mecarbil is 300 ng/mL to 750 ng/mL.

[0153] Omecamtiv mecarbil is a CYP3A4 substrate. Concomitant use of strong CYP3A4 inhibitors such as ketoconazole, or regimens containing ritonavir-or cobicistat may increase plasma concentrations of omecamtiv mecarbil. Concomitant use of strong CYP3A4 inducers, such as rifampin or carbamazepine may decrease plasma concentrations of omecamtiv mecarbil. Plasma concentrations of omecamtiv mecarbil may be re-checked following 2 weeks of initiation or discontinuation of a strong inhibitor or inducer of CYP3A4 to assess whether dose adjustment of omecamtiv mecarbil are warranted.

Omecamtiv Mecarbil, Salts, Hydrates, and Polymorphs Thereof

[0154] Omecamtiv mecarbil used in the disclosed methods can be present as a pharmaceutically acceptable salt, hydrate, or salt hydrate form, and can be formulated into any suitable pharmaceutical formulation.

[0155] As used herein, the term "pharmaceutically acceptable salts" include, but are not limited to salts with inorganic acids, such as hydrochloride, phosphate, diphosphate, sulfate, and like; as well as salts with an organic acid, such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, 2-hydroxyethylsulfonate, benzoate, salicylate, stearate, and alkanoate such as acetate, HOOC-$(CH_2)_n$-COOH where n is 0-4, and like. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare non-toxic pharmaceutically acceptable addition salts. In some embodiments, the pharmaceutically acceptable salt is a dihydrochloride salt.

[0156] As used herein, the term "hydrate" refers to the chemical entity formed by the interaction of water and a compound, including, for example, hemi-hydrates, monohydrates, dihydrates, trihydrates, etc. In some embodiments, the omecamtiv mecarbil hydrate or salt thereof, is omecamtiv mecarbil monohydrate or salt thereof. In some cases, omecamtiv mecarbil is present as omecamtiv mecarbil dihydrochloride monohydrate.

[0157] As used herein, the term "crystalline form," "polymorph," and "novel form" may be used interchangeably herein, and are meant to include all crystalline and amorphous forms of the compound, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to. In some embodiments, in conjunction with other above or below embodiments, the disclosed methods comprise administering omecamtiv mecarbil dihydrochloride monohydrate salt. In some embodiments, in conjunction with other above or below embodiments, the methods comprise administering omecamtiv mecarbil dihydrochloride hydrate Form A. In some embodiments, in conjunction with other above or below embodiments, the omecamtiv mecarbil used herein is a solvate.

[0158] Form A can be characterized by an X-ray powder diffraction (XRPD) pattern, obtained as set forth in WO2014/152270A1, having peaks at 6.6, 14.9, 20.1, 21.4, and 26.8 ± 0.2° 2θ using Cu Kα radiation. Form A optionally can be further characterized by an XRPD pattern having additional peaks at 8.4, 24.2, 26.0, 33.3 ±

0.2° 2θ using Cu Kα radiation. Form A optionally can be even further characterized by an XRPD pattern having additional peaks at 6.2, 9.7, 13.2, 14.3, 15.4, 16.3, 16.9, 18.9, 19.5, 20.7, 21.8, 22.8, 23.6, 25.1, 27.3, 27.7, 28.4, 29.4, 30.2, 31.2, 31.5, 31.9, 33.9, 34.5, 34.9, 36.1, 36.8, 37.7, 38.5, and 39.7± 0.2° 2θ using Cu Kα radiation. In various cases, Form A can be characterized by an XRPD pattern having peaks at 6.2, 6.6, 8.4, 9.7, 13.2, 14.3, 14.9, 15.4, 16.3, 16.9, 18.9, 19.5, 20.1, 20.7, 21.4, 21.8, 22.8, 23.6, 24.3, 25.1, 26.0, 26.8, 27.3, 27.7, 28.4, 29.4, 30.2, 31.2, 31.5, 31.9, 33.3, 33.9, 34.5, 34.9, 36.1, 36.8, 37.7, 38.5, and 39.7± 0.2° 2θ using Cu Kα radiation. In some embodiments, Form A can be characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 5 wherein by "substantially" is meant that the reported peaks can vary by ±0.2°. It is well known in the field of XRPD that while relative peak heights in spectra are dependent on a number of factors, such as sample preparation and instrument geometry, peak positions are relatively insensitive to experimental details.

[0159] In some embodiments, the omecamtiv mecarbil used in the described methods comprises omecamtiv mecarbil dihydrochloride Form B. In some embodiments, the omecamtiv mecarbil used in the described methods comprises omecamtiv mecarbil dihydrochloride Form C. Form B and Form C polymorphs of omecamtiv mecarbil are metastable anhydrous dihydrochloride forms, and can be formed under varied conditions and temperatures, as described in detail in WO2014/152270, the disclosure of which is incorporated by reference in its entirety.

[0160] Form B can be characterized by an XRPD pattern having peaks at 6.8, 8.8, 14.7, 17.7, and 22.3± 0.2° 2θ using Cu Kα radiation. Form B optionally can be further characterized by an XRPD pattern having additional peaks at 9.6, 13.5, 19.2, 26.2± 0.2° 2θ using Cu Kα radiation. Form B can be characterized by an XRPD pattern having peaks at 6.2, 6.8, 8.8, 9.6, 13.5, 14.4, 14.7, 15.4, 16.3, 17.0, 17.7, 18.3, 19.2, 19.9, 20.5, 20.8, 21.8, 22.3, 22.7, 23.0, 24.8, 25.1, 25.5, 26.2, 26.4, 26.8, 27.5, 28.5, 30.2, 30.6, 31.1, 31.5, 32.1, 32.7, 34.1, 34.4, 35.5, 35.9, 38.1, 38.9± 0.2° 2θ using Cu Kα radiation. In some embodiments, Form B can be characterized by an XRPD pattern substantially as depicted in Figure 6, wherein by "substantially" is meant that the reported peaks can vary by ±0.2°.

[0161] Form C can be characterized by an XRPD pattern having peaks at 6.7, 14.8, 17.4, 20.6, and 26.2± 0.2° 2θ using Cu Kα radiation. Form C optionally can be further characterized by an XRPD pattern having additional peaks at 8.7, 22.0, 27.1, and 27.7± 0.2° 2θ using Cu Kα radiation. Form C can be characterized by an XRPD pattern having peaks at 6.2, 6.7, 8.7, 9.6, 13.5, 14.5, 14.8, 15.4, 16.4, 17.1, 17.4, 18.4, 19.3, 19.5, 19.9, 20.6, 20.8, 21.8, 22.0, 22.5, 22.8, 24.3, 24.7, 25.1, 25.6, 26.2, 26.5, 27.1, 27.3, 27.7, 28.5, 30.0, 30.5, 31.0, 31.5, 32.2, 32.8, 34.1, 35.2, 36.0, 36.9, and 38.8± 0.2° 2θ using Cu Kα radiation. In some embodiments, Form C can be characterized by an XRPD pattern substantially as depicted in Figure 7, wherein by "substantially" is meant that the reported peaks can vary by ±0.2°.

Omecamtiv Mecarbil Formulations

[0162] The disclosed methods comprise administering a therapeutically effective amount omecamtiv mecarbil, or a pharmaceutically acceptable salt, a pharmaceutically acceptable hydrate, or a pharmaceutically acceptable

hydrate of a pharmaceutically acceptable salt thereof, such as omecamtiv mecarbil dihydrochloride monohydrate in a suitable formulation.

[0163] Exemplary pharmaceutical formulations administered to patients in the methods disclosed herein include modified release matrix tablets capable of releasing omecamtiv mecarbil evenly at a pace controlled by the diffusion of omecamtiv mecarbil through a gel layer formed by the hydration of the control release agents in the tablets. In some embodiments, in conjunction with other above or below embodiments, the present modified release matrix tablets demonstrate a minimal pH-dependent release in-vitro. In some embodiments, in conjunction with other above or below embodiments, complete release of omecamtiv mecarbil is achieved in both pH 2 and 6.8 dissolution medium within 24 hours, possibly resulting in less inter- and intra-subject variability and food effect. It is found that the present modified release matrix tablet dosage form is superior to the former immediate release dosage form in minimizing the plasma peak-trough ratio. As a result, the present modified release matrix tablets reduce plasma concentration fluctuation, leading to reduced side effects, and improved safety and efficacy. It is also expected that the present modified release matrix tablets will improve patient compliance by reducing the dosing frequency. Additionally, the present modified release matrix tablets are physicochemically stable—resulting in no physical attribute, assay, impurity, or dissolution profile changes after storage at 40 °C/75% RH for 6 months. Modified release may, in some embodiments, be extended release.

[0164] In some embodiments, in conjunction with other above or below embodiments, the exposure of omecamtiv mecarbil from two to twelve hours after dosing in humans is between 40 and 70 ng/mL. In some embodiments, in conjunction with other above or below embodiments, the exposure of omecamtiv mecarbil from two to twelve hours after dosing in humans remains between 40 and 55 ng/mL.

[0165] In some embodiments, in conjunction with other above or below embodiments, the omecamtiv mecarbil is released in the following intervals: ≤ 30% dose dissolved at 1 hour; 30-75% dose dissolved at 3 hours; and ≥ 80% dose dissolved at 12 hours.

[0166] In some embodiments, in conjunction with other above or below embodiments, the omecamtiv mecarbil is released in the following intervals: ≤ 30% dose dissolved at 2 hours; 30-75% dose dissolved at 6 hours; and ≥ 80% dose dissolved at 16 hours.

[0167] A typical pharmaceutical formulation as administered in the methods disclosed herein comprises omecamtiv mecarbil, or a pharmaceutically acceptable salt, a pharmaceutically acceptable hydrate, or a pharmaceutically acceptable hydrate of a pharmaceutically acceptable salt thereof; a control release agent; a pH modifying agent; a filler; and a lubricant.

[0168] In some embodiments, omecamtiv mecarbil can be administered as a tablet. For example, the tablet excipients may include one or more of fumaric acid, hypromellose, lactose monohydrate, microcrystalline cellulose, and magnesium stearate. The tablet may also comprise a film coating that may include one or more of polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

[0169] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 3-30% w/w of omecamtiv mecarbil, or a pharmaceutically acceptable salt, a pharmaceutically acceptable hydrate, or a pharmaceutically acceptable hydrate of a pharmaceutically acceptable salt thereof; 15-35% w/w control release agent; 20-45% w/w pH modifying agent; 25-65% w/w filler; and 0.1-1.0% w/w lubricant.

[0170] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 12-25 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 25-35 (w/w%) Methocel™ K100 M Prem CR; 20-30 (w/w%) microcrystalline cellulose, PH 102; 5-10 (w/w%) lactose monohydrate, FF 316; 12-25 (w/w%) fumaric acid; 0.1-2 (w/w%) intra-granular magnesium stearate; and 0.1-2 (w/w%) extra-granular magnesium stearate. As used herein throughout, Methocel™ K100 M Prem CR is hypromellose having a viscosity of 100,000 mPa.s at 2% concentration in water at 20 °C.

[0171] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 3-10 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 20-40 (w/w%) Methocel™ K100 M Prem CR; 30-42 (w/w%) microcrystalline cellulose, PH 102; 12-25 (w/w%) lactose monohydrate, FF 316; 4-11 (w/w%) fumaric acid; 0.1-2 (w/w%) intra-granular magnesium stearate; and 0.1-2 (w/w%) extra-granular magnesium stearate.

[0172] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 12-25 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 1-10 (w/w%) Methocel™ K100 M Prem CR; 12-27 (w/w%) Methocel™ K100 LV Prem CR; 20-35 (w/w%) microcrystalline cellulose, PH 102; 4-15 (w/w%) lactose monohydrate, FF 316; 12-25 (w/w%) fumaric acid; 0.1-2 (w/w%) intra-granular magnesium stearate; and 0.1-2 (w/w%) extra-granular magnesium stearate. As used herein throughout, Methocel™ K100 LV Prem CR is hypromellose having a viscosity of 100 mPa.s at 2% concentration in water at 20 °C.

[0173] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 3-10 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 1-10 (w/w%) Methocel™ K100 M Prem CR; 12-27 (w/w%) Methocel™ K100 LV Prem CR; 30-50 (w/w%) microcrystalline cellulose, PH 102; 15-25 (w/w%) lactose monohydrate, FF 316; 3-11 (w/w%) fumaric acid; 0.1-2 (w/w%) intra-granular magnesium stearate; and 0.1-2 (w/w%) extra-granular magnesium stearate.

[0174] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 18-19 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 28-32 (w/w%) Methocel™ K100 M Prem CR; 23-26 (w/w%) microcrystalline cellulose, PH 102; 7-9 (w/w%) lactose monohydrate, FF 316; 17-20 (w/w%) fumaric acid; 0.1-1 (w/w%) intra-granular magnesium stearate; and 0.1-1 (w/w%) extra-granular magnesium stearate.

[0175] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 5-7 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 27-33 (w/w%)

Methocel™ K100 M Prem CR; 35-38 (w/w%) microcrystalline cellulose, PH 102; 17-20 (w/w%) lactose monohydrate, FF 316; 6-9 (w/w%) fumaric acid; 0.1-1 (w/w%) intra-granular magnesium stearate; and 0.1-1 (w/w%) extra-granular magnesium stearate.

[0176] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 17-20 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 3-7 (w/w%) Methocel™ K100 M Prem CR; 18-22 (w/w%) Methocel™ K100 LV Prem CR; 26-30 (w/w%) microcrystalline cellulose, PH 102; 8-11 (w/w%) lactose monohydrate, FF 316; 17-20 (w/w%) fumaric acid; 0.1-1 (w/w%) intra-granular magnesium stearate; and 0.1-1 (w/w%) extra-granular magnesium stearate.

[0177] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 5-7 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 3-7 (w/w%) Methocel™ K100 M Prem CR; 18-22 (w/w%) Methocel™ K100 LV Prem CR; 37-43 (w/w%) microcrystalline cellulose, PH 102;18-22 (w/w%) lactose monohydrate, FF 316; 6-9 (w/w%) fumaric acid; 0.1-1 (w/w%) intra-granular magnesium stearate; and 0.1-1 (w/w%) extra-granular magnesium stearate.

[0178] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 18.37 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 30 (w/w%) Methocel™ K100 M Prem CR; 24.20 (w/w%) microcrystalline cellulose, PH 102; 8.07 (w/w%) lactose monohydrate, FF 316;18.37 (w/w%) fumaric acid; 0.5 (w/w%) intra-granular magnesium stearate; and 0.5 (w/w%) extra-granular magnesium stearate.

[0179] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 6.13 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 30 (w/w%) Methocel™ K100 M Prem CR; 36.81 (w/w%) microcrystalline cellulose, PH 102; 18.40 (w/w%) lactose monohydrate, FF 316; 7.66 (w/w%) fumaric acid; 0.5 (w/w%) intra-granular magnesium stearate; and 0.5 (w/w%) extra-granular magnesium stearate.

[0180] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 18.37 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 5 (w/w%) Methocel™ K100 M Prem CR; 20 (w/w%) Methocel™ K100 LV Prem CR; 27.95 (w/w%) microcrystalline cellulose, PH 102; 9.31 (w/w%) lactose monohydrate, FF 316; 18.37 (w/w%) fumaric acid; 0.5 (w/w%) intra-granular magnesium stearate; and 0.5 (w/w%) extra-granular magnesium stearate.

[0181] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 6.13 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 5 (w/w%) Methocel™ K100 M Prem CR; 20 (w/w%) Methocel™ K100 LV Prem CR; 40.14 (w/w%) microcrystalline cellulose, PH 102; 20.07 (w/w%) lactose monohydrate, FF 316; 7.66 (w/w%) fumaric acid; 0.5 (w/w%) intra-granular magnesium stearate; and 0.5 (w/w%) extra-granular magnesium stearate.

[0182] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 6.13 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 30 (w/w%)

Methocel™ K100 M Prem CR; 27.94 (w/w%) microcrystalline cellulose, PH 102; 27.94 (w/w%) lactose monohydrate, FF 316; 6.74 (w/w%) fumaric acid; 0.5 (w/w%) intra-granular magnesium stearate; and 0.75 (w/w%) extra-granular magnesium stearate.

[0183] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 9.20 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 30 (w/w%) Methocel™ K100 M Prem CR; 24.72 (w/w%) microcrystalline cellulose, PH 102; 24.71 (w/w%) lactose monohydrate, FF 316; 10.12 (w/w%) fumaric acid; 0.5 (w/w%) intra-granular magnesium stearate; and 0.75 (w/w%) extra-granular magnesium stearate.

[0184] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 12.27 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 30 (w/w%) Methocel™ K100 M Prem CR; 21.49 (w/w%) microcrystalline cellulose, PH 102; 21.49 (w/w%) lactose monohydrate, FF 316; 13.50 (w/w%) fumaric acid; 0.5 (w/w%) intra-granular magnesium stearate; and 0.75 (w/w%) extra-granular magnesium stearate.

[0185] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 6.13 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 30 (w/w%) Methocel™ K100 M Prem CR; 27.82 (w/w%) microcrystalline cellulose, PH 102; 27.81 (w/w%) lactose monohydrate, FF 316; 6.74 (w/w%) fumaric acid; 0.5 (w/w%) intra-granular magnesium stearate; and 1.0 (w/w%) extra-granular magnesium stearate.

[0186] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 9.20 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 30 (w/w%) Methocel™ K100 M Prem CR; 24.59 (w/w%) microcrystalline cellulose, PH 102; 24.59 (w/w%) lactose monohydrate, FF 316; 10.12 (w/w%) fumaric acid; 0.5 (w/w%) intra-granular magnesium stearate; and 1.0 (w/w%) extra-granular magnesium stearate.

[0187] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 12.27 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 30 (w/w%) Methocel™ K100 M Prem CR; 21.37 (w/w%) microcrystalline cellulose, PH 102; 21.36 (w/w%) lactose monohydrate, FF 316; 13.50 (w/w%) fumaric acid; 0.5 (w/w%) intra-granular magnesium stearate; and 1.0 (w/w%) extra-granular magnesium stearate.

[0188] In some embodiments, in conjunction with other above or below embodiments, the pharmaceutical formulation administered comprises about 12.27 (w/w%) omecamtiv mecarbil Di-HCl hydrate; 30 (w/w%) Methocel™ K100 M Prem CR; 31.04 (w/w%) microcrystalline cellulose, PH 102; 10.35 (w/w%) lactose monohydrate, FF 316; 15.34 (w/w%) fumaric acid; 0.5 (w/w%) intra-granular magnesium stearate; and 0.5 (w/w%) extra-granular magnesium stearate.

Combination Therapy

[0189] In some embodiments, in conjunction with embodiments above or below, the disclosed methods can comprise administering one or more additional therapeutics suitable for treating/ameliorating one or more cardiovascular conditions. In some embodiments, in conjunction with embodiments above or below, the disclosed methods comprise administering to the patient a therapeutically effective amount of an angiotensin-converting enzyme (ACE) inhibitor. In some embodiments, in conjunction with embodiments above or below, the disclosed methods comprise administering to the patient a therapeutically effective amount of a mineralocorticoid receptor antagonist (MRA).

[0190] In some cases, the ACE inhibitor comprises one or more agents selected from benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril.

[0191] In some cases, the MRA comprises one or more agents selected from spironolactone, eplerenone, canrenoic acid, canrenone, and drospirenone.

EMBODIMENTS

1. A method of treating heart failure in a patient having a left ventricular ejection fraction (LVEF) of less than 35% comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

2. The method of embodiment 1, wherein the patient has a LVF of less than 30%.

3. The method of embodiment 1, wherein the patient has a LVF of less than 28%.

4. The method of embodiment 1, wherein the patient has a LVF of less than 25%.

5. The method of embodiment 1, wherein the patient has a LVEF of less than 22%.

6. A method of treating heart failure in a patient who does not exhibit atrial fibrillation or atrial flutter comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

7. The method of embodiment 6, wherein the patient has a LVEF of less than 35%.

8. The method of embodiment 6, wherein the patient has a LVEF of less than 30%.

9. The method of embodiment 6, wherein the patient has a LVEF of less than 28%.

10. The method of embodiment 6, wherein the patient has a LVEF of less than 25%.

11. The method of embodiment 6, wherein the patient has a LVEF of less than 22%.

12. A method of treating heart failure in a patient having heart failure classified as Class III or IV as determined using the New York Heart Association (NYHA) classification comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

13. A method of treating heart failure in a patient having advanced heart failure comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

14. The method of embodiment 13, wherein the patient has heart failure classified as Class III or IV as determined using the New York Heart Association (NYHA) classification.

15. The method of embodiment 13 or 14, wherein the patient has a LVEF of less than 30%.

16. The method of any one of embodiments 13-15, wherein the patient has had at least one heart failure hospitalization within 6 months prior to the treatment.

17. The method of any one of embodiments 13-16, wherein the patient does not exhibit atrial fibrillation or atrial flutter.

18. A method of treating ischemic heart failure in a patient comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

19. A method of treating heart failure in a patient who has had a myocardial infarction comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

20. A method of treating heart failure in a patient who has a pretreatment level of NT-proBNP of at least 2,000 pg/mL comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

21. The method of embodiment 20, wherein the patient has a LVEF of less than 35%.

22. The method of embodiment 20, wherein the patient has a LVEF of less than 30%.

23. The method of embodiment 20, wherein the patient has a LVEF of less than 28%.

24. The method of embodiment 20, wherein the patient has a LVEF of less than 25%.

25. The method of embodiment 20, wherein the patient has a LVEF of less than 22%.

26. The method of any one of embodiments 20-25, wherein the patient does not exhibit atrial fibrillation or atrial flutter.

27. A method of treating heart failure in a patient who has low blood pressure, symptomatic hypotension, impaired renal function, or bradycardia comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

28. The method of embodiment 27, wherein the patient has not previously been treated with one or more of an angiotensin-converting enzyme inhibitor, an angiotensin II receptor blocker, a beta blocker, a diuretic, an aldosterone antagonist, an inotrope, neprilysin inhibitors, digitalis, and digoxin.

29. A method of treating heart failure in a patient who is unable to tolerate one or more of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, diuretics, aldosterone antagonists, inotropes, neprilysin inhibitors, digitalis, and digoxin comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

30. The method of embodiment 29, wherein the patient has low blood pressure, symptomatic hypotension, impaired renal function, or bradycardia.

31. A method of preventing stroke in a patient suffering from heart failure with reduced ejection fraction (HFrEF) comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

32. The method of claim 31, wherein the stroke is non-fatal.

33. The method of claim 31, wherein the stroke is fatal.

34. The method of any one of claim 31 to 33, wherein the stroke is ischemic.

35. The method of any one of claim 31 to 33, wherein the stroke is ischemic with hemorrhagic transformation.

36. The method of any one of claim 31 to 33, wherein the stroke is hemorrhagic.

37. A method of reducing the risk of heart failure events or death from cardiovascular causes in a heart failure patient comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

38. The method of claim 37, wherein the method reduces the risk of heart failure events in the patient.

39. The method of claim 37 or 38, wherein the patient has chronic heart failure with reduced ejection fraction.

40. The method of any one of claims 37-39, wherein the heart failure events are an urgent clinic visit, emergency department visit or hospitalization for worsening heart failure leading to treatment intensification beyond changed oral diuretic therapy.

41. The method of any one of claims 37-40, wherein the patient has a LVEF of less than 30%.

42. The method of any one of claims 37-40, wherein the patient has a LVEF of less than 28%.

43. The method of any one of claims 37-40, wherein the patient has a LVEF of less than 25%.

44. The method of any one of claims 37-40, wherein the patient has a LVEF of less than 22%.

45. The method of any one of claims 37-44, wherein the patient does not exhibit atrial fibrillation or atrial flutter.

46. The method of any one of claims 37-45, wherein the patient has advanced heart failure.

47. The method of any one of claims 37-46, wherein the patient has heart failure classified as Class III or IV as determined using the New York Heart Association (NYHA) classification.

48. The method of any one of claims 37-47, wherein the patient has had at least one heart failure hospitalization within 6 months prior to the treatment.

49. The method of any one of claims 1-48, wherein the patient is an inpatient.

50. The method of any one of claims 1-48, wherein the patient is an outpatient.

51. The method of any one of claims 1-50, wherein omecamtiv mecarbil is administered orally.

52. The method of claim 51, wherein omecamtiv mecarbil is administered as a tablet.

53. The method of any one of claims 1-52, comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil dihydrochloride hydrate.

54. The method of any one of claims 1-53, wherein omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof is administered as a modified release matrix tablet.

55. The method of any one of claims 1-54, wherein omecamtiv mecarbil is administered twice daily.

56. The method of claim 55, wherein omecamtiv mecarbil is administered in a dosage of 25 mg twice daily.

57. The method of claim 55, wherein omecamtiv mecarbil is administered in a dosage of 37.5 mg twice daily.

58. The method of claim 55, wherein omecamtiv mecarbil is administered in a dosage of 50 mg twice daily.

59. The method of any one of claims 1-58, wherein the patient has undergone cardiac resynchronization therapy (CRT) prior to treatment.

60. The method of any one of claims 1-59, wherein the patient has an implantable cardioverter defibrillator (ICD) device.

61. The method of any one of claims 1-60, further comprising administering to the patient a therapeutically effective amount of an angiotensin-converting enzyme inhibitor.

62. The method of any one of claims 1-61, further comprising administering to the patient a therapeutically effective amount of a mineralocorticoid receptor antagonist.

EXAMPLES

[0192] The following examples further illustrate the disclosed methods of treatment, but of course, should not be construed as in any way limiting its scope.

[0193] The following abbreviations are used in the Examples: ACEi refers to angiotensin-converting enzyme inhibitor; ARB refers to angiotensin receptor blocker; ARNi refers to angiotensin receptor-neprilysin inhibitor; BB refers to beta blocker; CRT refers to cardiac resynchronization therapy; ED refers to emergency department; eGFR refers to estimated glomerular filtration rate; HF refers to heart failure; hsTn refers to high-sensitivity troponin I; ICD refers to implantable cardioverter-defibrillator; KCCQ refers to Kansas City Cardiomyopathy Questionnaire; LVEF refers to left ventricular ejection fraction; MAGGIC refers to Meta-Analysis Global Group in Chronic HF; MRA refers to mineralocorticoid receptor antagonist; NEJM refers to The New England Journal of Medicine; NT-proBNP refers to N-terminal pro-B-type natriuretic peptide; NYHA refers to New York Heart Association; SBP refers to systolic blood pressure; and SGLT2 refers to sodium-glucose co-transporter 2.

[0194] The endpoints of studies and event definitions were based on ACC/AHA standards for endpoint definitions in cardiovascular clinical trials as described in Hicks et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials, J Am Coll Cardiol 2018;71:1021-34.

Patient Eligibility

[0195] Patient eligibility requirements included age 18-85 years, New York Heart Association functional class (NYHA) II-IV symptoms, and ejection fraction of 35% or less. Participants were currently hospitalized for heart failure (in-patients) or had either an urgent visit to the emergency department or a hospitalization for heart failure (outpatients) within one year prior to randomization. Participants had N-terminal pro-B-type natriuretic peptide

(NT-proBNP) concentration ≥ 400 pg/mL or BNP ≥ 125 pg/mL at screening (if in atrial fibrillation/flutter: NT-proBNP ≥1,200 pg/mL or BNP ≥375 pg/mL). Patients were required to receive standard drug and device therapy for heart failure consistent with regional clinical practice guidelines and doses optimized according to investigator judgment.

[0196] Key exclusion criteria for patients included current hemodynamic or clinical instability requiring mechanical or intravenous medication, systolic blood pressure (SBP) < 85 mmHg, estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73 m^2, recent acute coronary syndrome events or cardiovascular procedures (including planned), and other conditions that would adversely affect participation in the trial.

Study Procedures

All eligible participants were randomized 1:1 to oral administration of either placebo or omecamtiv mecarbil (pharmacokinetic-guided dosing: 25, 37.5 or 50 mg) twice daily. Pre-dose plasma concentrations of omecamtiv mecarbil were measured at weeks 2 and 6 with respective dose adjustments on weeks 4 and 8. The patient and investigator were blinded to the plasma concentrations and dispensed dose. The full schedule of assessments is provided in the protocol available at NEJM.org. Study drug was temporarily withheld if the participant experienced clinical signs or symptoms consistent with acute myocardial infarction or ischemia.

Study Outcomes

[0197] The primary outcome was a composite of the time to a heart failure event or cardiovascular death, whichever occurred first. A heart failure event was defined as an urgent clinic visit, emergency department visit or hospitalization for subjectively and objectively worsening heart failure leading to treatment intensification beyond changed oral diuretic therapy. Secondary outcomes were: the time to cardiovascular death; change in KCCQ Total Symptom Score (TSS) from baseline to Week 24 (scale from 0 to 100; higher score indicates fewer symptoms); time to first heart failure hospitalization; and time to all-cause death. All deaths, HF events, major cardiac ischemic events (myocardial infarction/ unstable angina hospitalization, and coronary revascularization), and strokes were adjudicated by a blinded external Clinical Events Committee (Duke Clinical Research Institute) using standardized definitions.

Summary of Results

[0198] Over a median of 21.8 months, the primary outcome occurred in 1523 of 4120 patients (37.0%) in the omecamtiv mecarbil group and in 1607 of 4112 patients (39.1%) in the placebo group (hazard ratio, 0.92; 95% CI 0.86, 0.99; P=0.025); 808 patients (19.6%) receiving omecamtiv mecarbil and 798 patients (19.4%) receiving placebo died from cardiovascular causes (hazard ratio, 1.01; 95% CI, 0.92 to 1.11; P=0.86), 1177 (28.6%) and 1236 (30.1%) experienced a first heart failure event (hazard ratio, 0.93; 95% CI, 0.86 to 1.00; P=0.063), and 1067 (25.9%) and 1065 (25.9%) died from any cause (hazard ratio 1.00; 95% CI, 0.92 to 1.09). The frequency of cardiac ischemic and ventricular arrhythmia events did not differ between treatment groups.

[0199] Patients enrolled as in patients were more symptomatic as suggested by their lower KCCQ total symptom score at baseline; those receiving omecamtiv mecarbil had a 2.5 point improvement in this score compared to those on placebo.

Statistical Analysis

[0200] A sample size of approximately 8,000 patients was chosen to provide 90% power to detect a hazard ratio of 0.8 for cardiovascular death assuming the following: a 10% annualized rate of cardiovascular death 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-cardiovascular death or study discontinuation over the course of the trial. The study was event-driven and was ended after approximately 1590 cardiovascular deaths. The overall type I error was 0.05 for 2-sided testing across primary and secondary endpoints with control for multiplicity testing. A single interim efficacy analysis was conducted after approximately two-thirds of the targeted number of cardiovascular deaths accrued with a one-sided alpha of 0.0005. Given the negligible impact of this interim on the final alpha, the full 0.05 was used in the final analysis consistent with the Haybittle-Peto approach. Efficacy analyses were performed according to randomized treatment group assignment (intention-to-treat) on the full analysis set which included all randomized patients except for 24 subjects from a single site excluded due to Good Clinical Practice violations. Time-to-event data were evaluated with Kaplan-Meier estimates and Cox proportional-hazards models stratified by randomization setting and region with treatment group and baseline eGFR as covariates. The mean differences in the KCCQ TSS change from baseline to Week 24 were estimated using a mixed model stratified by randomization setting (inpatient and outpatient) containing baseline TSS value, region, baseline eGFR, scheduled visit, treatment group, and the interaction of treatment group with scheduled visit. A joint omnibus F-test was used to test the treatment effect for the KCCQ TSS. An overall pooled estimate for the KCCQ TSS treatment difference to placebo were conducted using a likelihood based approach. The prespecified safety analyses included: serious adverse events; adverse events associated with discontinuation of study treatment; “adverse events of interest” i.e., ventricular arrhythmias requiring treatment and positively adjudicated major cardiac ischemic events (including myocardial infarction, hospitalization for unstable angina, coronary revascularization). The safety analyses were performed in patients who underwent randomization and received at least one dose of omecamtiv mecarbil or placebo with the same exclusion of the 24 subjects as in the full analysis set. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

Enrollment, Randomization, Treatment and Follow-up

[0201] 8,256 participants were randomized and 24 patients were excluded prior to database lock due to Good Clinical Practice violations. Accordingly, 8,232 patients were included in the efficacy analysis. At the end of the trial, 16 patients had unknown vital status (omecamtiv mecarbil: nine patients withdrew consent; placebo: six patients withdrew consent and one lost to follow-up). The baseline characteristics were balanced between the

two treatment groups (Table 1). The overall median duration of follow-up was 21.8 months (Q1, Q3; 15.4, 28.6 months).

Table 1. Baseline characteristics of patients

Demographics	**OM (N=4120)**	**Placebo (N=4112)**
Age (years), median (Q1, Q3)	66 (58, 73)	66 (58, 73)
Age (years), mean (SD)	64.5 (11.3)	64.5 (11.4)
Sex, female, n (%)	875 (21.2)	874 (21.3)
Race, n (%)*		
White	3196 (77.6)	3201 (77.8)
Asian	355 (8.6)	355 (8.6)
Black or African American	285 (6.9)	277 (6.7)
Other	284 (6.9)	279 (6.8)
Ethnicity, Hispanic/Latino n (%)	886 (21.5)	885 (21.5)
Geographic Region, n (%)		
Eastern Europe/ Russia	1344 (32.6)	1337 (32.5)
Western Europe/ South Africa/ Australasia	961 (23.3)	960 (23.3)
Latin and South America	787 (19.1)	787 (19.1)
US and Canada	693 (16.8)	693 (16.9)
Asia	335 (8.1)	335 (8.1)
Clinical Characteristics		
Medical Conditions, n (%)		
Coronary artery disease	2568 (62.3)	2560 (62.3)
Myocardial infarction	1693 (41.1)	1742 (42.4)
Percutaneous coronary intervention	1232 (29.9)	1206 (29.3)
Coronary artery bypass grafting	639 (15.5)	678 (16.5)
Peripheral artery disease	418 (10.1)	429 (10.4)
Stroke	377 (9.2)	377 (9.2)
Atrial fibrillation or flutter at screening	1146 (27.8)	1099 (26.7)
Hypertension	2910 (70.6)	2874 (69.9)
Type 2 diabetes mellitus	1652 (40.1)	1657 (40.3)
Chronic kidney disease	1475 (35.8)	1519 (36.9)
Chronic Obstructive Pulmonary Disease	665 (16.1)	680 (16.5)

Demographics	OM (N=4120)	Placebo (N=4112)
Asthma	218 (5.3)	222 (5.4)
Heart Failure History		
LVEF (%), median (Q1, Q3)	28 (22, 32)	27 (21, 32)
LVEF (%), mean (SD)	26.6 (6.3)	26.5 (6.3)
MAGGIC Score, mean (SD)	23.3 (6.3)	23.4 (6.4)
MAGGIC Score, median (Q1, Q3)	23 (19, 28)	23 (19, 28)
NYHA classification, n (%)		
Class II	2195 (53.3)	2173 (52.8)
Class III	1801 (43.7)	1815 (44.1)
Class IV	124 (3.0)	124 (3.0)
Ischemic heart failure etiology, n (%)	2193 (53.2)	2222 (54.0)
KCCQ Total Symptom Score, median (Q1, Q3)	68.8 (49, 87.5)	68.8 (49, 87.5)
Vitals and Laboratory Parameters		
Body mass index (kg/m^2), mean (SD)	28.5 (6.3)	28.4 (6.1)
Body mass index (kg/m^2), median (Q1, Q3)	27.6 (24.2, 31.7)	27.6 (24.2, 31.6)
SBP (mmHg), median (Q1, Q3)	116 (105, 128)	117 (105, 128)
SBP (mmHg), mean (SD)	116.3 (15.4)	116.6 (15.3)
Heart rate (beats/min), median (Q1, Q3)	71 (64, 80)	71 (64, 80)
Heart rate (beats/min), mean (SD)	72.4 (12.2)	72.3 (12.1)
NT-proBNP (pg/mL), median (Q1-Q3)	1977 (980, 4061)	2025 (1000, 4105)
hsTnI (ng/mL), median (Q3)	0.027 (0.052)	0.027 (0.052)
eGFR (mL/min/1.73m^2), median (Q1-Q3)	58.8 (44.3, 74.3)	58.7 (43.8, 73.7)
G≤2: >60	1964 (47.7)	1947 (47.3)
G3: 30-59	1882 (45.7)	1912 (46.5)
G4: 15-29	270 (6.6)	252 (6.1)
G5: <15	4 (<0.1)	1 (<0.1)
Medications and Cardiac Devices, n (%)		

Demographics	OM (N=4120)	Placebo (N=4112)
ACEi, ARB or ARNi	3583 (87.0)	3576 (87.0)
ARNi	819 (19.9)	782 (19.0)
BB	3881 (94.2)	3883 (94.4)
MRA	3199 (77.6)	3198 (77.8)
(ACEi, ARB, or ARNi) + MRA + BB	2709 (65.8)	2716 (66.1)
Digitalis Glycosides	687 (16.7)	698 (16.7)
SGLT2 Inhibitors	104 (2.5)	114 (2.8)
Ivabradine	255 (6.2)	278 (6.8)
Cardiac Resynchronization Therapy	592 (14.4)	566 (13.8)
Implantable Cardioverter Defibrillator	1326 (32.2)	1288 (31.3)

Outcomes

[0202] A first heart failure event or death from cardiovascular causes occurred in 1523 of 4120 patients (37.0%) in the omecamtiv mecarbil group and in 1607 of 4112 patients (39.1%) in the placebo group (hazard ratio, 0.92; 95% confidence interval [CI] 0.86, 0.99; P=0.025; Figure 1A and Table 2). For the two components of this time-to-first event composite, 1177 (28.6%) in patients receiving omecamtiv mecarbil and 1236 (30.1%) in the placebo group experienced a first heart failure event (hazard ratio, 0.93; 95% CI, 0.86 to 1.00; P=0.063; Figure 1B and Table 2); death from cardiovascular causes contributed 346 events (8.4%) and 371 events (9.0%) (Table 2). The effect of omecamtiv mecarbil was generally consistent across most prespecified subgroups with statistically the largest potential interaction observed for the ejection fraction subgroup (interaction effect p = 0.003; Figure 3).

[0203] The secondary outcome of time to death from cardiovascular causes occurred in 808 (19.6%) patients receiving omecamtiv mecarbil and 798 patients (19.4%) receiving placebo (hazard ratio, 1.01; 95% CI, 0.92 to 1.11; P=0.86; Figure 1C and Table 2). The pre-specified analysis of change from baseline to week 24 KCCQ total symptom score improvement by randomization setting (inpatient mean difference [95% CI]: 2.50 [0.54, 4.46], outpatient: -0.46 [-1.40, 0.48], joint p = 0.028) did not meet the threshold of p=0.002 based upon the multiplicity control testing procedure, thus it and the other two secondary outcomes are considered exploratory. A first hospitalization for heart failure occurred in 1142 patients (27.7%) in the omecamtiv mecarbil group and in 1179 (28.7%) in the placebo group (hazard ratio 0.95; 95% CI, 0.87 to 1.03; Table 2), while death due to all causes occurred in 1067 (25.9%) and 1065 (25.9%) patients, respectively (hazard ratio 1.00; 95% CI, 0.92 to 1.09; Figure 1D and Table 2).

[0204] The cumulative incidences of the primary outcome, heart failure events, death from cardiovascular causes and death from any cause were estimated with the use of the Kaplan–Meier method. Hazard ratios and

95% confidence intervals were estimated with the use of Cox regression models stratified by randomization location and region and treatment with omecamtiv mecarbil or placebo as explanatory variables. Analyses are based upon all participants who underwent randomization. The inset in each panel of Figures 1A-1D shows the same data on an enlarged y axis.

[0205] Other outcomes of interest included the effects of omecamtiv mecarbil on vital signs and selected laboratory values (Table 3). There was no significant difference in the change in systolic blood pressure at 24 or 48 weeks between the omecamtiv mecarbil and placebo groups; there was a small but significant decrease in heart rate in participants assigned to omecamtiv mecarbil compared to placebo at both timepoints. Omecamtiv mecarbil significantly decreased NT-proBNP concentrations at Week 24 compared to placebo.

Table 2. Primary and Secondary Cardiovascular Outcomes

	Omecamtiv Mecarbil (N = 4120)		**Placebo (N = 4112)**			
Variable	**Values**	**Events/ 100 patient-yrs**	**Values**	**Events/ 100 patient-yrs**	**Hazard or Rate Ratio or Difference (95% CI)**	**P value**
Primary composite outcome – no. (%)	1523 (37.0)	24.2	1607 (39.1)	26.3	0.92 (0.86, 0.99)	0.025
Cardiovascular death as first event	346 (8.4)	NA	371 (9.0)	NA	NA	NA
Heart failure event	1177 (28.6)	18.7	1236 (30.1)	20.3	0.93 (0.86, 1.00)	NA
Secondary outcomes						
Cardiovascular death	808 (19.6)	10.9	798 (19.4)	10.8	1.01 (0.92, 1.11)	0.86†
Change in KCCQ total symptom score at week 24, least squares mean (SE)						
Inpatients	23.7 (0.70)	-	21.2 (0.71)	-	2.5 (0.54, 4.46)	0.028†
Outpatients	5.8 (0.34)	-	6.3 (0.34)	-	-0.5 (-1.40, 0.48)	
Heart failure hospitalization	1142 (27.7)	18.0	1179 (28.7)	19.1	0.95 (0.87, 1.03)	NA
All-cause death	1067 (25.9)	14.4	1065 (25.9)	14.4	1.00 (0.92, 1.09)	NA

[0206] NA denotes not applicable because P values for efficacy outcomes are reported only for outcomes that were included in the hierarchical-testing strategy *The primary outcome was a composite of heart failure events (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes. The total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) ranges from 0 to

100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. †Non-significant. After statistical significance on the primary endpoint, CV death was tested against an alpha of 0.048 and change from baseline in the KCCQ TSS was tested against an alpha of 0.002.

[0207] In addition, the impact of LVEF on the therapeutic effect of omecamtiv mecarbil in cardiovascular outcomes was analyzed. The patient population data demonstrated that patients with more severely reduced ejection fraction were more likely to be younger, male, non-white, from the Americas or Western Europe, had ischemic cardiomyophathy, normal sinus rhythm, and other clinical markers of more severe HFrEF when compared to patients with less severely reduced ejection fraction. There was a significant heterogeneity in the effect of omecamtiv mecarbil on the primary composite endpoint with respect to LVEF (continuous interaction, p = 0.002). Omecamtiv mecarbil had progressively greater improvement in the primary composite endpoint with decreasing LVEF as demonstrated by the continuously improving hazard ratio (Figure 8A). The incidence of the PCE increased with decreasing EF and omecamtiv mecarbil produced increasingly greater absolute reductions in the PCE with decreasing EF (Figure 8B).

Safety

[0208] Excluding the discontinuations due to death, the study drug was stopped in 847 patients (20.6%) receiving omecamtiv mecarbil and 897 patients (21.9%) receiving placebo with 371 (9.0%) in the omecamtiv mecarbil group and 382 (9.3%) receiving placebo discontinuing due to an adverse event. Patients receiving omecamtiv mecarbil had no change in potassium or creatinine concentrations during the course of the trial compared to placebo. Patients receiving omecamtiv mecarbil had increased median concentrations of high sensitivity troponin-I from baseline of 0.004 ng/mL (lower limit of quantification, 0.010 ng/mL) compared to placebo at week 24. A total of 200 (4.9%) of participants receiving omecamtiv mecarbil had a positively adjudicated major cardiac ischemic event compared to a total of 188 (4.6%) receiving placebo, with myocardial infarction consisting of 122 (3.0%) and 118 (2.9%) of these events. Ventricular arrhythmias were similar in patients receiving omecamtiv mecarbil compared to placebo (Table 3).

Table 3. Laboratory Parameters and Safety Outcomes

Variable	Omecamtiv Mecarbil (N = 4110)	Placebo (N = 4101)	Relative Risk or Difference (95% CI)
Laboratory measures, change from baseline			
Systolic blood pressure – mmHg, mean (SD)			
Week 24	1.4 (15.3)	1.5 (15.6)	-0.13 (-0.85, 0.58)
Week 48	2.0 (16.1)	1.9 (16.0)	0.16 (-0.63, 0.96)
Heart rate – bpm, mean (SD)			
Week 24	-2.1 (12.6)	-0.5 (12.8)	-1.61 (-2.19, -1.02)
Week 48	-2.0 (13.1)	-0.2 (13.2)	-1.75 (-2.40, -1.10)
Potassium – mmol/L, mean (SD)			
Week 24	-0.01 (0.57)	-0.01 (0.57)	0.002 (-0.025, 0.028)

Week 48	-0.03 (0.59)	-0.02 (0.58)	-0.007 (-0.036, 0.022)
Creatinine – mg/dL, mean (SD)			
Week 24	0.03 (0.33)	0.02 (0.32)	0.007 (-0.008, 0.022)
Week 48	0.06 (0.39)	0.05 (0.38)	0.010 (-0.009, 0.029)
NT-proBNP – pg/mL, median (Q1, Q3)			
Week 24	-251 (-1180, 295)	-180 (-915, 441)	0.90 (0.86, 0.94)†
Troponin – ng/mL, median (Q1, Q3)			
Week 24	0.004 (-0.002, 0.021)	0.000 (-0.009, 0.008)	0.004 (0.003, 0.005)
Week 48	0.002 (-0.004, 0.018)	0.000 (-0.009, 0.008)	0.002 (0.001, 0.003)
Safety Outcomes			
Drug discontinuation due to an adverse event –no. (%)	371 (9.0)	382 (9.3)	0.97 (0.85, 1.11)
Serious adverse events –no. (%)	2373 (57.7)	2435 (59.4)	0.97 (0.94, 1.01)
Adverse events of interest – no. (%)			
Ventricular tachyarrhythmias (narrow SMQ)	290 (7.1)	304 (7.4)	0.95 (0.82, 1.11)
Torsade de pointes/ QT prolongation (narrow SMQ)	176 (4.3)	195 (4.8)	0.90 (0.74, 1.10)
Serious adverse ventricular arrhythmia requiring treatment	119 (2.9)	127 (3.1)	0.93 (0.73, 1.20)
Adjudicated major cardiac ischemic events– no. (%)	200 (4.9)	188 (4.6)	1.06 (0.87, 1.29)
Myocardial infarction	122 (3.0)	118 (2.9)	
Hospitalized for unstable angina	25 (0.6)	12 (0.3)	
Coronary revascularization	115 (2.8)	117 (2.9)	
Stroke	76 (1.8)	112 (2.7)	0.68 (0.51, 0.91)

[0209] Continuous variables were summarized as means ± standard deviations (SD) or medians and first and third quartiles (Q1, Q3), as appropriate. Categorical variables were summarized as counts and percentages. The safety population included all patients who underwent randomization and received at least one dose of omecamtiv mecarbil or placebo. The change from baseline on NT-proBNP analysis included all participants who underwent randomization. The difference column is the exponentiated change from baseline on the log scale using a mixed model containing the log baseline value, region, baseline eGFR, scheduled visit, treatment group and interaction of treatment with scheduled visit.

Adverse Events

[0210] Table 4 summarizes the adverse events reported in 1% or more of patients.

Table 4. Treatment-emergent serious adverse events by preferred term report.

Preferred Term	Placebo (N = 4101) n (%)	Omcamtiv Mecarbil (N = 4110) n (%)
Number of subjects reporting treatment-emergent serious adverse events	2435 (59.4)	2373 (57.7)
Cardiac failure	1045 (25.5)	988 (24.0)
Cardiac failure acute	251 (6.1)	212 (5.2)
Pneumonia	179 (4.4)	171 (4.2)
Cardiac failure chronic	170 (4.1)	156 (3.8)
Cardiac failure congestive	154 (3.8)	147 (3.6)
Acute kidney injury	138 (3.4)	129 (3.1)
Ventricular tachycardia	129 (3.1)	106 (2.6)
Atrial fibrillation	113 (2.8)	94 (2.3)
Cardiogenic shock	68 (1.7)	75 (1.8)
Acute myocardial infarction	64 (1.6)	71 (1.7)
Death	49 (1.2)	65 (1.6)
Angina unstable	49 (1.2)	63 (1.5)
Chronic obstructive pulmonary disease	38 (0.9)	63 (1.5)
Sudden death	58 (1.4)	52 (1.3)
Sepsis	60 (1.5)	51 (1.2)
Cardiac arrest	64 (1.6)	50 (1.2)
Hypotension	37 (0.9)	49 (1.2)
Syncope	46 (1.1)	42 (1.0)
Angina pectoris	40 (1.0)	41 (1.0)
Septic shock	32 (0.8)	37 (0.9)
Myocardial infarction	54 (1.3)	36 (0.9)
Ischaemic stroke	38 (0.9)	36 (0.9)
Chronic kidney disease	36 (0.9)	36 (0.9)
Ventricular fibrillation	49 (1.2)	30 (0.7)
Sudden cardiac death	37 (0.9)	27 (0.7)
Renal failure	31 (0.8)	25 (0.6)
Renal impairment	29 (0.7)	25 (0.6)
Respiratory tract infection	24 (0.6)	15 (0.4)

Outcomes by Ejection Fraction

Baseline characteristics for patients were further evaluated by quartiles of EF

[0211] Continuous variables were summarized via means and standard deviations or medians and interquartile ranges, as appropriate. Categorical variables are summarized with counts and percentages. Tests of trend across categories were conducted via linear regression, Cuzick's non-parametric trend test, and Chi-squared tests of trend, respectively. Treatment effects on continuous outcomes were assessed via linear regression models adjusted for the corresponding baseline value of the parameter of interest. Survival analyses

were conducted using Poisson regression models to estimate incidence rates, rate differences, and rate ratios and Cox proportional hazards models to estimate hazard ratios. Treatment effect hazard ratios were adjusted for eGFR and stratified by region and inpatient status as in the primary GALACTIC-HF analysis. To allow for potentially non-linear associations between ejection fraction and time-to-event outcomes, restricted cubic splines were utilized in the Poisson regression models with 3 knots. All analyses were conducted using STATA 16 (College Station, TX). P-values <0.05 were considered statistically significant. Due to the exploratory nature of these analyses, no adjustments were made for multiple comparisons.

[0212] Of the 8,232 participants analyzed, there were 4,456 patients with an EF ≤28%, the median ejection fraction in the trial (Tables 5 and 6; **FIGURES 13A and 13B**). Method of ejection fraction measurement is shown in Table 19.

Table 5: Baseline characteristics of GALACTIC-HF patients Ejection Fraction Quartiles

	EF ≤22% (N=2246)	**EF 23-28% (N=2210)**	**EF 29-32% (N=2026)**	**EF ≥33% (N=1750)**	**p-Value**
Demographics					
Age (years), mean (SD)	62.5 (11.8)	64.1 (11.6)	65.7 (10.9)	66.4 (10.5)	<0.001
Sex, female, n (%)	422 (18.8%)	451 (20.4%)	455 (22.5%)	421 (24.1%)	<0.001
Race, n (%)					<0.001
Asian	171 (7.6%)	224 (10.1%)	179 (8.8%)	136 (7.8%)	
Black or African American	243 (10.8%)	156 (7.1%)	95 (4.7%)	68 (3.9%)	
Other*	200 (8.9%)	162 (7.3%)	118 (5.8%)	83 (4.7%)	
White	1632 (72.7%)	1668 (75.5%)	1634 (80.7%)	1463 (83.6%)	
Geographic Region, n (%)					<0.001
Asia	152 (6.8 %)	214 (9.7 %)	174 (8.6 %)	130 (7.4 %)	
Eastern Europe/ Russia	476 (21.2%)	617 (27.9%)	783 (38.6%)	805 (46.0%)	
Latin and South America	438 (19.5%)	504 (22.8%)	364 (18.0%)	268 (15.3%)	
US and Canada	581 (25.9%)	341 (15.4%)	259 (12.8%)	205 (11.7%)	
Western Europe/ South Africa/ Australasia	599 (26.7%)	534 (24.2%)	446 (22.0%)	342 (19.5%)	
Randomization Setting: In-patient	592 (26.4%)	552 (25.0%)	487 (24.0%)	453 (25.9%)	0.50
Clinical Characteristics					
Medical Conditions, n (%)					
Coronary artery disease	1267 (56)	1320 (60)	1323 (65)	1218 (70)	<0.001
Stroke	214 (10)	194 (9)	250 (12)	161 (9)	0.80
Atrial fibrillation or flutter history	912 (41)	884 (40)	889 (44)	790 (45)	<0.001
Atrial fibrillation or flutter at Screening	547 (24.4%)	561 (25.4%)	609 (30.1%)	528 (30.2%)	<0.001
Hypertension	1431 (64)	1483 (67)	1503 (74)	1367 (78)	<0.001
Type 2 diabetes mellitus	869 (39)	880 (40)	817 (40)	743 (43)	<0.001
Chronic Obstructive Pulmonary Disease	352 (16)	360 (16)	332 (16)	301 (17)	0.21
Heart Failure History					
LVEF (%), median [Q1, Q3]	20 [15, 20]	25 [25, 27]	30 [30, 31]	34 [33, 35]	N/A
Time from last HF event (months), median (Q1, Q3; Outpatients only)	2.9 [1.6, 5.8]	3.1 [1.6, 6.1]	3.3 [1.6, 6.5]	3.4 [1.5, 6.8]	0.039
Time from last HF Hospitalization (months), median (Q1, Q3; Outpatients only)	3.0 [1.6, 5.9]	3.2 [1.6, 6.2]	3.4 [1.7, 6.6]	3.6 [1.6, 6.9]	0.043
MAGGIC Score, median (Q1, Q3)	25 (21, 30)	24 (20, 28)	22 (17, 26)	21 (17, 25)	<0.001
NYHA classification, n (%)					0.016
Class II	1160 (52)	1164 (53)	1085 (54)	959 (55)	
Class III	1007 (45)	968 (44)	889 (44)	752 (43)	
Class IV	79 (4)	78 (4)	52 (3)	39 (2)	

	EF ≤22% (N=2246)	EF 23-28% (N=2210)	EF 29-32% (N=2026)	EF ≥33% (N=1750)	p-Value
Ischemic heart failure etiology, n (%)	1033 (46)	1153 (52)	1141 (56)	1088 (62)	<0.001
KCCQ Total Symptom Score, median [Q1, Q3]	69 [48, 88]	70 [49, 88]	71 [50, 88]	69 [49, 85]	0.77
Outpatient	75 [56, 92]	75 [54, 92]	75 [56, 92]	73 [54, 90]	0.05
Inpatient	51 [29, 69]	53 [33, 73]	55 [35, 72]	54 [31, 74]	0.022
Vitals and Laboratory Parameters					
Body mass index (kg/m^2), mean (SD)	27.9 (6.3)	28.2 (6.2)	28.9 (6.0)	29.1 (6.1)	<0.001
SBP (mmHg), mean (SD)	112 (15)	115 (15)	119 (15)	121 (14)	<0.001
Heart rate (beats/min), mean (SD)	74 (12)	72 (12)	72 (12)	72 (12)	<0.001
NT-proBNP (pg/mL), median [Q1-Q3]	2524 [1250,5296]	2035 [1057,4157]	1866 [924,3655]	1615 [755,3245]	<0.001
hsTnI (ng/L), median [Q3]	31 [58]	29 [55]	26 [48]	23 [43]	<0.001
eGFR (mL/min/1.73m^2), median [Q1,Q3]	59 [44, 74]	59 [44, 75]	59 [43, 74]	58 [45, 74]	0.72
Medications and Cardiac Devices, n (%)					
ACEi, ARB or ARNi	1900 (85)	1933 (88)	1787 (88)	1539 (88)	<0.001
ARNi	534 (24)	468 (21)	351 (17)	248 (14)	<0.001
BB	2086 (93)	2101 (95)	1922 (95)	1655 (95)	0.022
MRA	1715 (76)	1792 (81)	1585 (78)	1305 (75)	0.10
(ACEi, ARB, or ARNi) + MRA + BB	1413 (63)	1511 (68)	1387 (68)	1114 (64)	0.37
Digitalis Glycosides	450 (20)	380 (17)	304 (15)	251 (14)	<0.001
SGLT2 Inhibitors	64 (3)	67 (3)	44 (2)	43 (3)	0.19
Ivabradine	172 (8)	165 (8)	106 (5)	90 (5)	<0.001
Cardiac Resynchronization Therapy	454 (20)	321 (15)	231 (11)	152 (9)	<0.001
Implantable Cardioverter Defibrillator	972 (43)	745 (34)	534 (26)	363 (21)	<0.001

*Includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or Multiple self-identified races ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; CRT, cardiac resynchronization therapy; ED, emergency department; eGFR, estimated glomerular filtration rate; hsTnI, high-sensitivity troponin I; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic HF; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT2, sodium-glucose co-transporter 2.

Table 6: Baseline Characteristics by Ejection Fraction Quartile:

	EF ≤22% (N=2246)		EF 23-28% (N=2210)		EF 29-32% (N=2026)		EF ≥33% (N=1750)	
	OM	Placebo	OM	Placebo	OM	Placebo	OM	Placebo
	n=1127	n=1119	n=1086	n=1124	n=1015	n=1011	n=892	n=858
Demographics								
Age in years	62.1 (± 11.9)	62.9 (± 11.6)	64.2 (± 11.5)	64.0 (± 11.8)	65.8 (± 11.0)	65.6 (± 10.8)	66.6 (± 10.1)	66.1 (± 11.0)
Sex, Female	215 (19.1%)	207 (18.5%)	205 (18.9%)	246 (21.9%)	228 (22.5%)	227 (22.5%)	227 (25.4%)	194 (22.6%)
Race								
Asian	91 (8.1%)	80 (7.1%)	114 (10.5%)	110 (9.8 %)	86 (8.5%)	93 (9.2%)	64 (7.2%)	72 (8.4%)
Black	118 (10.5%)	125 (11.2%)	77 (7.1%)	79 (7.0%)	49 (4.8%)	46 (4.5%)	41 (4.6%)	27 (3.1%)
Other	102 (9.1%)	98 (8.8%)	79 (7.3%)	83 (7.4%)	65 (6.4%)	53 (5.2%)	38 (4.3%)	45 (5.2%)
White	816 (72.4%)	816 (72.9%)	816 (75.1%)	852 (75.8%)	815 (80.3%)	819 (81.0%)	749 (84.0%)	714 (83.2%)
Geographic Region								

	EF ≤22% (N=2246)		EF 23-28% (N=2210)		EF 29-32% (N=2026)		EF ≥33% (N=1750)	
	OM	Placebo	OM	Placebo	OM	Placebo	OM	Placebo
	n=1127	n=1119	n=1086	n=1124	n=1015	n=1011	n=892	n=858
Asia	82 (7.3%)	70 (6.3%)	109 (10.0%)	105 (9.3%)	84 (8.3%)	90 (8.9%)	60 (6.7%)	70 (8.2%)
Eastern Europe/Russia	232 (20.6%)	244 (21.8%)	304 (28.0%)	313 (27.8%)	397 (39.1%)	386 (38.2%)	411 (46.1%)	394 (45.9%)
Latin America	228 (20.2%)	210 (18.8%)	235 (21.6%)	269 (23.9%)	196 (19.3%)	168 (16.6%)	128 (14.3%)	140 (16.3%)
US And Canada	287 (25.5%)	294 (26.3%)	171 (15.7%)	170 (15.1%)	121 (11.9%)	138 (13.6%)	114 (12.8%)	91 (10.6%)
Western Europe/South Africa/Australasia	298 (26.4%)	301 (26.9%)	267 (24.6%)	267 (23.8%)	217 (21.4%)	229 (22.7%)	179 (20.1%)	163 (19.0%)
Randomization Setting: In-patient	289 (25.6%)	303 (27.1%)	266 (24.5%)	286 (25.4%)	241 (23.7%)	246 (24.3%)	248 (27.8%)	205 (23.9%)
Clinical Characteristics								
Atrial Fibrillation or Flutter at Screening	276 (24.5%)	271 (24.2%)	274 (25.2%)	287 (25.5%)	310 (30.5%)	299 (29.6%)	286 (32.1%)	242 (28.2%)
Hypertension Hx	712 (63.2%)	719 (64.3%)	753 (69.3%)	730 (64.9%)	737 (72.6%)	766 (75.8%)	708 (79.4%)	659 (76.8%)
Type 2 diabetes mellitus	420 (37.3%)	449 (40.1%)	430 (39.6%)	450 (40.0%)	411 (40.5%)	406 (40.2%)	391 (43.8%)	352 (41.0%)
History of stroke	103 (9.1%)	111 (9.9%)	96 (8.8%)	98 (8.7%)	99 (9.8%)	86 (8.5%)	79 (8.9%)	82 (9.6%)
Ischemic heart failure etiology	497 (44.1%)	536 (47.9%)	566 (52.1%)	587 (52.2%)	570 (56.2%)	571 (56.5%)	560 (62.8%)	528 (61.5%)
History of Myocardial Infarction	377 (33.5%)	452 (40.4%)	443 (40.8%)	461 (41.0%)	441 (43.4%)	443 (43.8%)	432 (48.4%)	386 (45.0%)
History of Coronary Artery Bypass Surgery	152 (13.5%)	174 (15.5%)	166 (15.3%)	187 (16.6%)	164 (16.2%)	171 (16.9%)	157 (17.6%)	146 (17.0%)
History of Percutaneous Coronary Revascularization	272 (24.1%)	320 (28.6%)	333 (30.7%)	330 (29.4%)	328 (32.3%)	295 (29.2%)	299 (33.5%)	261 (30.4%)
LVEF - %	18.3 (± 3.1)	18.1 (± 3.2)	25.5 (± 1.5)	25.5 (± 1.5)	30.4 (± 0.9)	30.4 (± 0.9)	34.2 (± 0.9)	34.2 (± 0.8)
NYHA Classification								
Class II	587 (52.1%)	573 (51.2%)	570 (52.5%)	594 (52.8%)	546 (53.8%)	539 (53.3%)	492 (55.2%)	467 (54.4%)
Class III	503 (44.6%)	504 (45.0%)	474 (43.6%)	494 (44.0%)	445 (43.8%)	444 (43.9%)	379 (42.5%)	373 (43.5%)
Class IV	37 (3.3%)	42 (3.8%)	42 (3.9%)	36 (3.2%)	24 (2.4%)	28 (2.8%)	21 (2.4%)	18 (2.1%)
KCCQ Total Symptom Score	68.8 [47.9, 87.5]	67.7 [47.9, 87.5]	68.8 [49.0, 87.5]	70.8 [49.0, 89.6]	70.8 [50.0, 88.5]	70.8 [50.0, 87.5]	69.8 [47.9, 85.4]	66.7 [49.0, 85.4]
Outpatient	75.0 [56.2, 91.7]	75.0 [56.2, 91.7]	74.0 [54.2, 90.6]	77.1 [56.2, 91.7]	75.0 [54.7, 91.7]	75.0 [57.3, 91.7]	73.4 [54.2, 87.5]	72.9 [54.2, 89.6]
Inpatient	50.0 [32.3, 68.8]	52.1 [27.1, 67.7]	54.7 [34.4, 75.0]	53.1 [33.3, 70.8]	58.3 [38.5, 74.0]	52.1 [33.3, 68.8]	55.2 [33.3, 77.1]	52.1 [29.2, 69.3]
SBP — mmHg	111.4 (± 14.9)	112.5 (± 14.9)	115.5 (± 15.2)	114.9 (± 15.2)	118.4 (± 15.4)	119.2 (± 15.1)	120.9 (± 14.4)	121.3 (± 14.3)
Heart rate — (bpm)	73.9 (± 12.3)	73.2 (± 12.3)	71.7 (± 12.1)	72.8 (± 12.0)	72.3 (± 12.1)	71.5 (± 11.8)	71.6 (± 12.3)	71.6 (± 12.0)

	EF ≤22% (N=2246)		EF 23-28% (N=2210)		EF 29-32% (N=2026)		EF ≥33% (N=1750)	
	OM	Placebo	OM	Placebo	OM	Placebo	OM	Placebo
	n=1127	n=1119	n=1086	n=1124	n=1015	n=1011	n=892	n=858
NT-proBNP — pg/mL	2512 [1318, 5406]	2527 [1206, 5240]	2072 [1108, 4250]	1998 [1025, 4079]	1800 [901, 3655]	1932 [940, 3653]	1569 [740, 3066]	1650 [782, 3367]
Cardiac Troponin I (ng/L)	32 [14, 57]	31 [16, 59]	29 [14, 55]	28 [13, 55]	26 [12, 49]	26 [11, 47]	23 [10, 41]	23 [11, 45]
eGFR — mL/min/1.73m^2	58.9 [44.5, 74.8]	58.6 [43.8, 72.5]	58.3 [43.4, 73.5]	59.5 [44.3, 75.5]	60.8 [44.3, 75.6]	57.3 [42.6, 72.4]	57.3 [45.1, 72.8]	59.4 [45.0, 74.5]
Heart Failure Therapies								
ACEi, ARB or ARNi	942 (83.6%)	958 (85.6%)	949 (87.4%)	984 (87.5%)	901 (88.8%)	886 (87.6%)	791 (88.7%)	748 (87.2%)
ARNi	265 (23.5%)	269 (24.0%)	243 (22.4%)	225 (20.0%)	183 (18.0%)	168 (16.6%)	128 (14.3%)	120 (14.0%)
BB	1047 (92.9%)	1039 (92.9%)	1026 (94.5%)	1074 (95.6%)	954 (94.0%)	968 (95.7%)	853 (95.6%)	802 (93.5%)
MRA	868 (77.0%)	847 (75.7%)	876 (80.7%)	916 (81.5%)	797 (78.5%)	788 (77.9%)	658 (73.8%)	647 (75.4%)
SGLT2 Inhibitors	31 (2.8%)	33 (2.9%)	31 (2.9%)	36 (3.2%)	23 (2.3%)	21 (2.1%)	19 (2.1%)	24 (2.8%)
Ivabradine	90 (8.0%)	82 (7.3%)	77 (7.1%)	88 (7.8%)	49 (4.8%)	57 (5.6%)	39 (4.4%)	51 (5.9%)
Digitalis glycosides	226 (20.1%)	224 (20.0%)	191 (17.6%)	189 (16.8%)	142 (14.0%)	162 (16.0%)	128 (14.3%)	123 (14.3%)
Cardiac Resynchronization Therapy	233 (20.7%)	221 (19.7%)	164 (15.1%)	157 (14.0%)	108 (10.6%)	123 (12.2%)	87 (9.8 %)	65 (7.6 %)
Implantable Cardioverter Defibrillator	485 (43.0%)	487 (43.5%)	389 (35.8%)	356 (31.7%)	269 (26.5%)	265 (26.2%)	183 (20.5%)	180 (21.0%)

Table 19: Method of ejection fraction measurement:

Method of Ejection Fraction Measurement	**Omecamtiv mecarbil N (%)**	**Placebo N (%)**
Echocardiogram	4006 (97.2%)	3997 (97.2%)
Cardiac MRI	35 (0.8%)	39 (0.9%)
SPECT Nuclear Imaging	33 (0.8%)	25 (0.6%)
Left ventriculography (Cineangiography)	17 (0.4%)	17 (0.4%)
Radionuclide ventriculography (MUGA)	17 (0.4%)	16 (0.4%)
Cardiac CT	10 (0.2%)	14 (0.3%)
Cardiac PET	1 (0.0%)	3 (0.1%)

Missing	1 (0.0%)	1 (0.0%)

[0213] Due to digit preference for ejection fraction assessment, over 70% of the patients had an EF ≤30%. When assessed by quartiles, patients with lower ejection fractions were younger, more likely to be male and non-white, and less likely to be enrolled in Eastern Europe or Russia and more likely to be enrolled in the United States, Canada, Western Europe, South Africa, or Australasia. Patients with lower ejection fraction were more likely to have a non-ischemic etiology of heart failure, NYHA III/IV functional class, lower body mass index, lower systolic blood pressure, higher heart rate, higher NT-proBNP, higher cardiac troponin I, and were less likely to have coronary artery disease, hypertension, type 2 diabetes mellitus, or atrial fibrillation/ flutter. Lower ejection fraction was associated with greater symptom burden in patients enrolled as inpatients (lower KCCQ-TSS), but there was no meaningful difference in the outpatients. There was no difference in the proportion of patients receiving triple therapy [(ACEi, ARB, or ARNi) + MRA + BB] among the EF quartiles. Patients with lower ejection fractions had higher use of ARNi, ivabradine, digitalis glycosides, cardiac resynchronization therapy and implantable cardioverter defibrillators compared to patients with higher ejection fractions.

Relationship between Ejection Fraction and Clinical Outcomes

[0214] Within the group of patients with HFrEF enrolled in GALACTIC-HF, the incidence of clinical outcomes increased with decreasing ejection fraction (Table 7).

Table 7. Clinical Outcomes

Outcome by EF Quartiles	**OM**		**Placebo**			
	n/N (%)	Rate[1]	n/N (%)	Rate[1]	HR (95% CI); p-value	ARR[1]
Primary Outcome					Interaction p = 0.013	
EF ≥33%	298/892 (33%)	20.5	280/858 (33%)	20.0	0.99 (0.84, 1.16)	-0.4
EF 29-32%	375/1015 (37%)	23.8	356/1011 (35%)	22.4	1.11 (0.96, 1.28)	-1.4
EF 23-28%	393/1086 (36%)	24.0	449/1124 (40%)	27.2	0.85 (0.74, 0.97)	3.3
EF ≤22%	457/1127 (41%)	28.3	522/1119 (47%)	35.6	0.83 (0.73, 0.95)	7.4
First HF Event					Interaction p = 0.004	
EF ≥33%	236/892 (26%)	16.2	208/858 (24%)	14.9	1.04 (0.86, 1.25)	-1.3
EF 29-32%	286/1015 (28%)	18.2	269/1011 (27%)	16.9	1.13 (0.96, 1.33)	-1.3
EF 23-28%	304/1086 (28%)	18.5	345/1124 (31%)	20.9	0.84 (0.72, 0.98)	2.4
EF ≤22%	351/1127 (31%)	21.7	414/1119 (37%)	28.3	0.81 (0.70, 0.93)	6.6
1st HF Hospitalization					Interaction p = 0.004	
EF ≥33%	228/892 (26%)	15.5	201/858 (23%)	14.3	1.03 (0.85, 1.24)	-1.2
EF 29-32%	279/1015 (27%)	17.6	251/1011 (25%)	15.5	1.19 (1.01, 1.42)	-2.1

EF 23-28%	295/1086 (27%)	17.8	327/1124 (29%)	19.6	0.86 (0.74, 1.01)	1.8
EF ≤22%	340/1127 (30%)	20.9	400/1119 (36%)	26.9	0.82 (0.71, 0.94)	6.1
CV Death					Interaction p = 0.14	
EF ≥33%	153/892 (17%)	9.0	136/858 (16%)	8.4	1.06 (0.84, 1.33)	-0.6
EF 29-32%	196/1015 (19%)	10.5	162/1011 (16%)	8.5	1.26 (1.02, 1.55)	-2.0
EF 23-28%	207/1086 (19%)	10.8	235/1124 (21%)	11.8	0.88 (0.73, 1.07)	1.0
EF ≤22%	252/1127 (22%)	13.0	265/1119 (24%)	14.1	0.96 (0.80, 1.14)	1.1
All-cause Death					Interaction p = 0.38	
EF ≥33%	200/892 (22%)	11.8	189/858 (22%)	11.7	0.98 (0.80, 1.20)	-0.1
EF 29-32%	260/1015 (26%)	13.9	226/1011 (22%)	11.9	1.19 (0.99, 1.42)	-2.0
EF 23-28%	278/1086 (26%)	14.4	315/1124 (28%)	15.8	0.89 (0.76, 1.05)	1.4
EF ≤22%	329/1127 (29%)	17.0	335/1119 (30%)	17.8	0.98 (0.84, 1.14)	0.8

[1]per 100 patient years; ARR = absolute risk reduction

[0215] As noted by the rates in the placebo group, the incidence of the primary outcome of first heart failure event or cardiovascular death in patients in the lowest EF quartile (EF ≤22%; 35.6 per 100 patient-years) was almost 80% greater than in the highest EF quartile (EF ≥33%; 20 per 100 patient-years). The incidence of first heart failure event was 90% greater (28.3 versus 14.9 events per 100 patient-years) and of cardiovascular death was 68% greater (14.1 versus 8.4 deaths per 100 patient-years) in the lowest EF compared to the highest EF quartile. Participants in the placebo group had significant improvements in the KCCQ-TSS at Week 24 compared to baseline, with greater improvements in those enrolled as inpatients, but there was no modification of this effect by EF quartile (Table 8).

Table 8. Change from baseline in KCCQ Total Symptom Score by Ejection Fraction Quartiles and Treatment Group

KCCQ Total Symptom Score -- Least squares mean (95% CI)	**EF ≤22%**	**EF 23-28%**	**EF 29-32%**	**EF ≥33%**
Outpatient				
Placebo	6.37 (5.02, 7.73)	6.30 (5.00, 7.59)	5.95 (4.67, 7.22)	6.60 (5.21, 8.00)
Omecamtiv mecarbil	7.08 (5.75, 8.40)	5.61 (4.30, 6.92)	5.30 (4.02, 6.58)	5.18 (3.78, 6.59)
Inpatient				
Placebo	23.59 (20.77, 26.40)	21.35 (18.60, 24.10)	18.14 (15.29, 21.00)	21.31 (18.49, 24.13)
Omecamtiv mecarbil	27.70 (24.86, 30.54)	21.51 (18.71, 24.30)	22.34 (19.42, 25.25)	22.09 (19.61, 24.57)

Within each randomization setting subgroup least squares mean is from the mixed model which includes baseline total symptom score value, region, baseline eGFR, scheduled visit, treatment group and interaction of treatment with scheduled visit as covariates.

Influence of Ejection Fraction on the Treatment Effect of Omecamtiv Mecarbil

[0216] Omecamtiv mecarbil significantly decreased the primary endpoint of the time-to-first heart failure event or cardiovascular death in the overall trial population (HR 0.92; p=0.025). The statistical analysis plan pre-specified the assessment of the primary endpoint in the ejection fraction subgroups above and below the median value (≤28%) and there was a significant modification of the treatment effect of omecamtiv mecarbil by ejection fraction (interaction effect, p = 0.004). In patients with EF ≤28%, there was a 16% reduction in the time-to-first heart failure event or cardiovascular death (HR 0.84, 95%CI 0.77-0.92; p = 0.0003) compared to no difference in patients with EF >28% (HF 1.04, 95%CI 0.94-1.16; p = 0.45). Analysis by quartiles of ejection fraction of the modifying effect on the primary composite endpoint (interaction p = 0.013; Table 7, **FIGURE 22**) by treatment with omecamtiv mecarbil demonstrated a 15 and 17% relative risk reduction in the lower two quartiles of ejection fraction, respectively. Analysis of ejection fraction as a continuous variable (interaction effect, p = 0.004) demonstrated a progressively larger treatment effect of omecamtiv mecarbil with decreasing ejection fraction (**FIGURE 9**; Table 7). The difference in the incidence of the primary composite endpoint increased disproportionately between the placebo and omecamtiv mecarbil treatment groups with lower ejection fractions (**FIGURE 10A**, such that absolute risk reduction by omecamtiv mecarbil progressively increased with decreasing ejection fraction (**FIGURE 10B**). In the lowest ejection fraction quartile, omecamtiv mecarbil resulted in an absolute reduction of 7.4 events per 100 patient-years, with a number-needed-to-treat of 11.8 patients over 3-years necessary to prevent an event (Table 7).

[0217] The beneficial effect of treatment with omecamtiv mecarbil on the primary outcome was driven predominantly by the significant reduction in heart failure events and ejection fraction was a significant modifier of this treatment effect (interaction p = 0.004 by ejection fraction quartile, interaction p = 0.001 by ejection fraction as continuous variable; Table 7). Ejection fraction had a similar modifying effect on the progressive reduction of heart failure hospitalizations by omecamtiv mecarbil (interaction p = 0.004 by ejection fraction quartile, interaction p = 0.001 by ejection fraction as continuous variable; **FIGURE 11A**; Table 7). Consistent with the primary composite endpoint, the incidence rate of heart failure hospitalizations increases with decreasing ejection fraction in both the placebo and omecamtiv mecarbil treated patients (**FIGURE 11B**), but was significantly impacted by treatment with omecamtiv mecarbil, and showed a progressively greater reduction in the absolute difference with decreasing ejection fraction. Ejection fraction significantly modified the treatment of effect of omecamtiv mecarbil on total heart failure events and hospitalizations as well (interaction p = 0.006 and 0.009, respectively; Table 20). Omecamtiv mecarbil had no overall effect on cardiovascular death, neither in the overall population nor as a function of baseline ejection fraction (interaction p = 0.14 by ejection fraction quartile; **FIGURE 12A**, Table 7). As expected, the incidence of cardiovascular death increased comparably in both the placebo and omecamtiv mecarbil arms with decreasing ejection fraction (**FIGURE 12B**, Table 7). Similarly, there was no effect of omecamtiv mecarbil on all-cause mortality (Table 7). The proportional hazards assumption was evaluated for all hazard ratios presented in Table 2 via a test of Schoenfeld residuals. No significant violations were detected (all p > 0.2).

Table 20: Total heart failure events/hospitalizations by ejection fraction quartiles:

Outcome by EF Quartiles	Omecamtiv Mecarbil		Placebo			
	Events	Rate (per 100 pt-yrs)	Events	Rate (per 100 pt-yrs)	Ratio (95% CI)	ARR (per 100 pt-yrs)
Total HF Events					Interaction p = 0.006	
EF ≥33%	483	28.5	386	23.8	1.13 (0.90, 1.43)	-4.7
EF 29-32%	506	27.1	526	27.7	1.14 (0.93, 1.40)	0.6
EF 23-28%	577	30.0	678	34.0	0.83 (0.68, 1.01)	4.0
EF ≤22%	719	37.1	909	48.4	0.83 (0.70, 1.01)	11.3
Total HF Hospitalizations					Interaction p = 0.009	
EF ≥33%	449	26.5	372	22.9	1.12 (0.89, 1.43)	-3.6
EF 29-32%	472	25.3	478	25.2	1.18 (0.96, 1.46)	-0.1
EF 23-28%	541	28.1	624	31.3	0.84 (0.69, 1.02)	3.2
EF ≤22%	679	35.1	846	45.0	0.84 (0.70, 1.01)	9.9

Other Outcomes and Safety of Omecamtiv Mecarbil by Ejection Fraction

[0218] Despite the reduction in heart failure events with omecamtiv mecarbil, there was no consistent beneficial effect on symptoms as a function of EF as assessed by the KCCQ-TSS in either the subjects enrolled from the inpatient or outpatient settings. However, there was a greater reduction in NT-proBNP by omecamtiv mecarbil in patients with lower ejection fraction such that the lowest EF quartile had a 22% reduction (p<0.001) while the highest EF quartile showed only a 3% change (p=0.54; interaction p <0.001) (Table 9).

Table 9. Omecamtiv Mecarbil Treatment Effects from Baseline to Week 24 of Selected Vital Signs and Laboratory Values

Variable Treatment Difference (95% CI) p-value	**EF ≤22% (N=2246)**	**EF 23-28% (N=2210)**	**EF 29-32% (N=2026)**	**EF ≥33% (N=1750)**	**p-Value**
KCCQ Total Symptom Score Least squares mean (95%CI)	+1.6 (-0.2, +3.3) 0.08	-0.6 (-2.3, +1.2) 0.52	+0.3 (-1.4, +2.0) 0.74	-1.0 (-2.8, +0.9) 0.30	0.10
Inpatient -- Least squares mean (95%CI)	+4.9 (+0.8, +8.9) 0.018	+0.2 (-3.7, +4.1) 0.91	+4.8 (+0.6, +8.9) 0.024	-0.0 (-3.9, +3.9) 0.99	0.33
Outpatient -- Least squares mean (95%CI)	+0.7 (-1.2, +2.6) 0.47	-0.6 (-2.5, +1.2) 0.52	-0.8 (-2.6, +1.1) 0.42	-1.5 (-3.5, +0.5) 0.13	0.12
Systolic BP (mmHg)	0.9 (-0.4, 2.2) 0.19	-0.6 (-1.9, 0.8) 0.40	-0.6 (-1.9, 0.7) 0.34	-1.2 (-2.7, 0.2) 0.09	0.038
Heart rate (bpm)	-1.6 (-2.5, -0.6) 0.001	-1.7 (-2.7, -0.8) 0.001	-1.9 (-2.9, -0.9) <0.001	-1.1 (-2.1, -0.1) 0.032	0.62
Potassium (mmol/L)	0.01 (-0.04, 0.05) 0.76	-0.01 (-0.06, 0.03) 0.76	-0.01 (-0.06, 0.03) 0.59	0.02 (-0.03, 0.06) 0.53	0.87
Creatinine (mg/dL)	-0.01 (-0.04, 0.02) 0.53	0.01 (-0.02, 0.04) 0.53	0.01 (-0.02, 0.04) 0.58	0.02 (-0.01, 0.05) 0.24	0.22
NT-proBNP (Ratio)	0.78 (0.71, 0.85) <0.001	0.90 (0.83, 0.98) <0.001	0.95 (0.87, 1.04) 0.28	0.97 (0.89, 1.06) 0.54	<0.001

Variable Treatment Difference (95% CI) p-value	EF ≤22% (N=2246)	EF 23-28% (N=2210)	EF 29-32% (N=2026)	EF ≥33% (N=1750)	p-Value
Troponin I (Ratio)	1.19 (1.11, 1.27) <0.001	1.29 (1.21, 1.38) <0.001	1.27 (1.18, 1.36) <0.001	1.27 (1.18, 1.37) <0.001	0.22
Troponin I (ng/L)	5 (4, 6) <0.001	4 (3, 5) <0.001	4 (3, 5) <0.001	3 (2, 4) <0.001	0.055

*Values represent treatment effects as evaluated by between-group differences of change from baseline to Week 24. Least squares mean is from the mixed model which includes baseline total symptom score value, region, baseline eGFR, scheduled visit, treatment group and interaction of treatment with scheduled visit as covariates. Troponin I assay had limit of detection of 6 ng/L with an upper reference limit of 40 ng/L.

[0219] Omecamtiv mecarbil treatment resulted in a small reduction in heart rate (treatment difference of 1.1 to 1.9 bpm across the EF quartiles) and increase in troponin I (median 3-5 ng/L across the EF quartiles; limit of detection, 6 ng/L; upper reference limit, 40 ng/L) which did not differ by EF quartile. There was no significant effect on systolic blood pressure, serum potassium or creatine across the EF quartiles compared to placebo. There were also no significant differences noted in the incidence of adverse events between the omecamtiv mecarbil and placebo treated groups, except for an apparent reduction in the incidence of adjudicated stroke for patients treated with omecamtiv mecarbil (Table 10 and Table 23A).

[0220] Omecamtiv mecarbil provided similar benefit in patients with and without a history of stroke. The time to first stroke event was significantly reduced in patients allocated to omecamtiv mecarbil. A history of stroke was present in 754 (9.2%) participants, who were older and more likely to be non-White, have atrial fibrillation/ flutter, hypertension, diabetes mellitus, or ischemic heart disease, worse NYHA class and eGFR, and higher baseline NT-proBNP or troponin. Patients with a history of stroke had similar beneficial effect of omecamtiv mecarbil on the primary endpoint (HR 0.86; 95%CI 0.70,1.07; p=0.18) as in patients with no stroke (HR 0.93; 95%CI 0.87,1.00; p=0.06). Multivariate predictors of the incident 194 first stroke events included non-White race, history of stroke or percutaneous coronary intervention (PCI), and elevated baseline troponin or systolic blood pressure (Table 24). Patients randomized to omecamtiv mecarbil had a significant 35% reduction in the risk of first fatal or non-fatal stroke (**Figure 24**) and a 42% reduction in fatal stroke (HR: 0.56; 95%CI 0.31, 0.99; p = 0.048). The effect of omecamtiv mecarbil on risk of non-fatal and fatal stroke by history of stroke is shown in **Figure 25** (with history of stroke--HR: 0.23; 95%CI 0.09, 0.56; p=0.001, and no history of stroke-- HR: 0.78; 95%CI 0.57, 1.06; p=0.11). The effect of omecamtiv mecarbil on risk of non-fatal and fatal stroke by history of atrial fibrillation is shown in **Figure 26** (with history of atrial fibrillation--HR: 0.49; 95%CI 0.32, 0.76; p=0.001, and no history of atrial fibrillation--HR: 0.81; 95%CI 0.55, 1.19; p=0.29). The effect of omecamtiv mecarbil on new onset atrial fibrillation/flutter is shown in **Figure 27** (no AF/F at screening--HR: 0.70; 95%CI 0.50, 0.99; p=0.044, and no history of AF/F-- HR: 0.60; 95%CI 0.37, 1.00; p=0.048). Omecamtiv mecarbil significantly reduced non-fatal and fatal strokes in patients with heart failure with reduced ejection fraction in the context of significantly reducing new onset atrial fibrillation. Characteristics by baseline history of stroke are shown in Table 25.

Table 10. Other Outcomes and Adverse Events of Special Interest

Safety outcomes Omecamtiv Mecarbil: n (%) Placebo: n (%) Relative Risk (95% CI) p-value	**EF ≤22% (N=2246)**	**EF 23-28% (N=2210)**	**EF 29-32% (N=2026)**	**EF ≥33% (N=1750)**
Any treatment Emergent Serious Adverse Events	OM: 683 (60.7%) P: 719 (64.6%) RR: 0.94 (0.88, 1.00) p = 0.05	OM: 616 (56.9%) P: 666 (59.3%) 0.96 (0.89, 1.03) 0.26	OM: 579(57.3%) P: 585 (58.0%) 0.99 (0.92, 1.07) 0.77	OM: 495 (55.5%) P: 465 (54.3%) 1.02 (0.94, 1.11) 0.62
Adverse Event: Ventricular Tachyarrhythmia	OM: 97 (9.8 %) P: 99 (9.8 %) RR: 1.00 (0.76, 1.30) p = 1.00	OM: 80 (8.3 %) P: 85 (8.5 %) 0.98 (0.73, 1.31) 0.98	OM: 62 (6.9 %) P: 65 (7.2 %) 0.96 (0.69, 1.34) 0.81	OM: 51 (6.4 %) P: 55 (7.3 %) 0.88 (0.61, 1.27) 0.48
Serious Adverse Event: Ventricular Arrhythmia Requiring Treatment	OM: 41 (3.6 %) P: 46 (4.1 %) RR: 0.88 (0.58, 1.33) p = 0.55	OM: 35 (3.2 %) P: 35 (3.1 %) 1.04 (0.65, 1.65) 0.87	OM: 21 (2.1 %) P: 27 (2.7 %) 0.78 (0.44, 1.37) 0.38	OM: 22 (2.5 %) P: 19 (2.2 %) 1.11 (0.61, 2.04) 0.73
Adjudicated First Major Cardiac Ischemic Events	OM: 54 (4.8 %) P: 45 (4.0 %) RR: 1.19 (0.81, 1.75) p = 0.39	OM: 47 (4.3 %) P: 49 (4.4 %) 1.00 (0.67, 1.47) 0.98	OM: 41 (4.1 %) P: 38 (3.8 %) 1.08 (0.70, 1.66) 0.73	OM: 58 (6.5 %) P: 56 (6.5 %) 0.99 (0.70, 1.42) 0.99
Positively Adjudicated Myocardial Infarction	OM: 37 (3.3 %) P: 30 (2.7 %) RR: 1.22 (0.76, 1.96) p = 0.41	OM: 29 (2.7 %) P: 34 (3.0 %) 0.89 (0.54, 1.44) 0.62	OM: 22 (2.2 %) P: 22 (2.2 %) 1.00 (0.56, 1.79) 1.00	OM: 34 (3.8 %) P: 32 (3.7 %) 1.02 (0.64, 1.64) 0.94
Adjudicated First Stroke	OM: 17 (1.5 %) P: 26 (2.3 %) RR: 0.65 (0.35, 1.18) p = 0.15	OM: 19 (1.8 %) P: 37 (3.3 %) 0.53 (0.31, 0.92) 0.022	OM: 24 (2.4 %) P: 29 (2.9 %) 0.83 (0.48, 1.41) 0.48	OM: 16 (1.8 %) P: 20 (2.3 %) 0.77 (0.40, 1.47) 0.42

Table 23A. Adjudicated type of first stroke event

	Omecamtiv Mecarbil (n = 4110)	**Placebo (n = 4101)**

Ischemic (Non-hemorrhagic)	65 (1.6 %)	84 (2.0 %)
Ischemic with hemorrhagic transformation	5 (0.1 %)	15 (0.4 %)
Hemorrhagic	3 (0.1 %)	9 (0.2 %)
Undetermined	3 (0.1 %)	4 (0.1 %)

Table 24. Multivariate predictors of non-fatal and fatal stroke.

Covariates	**p-value**	**Hazard Ratio (95% CI)**
(n=8120)	**(n=193 events)**	
Race (ref. = White)	<0.001	
Asian		2.05 (1.33, 3.16)
Black		1.96 (1.20, 3.19)
Other		1.92 (1.17, 3.16)
History of stroke	0.002	1.85 (1.26, 2.71)
PCI	0.003	1.58 (1.17, 2.12)
Troponin (per doubling)	0.006	1.15 (1.04, 1.26)
AFF	0.008	1.51 (1.12, 2.05)
SBP (per 10 mmHg)	0.015	1.12 (1.02, 1.23)

CI= 95% confidence interval. PCI = percutaneous coronary interventions. AFF = atrial fibrillation or atrial flutter. SBP = systolic blood pressure.

Table 25. Characteristics by baseline history of stroke

	No h/o Stroke	**H/o Stroke**	**p-value**
	(n=7478)	**(n=754)**	
Demographics			
Age - yr	64.3 ± 11.4	67.0 ± 10.1	p<0.001
Sex, Female	1595 (21.3%)	154 (20.4%)	p=0.56
Race: Asian/ Black/ Other/ White	8/ 7/ 7/ 78 %	12/ 8/ 4/ 77%	p<0.001
Region:			p<0.001
Asia	587 (7.8 %)	83 (11.0%)	
E Europe/Russia	2431 (32.5%)	250 (33.2%)	
Latin America	1474 (19.7%)	100 (13.3%)	
US And Canada	1234 (16.5%)	152 (20.2%)	
W Europe/South Africa/Australasia	1752 (23.4%)	169 (22.4%)	

In-patient	1886 (25.2%)	198 (26.3%)	p=0.53
Clinical Characteristics			
A Fib/ Flutter (Screening)	1988 (26.6%)	257 (34.1%)	p<0.001
Hypertension Hx	5185 (69.3%)	599 (79.4%)	p<0.001
Type 2 diabetes mellitus	2951 (39.5%)	358 (47.5%)	p<0.001
History of stroke	0 (0.0 %)	754 (100.0%)	p<0.001
Ischemic HF etiology	3943 (52.7%)	472 (62.6%)	p<0.001
H/o MI	3051 (40.8%)	384 (50.9%)	p<0.001
H/o CABG	1166 (15.6%)	151 (20.0%)	p=0.002
H/o PCI	2183 (29.2%)	255 (33.8%)	p=0.008
LVEF - %	26.6 ± 6.3	26.5 ± 6.3	p=0.84
NYHA II/III/IV	54/ 43/ 3%	47/ 50/ 3%	p=0.004
KCCQ Total Symptom Score	70 [49, 88]	67 [49, 85]	p=0.038
SBP — mmHg	117 ± 15	117 ± 16	p=0.99
Heart rate — beats/min	73 ± 12	72 ± 12	p=0.046
NT-proBNP — pg/mL	1961 [976, 4025]	2388 [1272, 4505]	p<0.001
Troponin I — ng/L	26 [13, 50]	30 [18 , 58]	p<0.001
eGFR - mL/min/1.73m2	59 [44, 75]	55 [43, 69]	p<0.001
Baseline BMI (kg/m2)	29 ± 6	28 ± 6	p<0.001
Heart Failure Therapies			
ACEi, ARB or ARNi	6511 (87.1%)	648 (85.9%)	p=0.38
ARNi	1452 (19.4%)	149 (19.8%)	p=0.82
BB	7059 (94.4%)	704 (93.4%)	p=0.25
MRA	5824 (77.9%)	573 (76.0%)	p=0.24
SGLT2 Inhibitors	198 (2.6 %)	20 (2.7 %)	p=0.99
Ivabradine	499 (6.7 %)	34 (4.5 %)	p=0.021
Digitalis glycosides	1256 (16.8%)	129 (17.1%)	p=0.83
CRT	1017 (13.6%)	141 (18.7%)	p<0.001
ICD	2345 (31.4%)	269 (35.7%)	p=0.015

H/o = history of. HF = heart failure. MI = myocardial infarction. CABG = coronary artery bypass. PCI = percutaneous coronary interventions. LVEF = left ventricular ejection fraction. NYHA = New York Heart Association. KCCQ - Kansas City Cardiomyopathy Questionnaire. SBP = systolic blood pressure. eGFR = estimated glomerular filtration rate. BMI = Body Mass Index. ACEi = Angiotensin-converting enzyme inhibitors. ARB = Angiotensin receptor blockers. ARNi = Angiotensin receptor neprilysin inhibitor. BB = Beta blockers. MRA = Mineralocorticoid receptor antagonists. SGLT2 = Sodium--glucose cotransporter 2. CRT = Cardiac resynchronization therapy. ICD = implantable cardioverter-defibrillator.

[0221] The evaluation of EF by quartiles in the current analysis has subgroups of approximately 2,000 patients with 578 to 979 events in each quartile, subgroups in themselves larger than many studies. These investigations are supported by analyses of ejection fraction as a continuous variable incorporating the data from all 8,232

patients. While the statistical analysis plan from GALACTIC-HF pre-specified multiple sub-groups for evaluation and is subject to issues related to multiplicity testing, the univariate interaction p-value for the treatment-covariate interaction was 0.004, making it highly unlikely to be due to chance. In addition, there is biological plausibility for this effect modification and the findings are internally consistent.

Patients having More Advanced Heart Failure

Statistical Approach

[0222] Baseline characteristics for patients classified as more advanced HF compared to those without were evaluated using appropriate summary statistics. Outcomes for patients with or without more advanced HF were compared using Cox proportional hazards models and Kaplan-Meier curves. Interaction terms were used to assess whether omecamtiv mecarbil had a differential effect on outcome by advanced HF status. Absolute event rates were described using rate per 100 patient-years. As a sensitivity analysis, the event rates and treatment effect of omecamtiv mecarbil for patients was assessed by specific advanced HF criteria met, as well as the total number of criteria met. For quality-of-life data as assessed by the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ TSS), linear regression adjusted for baseline scores was used to compare treatment effects of omecamtiv mecarbil compared to placebo. Safety and tolerability data for patients with advanced HF vs. those without were summarized using descriptive statistics. P value ≤ 0.05 was considered statistically significant for all analyses.

Results

[0223] Of patients enrolled in GALACTIC-HF, 2258 (27%) met the specified criteria for more advanced HF, of which 1106 were randomized to treatment with omecamtiv mecarbil and 1152 to placebo. Baseline characteristics stratified by those patients with or without more advanced HF are shown in Table 11.

Table 11. Baseline Characteristics by Advanced Heart Failure Classification

	n=2258	n=5974	
Demographics			
Age - yr	64.5 ± 11.6	64.5 ± 11.3	p=0.75
Sex, Female	477 (21.1%)	1272 (21.3%)	p=0.87
Race			p<0.001
Asian	153 (6.8 %)	557 (9.3 %)	
Black	177 (7.8 %)	385 (6.4 %)	
Other	129 (5.7 %)	434 (7.3 %)	
White	1799 (79.7%)	4598 (77.0%)	
Geographic Region			p<0.001
Asia	141 (6.2 %)	529 (8.9 %)	
Eastern Europe/Russia	810 (35.9%)	1871 (31.3%)	
Latin America	324 (14.3%)	1250 (20.9%)	
US And Canada	434 (19.2%)	952 (15.9%)	
Western Europe/South Africa/Australasia	549 (24.3%)	1372 (23.0%)	
Randomization Setting: In-patient	937 (41.5%)	1147 (19.2%)	p<0.001

Clinical Characteristics			
Atrial Fibrillation or Flutter at Screening	717 (31.8%)	1528 (25.6%)	p<0.001
Hypertension History	1573 (69.7%)	4211 (70.5%)	p=0.46
Type 2 diabetes mellitus	954 (42.2%)	2355 (39.4%)	p=0.020
History of stroke	240 (10.6%)	514 (8.6 %)	p=0.004
Ischemic heart failure etiology	1213 (53.7%)	3202 (53.6%)	p=0.92
History of Myocardial Infarction	960 (42.5%)	2475 (41.4%)	p=0.37
LVEF - %	23.4 ± 5.2	27.8 ± 6.2	p<0.001
NYHA Classification			p<0.001
Class II	0 (0.0 %)	4368 (73.1%)	
Class III	2085 (92.3%)	1531 (25.6%)	
Class IV	173 (7.7 %)	75 (1.3 %)	
KCCQ Total Symptom Score	56.2 [36.5, 77.1]	74.0 [54.2, 90.6]	p<0.001
Outpatient	63.5 [44.8, 83.3]	77.1 [58.3, 91.7]	p<0.001
Inpatient	47.4 [29.2,66.7]	57.3 [37.5,76.0]	p<0.001
SBP — mmHg	113.8 ± 15.0	117.5 ± 15.4	p<0.001
Heart rate — beats/min	74.3 ± 12.5	71.7 ± 11.9	p<0.001
NT-proBNP — pg/mL	2804 [1450, 5795]	1768 [878 ,3521]	p<0.001
Cardiac Troponin I — ng/L	34 [18, 64]	25 [11, 47]	p<0.001
eGFR — mL/min/1.73m2	55.1 [41.8, 69.9]	60.0 [45.4, 75.5]	p<0.001
Heart Failure Therapies			
ACEi, ARB or ARNi	1873 (82.9%)	5286 (88.5%)	p<0.001
ARNi	447 (19.8%)	1154 (19.3%)	p=0.62
BB	2093 (92.7%)	5670 (94.9%)	p<0.001
MRA	1768 (78.3%)	4629 (77.5%)	p=0.43
SGLT2 Inhibitors	50 (2.2 %)	168 (2.8 %)	p=0.13
Ivabradine	188 (8.3 %)	345 (5.8 %)	p<0.001
Digitalis glycosides	436 (19.3%)	949 (15.9%)	p<0.001
Cardiac Resynchronization Therapy	372 (16.5%)	786 (13.2%)	p<0.001
Implantable Cardioverter Defibrillator	807 (35.7%)	1807 (30.2%)	p<0.001

LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, KCCQ = Kansas City Cardiomyopathy Questionnaire, SBP = systolic blood pressure, NT-proBNP = amino-terminal-b-type natriuretic peptide, eGFR = estimated glomerular filtration rate, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, ARNi = angiotensin receptor neprilysin inhibitor, BB = beta blocker, MRA = mineralocorticoid receptor antagonists, SGLT2 = sodium glucose co-transport-2

[0224] As anticipated, patients with more advanced HF had markers of more severe disease, including lower ejection fraction, greater NYHA class, higher NT-proBNP concentrations, lower systolic blood pressure, worse renal function, and worse quality of life as assessed by the KCCQ TSS. Patients with more advanced HF were less likely to be treated with renin-angiotensin-aldosterone system (RAAS) modulators and beta blockers at baseline but more likely to have cardiac resynchronization therapy (CRT) or an implantable cardioverter defibrillator (ICD). Patients with more advanced HF were at significantly higher risk, with event rates for placebo treated patients that were approximately twice those of patients without more advanced HF for the primary endpoint (42.6 events/100 pt-years vs. 21.3), cardiovascular mortality (17.3 events/100 patient-years vs. 8.5), and all-cause mortality (21.7 events/100 pt-years vs. 11.9).

Efficacy and Safety of Omecamtiv Mecarbil in More Advanced Heart Failure

[0225] Patients classified as more advanced HF had a greater treatment benefit from omecamtiv mecarbil treatment than those without more advanced HF. For the primary endpoint, patients with more advanced HF had a 20% risk reduction (HR = 0.80, 95% CI 0.71 to 0.90), whereas patients without more advanced HF had no significant treatment effect (HR = 0.99. 95% CI 0.91 to 1.08, p value for interaction = 0.005). These results were similar for cardiovascular mortality (patients with more advanced HF (HR = 0.88, 95% CI 0.75 to 0.1.03) compared to patients with less advanced HF (HR = 1.10, 95% CI 0.97 to 1.25, p value for interaction = 0.028)). Kaplan-Meier curves comparing patients with and without more advanced HF for each of these endpoints are shown in **FIGURES 14A and 14B**. As an additional sensitivity analysis, the event rate and treatment effect of omecamtiv mecarbil was assessed based on which and how many advanced heart HF criteria were met (**FIGURES 15A and 15B**). The observed benefits of omecamtiv mecarbil were greatest in patients meeting all 3 advanced HF criteria, which were also the group with the highest overall risk. The combination of a 20% relative risk reduction in the primary endpoint in the context of high baseline risk translated to an absolute risk reduction of 8.3 events/100 patientt-years (NNT = 12). These results were broadly consistent across a variety of other secondary outcomes from the GALACTIC-HF trial, as shown in Table 12. For the KCCQ, we did not identify a differential effect on the total symptom score (TSS) by advanced HF status (advanced HF inpatient 1.1 increase and outpatient 1.7 decrease in TSS, compared to non-advanced HF (inpatient 3.3 increase, outpatient 0.2 decrease in TSS, p for interaction = 0.09).

[0226] Safety data for omecamtiv mecarbil vs. placebo by advanced HF category are summarized in Table 13.

Table 12. Event Rates by Treatment Assignment and Advanced HF classification

	n/N	Rate[1]	n/N	Rate[1]	HR (95% CI); p-value	ARR[1]
More Advanced Heart Failure						
Primary Endpoint	510/1106 (46%)	34.3	611/1152 (53%)	42.6	0.80 (0.71, 0.90); p<0.001	8.3
CV Death as 1st Primary Event	107/1106 (10%)	7.2	142/1152 (12%)	9.9		
HF Hosp as 1st Primary Event	385/1106 (35%)	25.9	441/1152 (38%)	30.8		
Urgent Outpatient Visit as 1st Primary Event	18/1106 (2%)	1.2	28/1152 (2%)	2.0		
CV Death	288/1106 (26%)	15.5	332/1152 (29%)	17.3	0.88 (0.75, 1.03); p=0.11	1.8
Heart Failure Hospitalization	385/1081 (36%)	26.2	450/1136 (40%)	31.4	0.84 (0.73, 0.96); p=0.013	5.2
All-cause Death	365/1081 (34%)	20.1	409/1136 (36%)	21.6	0.92 (0.80, 1.06); p=0.26	1.5
Less Advanced Heart Failure						

Primary Outcome	1013/3014 (34%)	21.1	996/2960 (34%)	21.3	0.99 (0.91, 1.08); p=0.84	0.2
CV Death as 1st Primary Event	239/3014 (8%)	5.0	229/2960 (8%)	4.9		
HF Hosp as 1st Primary Event	722/3014 (24%)	15.0	692/2960 (23%)	14.8		
Urgent Outpatient Visit as 1st Primary Event	52/3014 (2%)	1.1	75/2960 (3%)	1.6		
CV Death	520/3014 (17%)	9.3	466/2960 (16%)	8.5	1.10 (0.97, 1.25); p=0.14	-0.8
Heart Failure Hospitalization	746/3014 (25%)	15.4	724/2960 (24%)	15.3	1.01 (0.91, 1.12); p=0.88	-0.1
All-cause Death	692/3014 (23%)	12.4	649/2960 (22%)	11.9	1.05 (0.94, 1.17); p=0.37	-0.6
CV = cardiovascular, HF = heart failure, HR = hazard ratio, CI = confidence interval, ARR = absolute risk reduction						

[1]per 100 patient years; ARR = absolute risk reduction

Table 13. Safety by Treatment Status and Advanced HF Classification

Advanced Heart Failure	n=1079	n=1132		
Any treatment-emergent serious adverse event	742 (67.3%)	790 (68.8%)	p=0.43	0.98 (0.92, 1.03)
AE: ventricular tachyarrhythmia	80 (8.0%)	86 (8.1%)	p=0.89	0.98 (0.73, 1.31)
Positively Adjudicated MI	42 (3.8%)	29 (2.5%)	p=0.08	1.51 (0.95, 2.40)
First Stroke	18 (1.6%)	31 (2.7%)	p=0.08	0.60 (0.34, 1.07)
Not Advanced Heart Failure	n=2959	n=2920		
Any treatment-emergent serious adverse event	1631 (54.2%)	1645 (55.7%)	p=0.26	0.97 (0.93, 1.02)
AE: ventricular tachyarrhythmia	210 (7.9%)	218 (8.4%)	p=0.58	0.95 (0.79, 1.14)
Positively Adjudicated MI	80 (2.7%)	89 (3.0%)	p=0.41	0.88 (0.66, 1.19)
First Stroke	58 (1.9%)	81 (2.7%)	p=0.037	0.70 (0.50, 0.98)
SAE = serious adverse event, AE = adverse event, MI = myocardial infarction				

[0227] Patients with more advanced HF were more likely to have treatment emergent serious adverse events than patients without, but these were similar between omecamtiv mecarbil treated patients (67%) and placebo (69%). There were no significant differences in serious adverse events related to ventricular tachyarrhythmias between omecamtiv mecarbil and placebo in the more advanced HF patients (7.9% for omecamtiv vs. 8.1% for placebo). In more advanced HF patients, there were numerically more myocardial infarctions with omecamtiv mecarbil compared to placebo (3.8% vs. 2.5% %, p = 0.08) but fewer strokes (1.6% vs. 2.7%, p = 0.08). Data on tolerability and changes in biomarkers are shown in Table 4. As in the overall trial, treatment with omecamtiv mecarbil in patients with more advanced HF did not lead to changes in blood pressure, worsening of renal function, or worsening of potassium compared to placebo. Heart rate was modestly lowered with omecamtiv mecarbil compared to placebo (1.9 beats/minute difference in change from 0 to 24 weeks, $p < 0.001$ for

omecamtiv mecarbil vs. placebo). In the more advanced HF population, treatment with omecamtiv mecarbil was associated with a significant decrease in NT-proBNP and a small increase in circulating cardiac troponin (Table 14).

Table 14. Tolerability by Treatment and Advanced HF status

	OM	Placebo	OM	Placebo	Ratio or Difference	p-value
Advanced HF						
Systolic BP (mm Hg) week 0 to 24 (n = 1849)	114.0±15.3	113.5±14.7	116.7±17.3	116.0±17.7	0.6 (-0.7, 2.0)	p=0.35
Heart rate (beats/min) week 0 to 24 (n = 1850)	74.5±12.7	74.1±12.3	71.2±12.3	73.0±12.8	-1.9 (-2.9, -0.8)	p<0.001
Potassium (mmol/L) week 0 to 24 (n = 1761)	4.53±0.57	4.56±0.56	4.52±0.57	4.56±0.58	-0.03 (-0.08, 0.02)	p=0.27
Creatinine (mg/dl) week 0 to 24 (n = 1787)	1.39±0.50	1.36±0.48	1.37±0.55	1.38±0.56	-0.01 (-0.04, 0.02)	p=0.53
NT-proBNP (pg/ml) week 0 to 24 [Ratio] (n = 1773)	2758 [1480, 5838]	2834 [1416, 5732]	1837 [856, 4043]	2030 [918, 4703]	0.86 (0.78, 0.95)	p=0.002
Troponin I (ng/L) week 0 to 24 [Median Difference] (n = 1613)	34 [18, 64]	34 [18, 64]	41 [18, 74]	30 [14, 60]	5 (3, 7)	p<0.001
Troponin I (ng/L) week 0 to 24 [Ratio] (n = 1613)	34 [18, 64]	34 [18, 64]	41 [18, 74]	30 [14, 60]	1.30 (1.21, 1.40)	p<0.001
Non-Advanced HF						
Systolic BP (mm Hg) week 0 to 24 (n = 5383)	117.1±15.4	117.9±15.4	118.4±16.8	119.6±17.9	-0.7 (-1.5, 0.1)	p=0.07
Heart rate (beats/min) week 0 to 24 (n = 5383)	71.7±12.0	71.6±11.9	69.6±11.3	71.0±11.6	-1.4 (-2.0, -0.9)	p<0.001
Potassium (mmol/L) week 0 to 24 (n = 5251)	4.57±0.51	4.57±0.51	4.56±0.51	4.55±0.52	0.01 (-0.02, 0.03)	p=0.58
Creatinine (mg/dl) week 0 to 24 (n = 5278)	1.27±0.45	1.28±0.45	1.29±0.49	1.28±0.48	0.01 (-0.00, 0.03)	p=0.14
NT-proBNP (pg/ml) week 0 to 24 [Ratio] (n = 5261)	1753 [864, 3479]	1795 [893, 3540]	1274 [531, 2731]	1391 [613, 2987]	0.91 (0.86, 0.95)	p<0.001
Troponin I (ng/L) week 0 to 24 [Median Difference] (n = 4758)	25 [11, 47]	25 [11, 47]	31 [13, 63]	22 [10, 45]	4 (3, 5)	p<0.001
Troponin I (ng/L) week 0 to 24 [Ratio] (n = 4758)	25 [11, 47]	25 [11, 47]	31 [13, 63]	22 [10, 45]	1.24 (1.19, 1.29)	p<0.001
BP = blood pressure, NT-proBNP = amino-terminal-b-type natriuretic peptide						

Effect of OM by baseline NT-ProBNP Level

[0228] Natriuretic peptides are fundamental to the understanding of the pathophysiology of heart failure, its diagnosis, assessment of prognosis and treatment. Elevation of N-terminal pro-B-type natriuretic peptide (NT-proBNP) is pathognomonic of heart failure with reduced ejection fraction (HFrEF) and higher blood concentrations of this and other natriuretic peptides are associated with higher rates of non-fatal and fatal outcomes. Conversely, pharmacological therapies that are effective in reducing the risk of hospitalization for worsening heart failure and the risk of death in patients with HFrEF also reduce natriuretic peptides. A newly developed therapy for HFrEF, omecamtiv mecarbil, directly augments cardiac contractility by selectively binding to cardiac myosin, increasing the number of myosin heads (force generators) that bind to the actin filament and initiate the power-stroke at the start of systole. In phase 2 trials in patients with HFrEF, both short-term intravenous treatment and longer-term oral therapy with omecamtiv mecarbil improved cardiac performance and, in the latter, over a 20-week period, reduced left ventricular systolic and diastolic volumes, plasma natriuretic peptide concentrations and heart rate. As a result, the Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure trial (GALACTIC-HF) was conducted to assess whether treatment with omecamtiv mecarbil would improve outcomes in patients with HFrEF, enrolled either as outpatients and in-patients with decompensated heart failure. Over a median of 22 months, omecamtiv mecarbil reduced the risk of risk of the primary composite outcome of a worsening heart failure event or cardiovascular death by 8% (hazard ratio 0.92; 95% confidence interval, 0.86 to 0.99; P = 0.03). Before completion of the trial, we prespecified that the effect of randomized treatment would be examined according to baseline NT-proBNP, either less than or equal to median value, or greater than median value (≤median, >median), in relation to randomization setting (outpatient or inpatient), excluding individuals with atrial fibrillation/flutter (AF/F). Here we report the effect of omecamtiv mecarbil according to baseline NT-proBNP level in patients without AF/F and in the overall population. In addition, we describe the effect of omecamtiv mecarbil using NT-proBNP as a continuous as well as a categorical measure and describe the effect of omecamtiv mecarbil on NT-proBNP level.

NT-proBNP and cardiac troponin I measurements

[0229] NT-proBNP was measured at baseline and at 2, 6, 24, 48 and 96 weeks after randomization. Plasma NT-proBNP was measured in a central laboratory (Q Squared Solutions) using the Roche Elecsys NT-proBNP two-site electrochemiluminescence immunoassay (analytical range 50-35000 pg/mL).

Statistical Analysis

[0230] Although the primary outcome was a composite of heart failure event or cardiovascular death, the trial was designed to provide 90% power to detect a hazard ratio of 0.8 for cardiovascular death, giving a sample size of approximately 8,000 patients. The trial was event-driven, with a target of approximately 1590 cardiovascular deaths. Efficacy analyses were performed according to randomized treatment group assignment (intention-to-treat) on the full analysis set which included all randomized patients except for 24 subjects from a single site

excluded due to Good Clinical Practice violations. Baseline characteristics were summarized as frequencies with percentages, means with standard deviation (SD), or medians with interquartile ranges. Differences in baseline characteristics were tested using the Cochrane-Armitage trend test for categorical variables and the analysis of variance test for continuous variables. The difference between treatment groups in NT-proBNP at the time points after randomization in surviving patients was analyzed using an analysis of covariance model, with treatment-group assignment as a fixed-effect factor and baseline NT-proBNP as a covariate. The results of the analyses of covariance are presented as least-squares mean differences with corresponding 95%CIs. Time-to-event data were evaluated with Kaplan-Meier estimates and Cox proportional-hazards models with baseline hazards stratified by randomization setting and region and with treatment group and baseline eGFR as covariates. The safety analyses were performed in patients who underwent randomization and received at least one dose of omecamtiv mecarbil or placebo. All analyses were conducted using STATA version 15.1 (College Station, TX) and SAS version 9.4 (SAS Institute, Cary, NC). A P-value of 0.05 was considered statistically significant.

Results

[0231] A NT-proBNP measurement at baseline was available for 8206 of the 8232 patients randomized. Of these, 5971 patients did not have AF/F on their baseline ECG. The median (Q1, Q3) NT-proBNP level at baseline was 1675 (812-3579) pg/ml among patients not in AF/F and 1998 (993-4079) pg/mL in all patients randomized.

[0232] Baseline characteristics according to median baseline NT-proBNP concentration are presented in Table 15 for participants without AF/F and in the overall population.

Table 15. Baseline characteristics of patients according to pre-randomization NT-proBNP level (≤median or >median) in the prespecified analysis population (no atrial fibrillation/flutter at baseline) and in all patients randomized.

	No AF/F			All patients		
NT-proBNP	**≤ median** N=2987	**>median** N=2984	P-value	**≤ median** N=4105	**>median** N=4101	P-value
Age (years), mean (SD)	61.6±11.4	64.9±11.5	<0.001	62.5±11.3	66.5±11.0	<0.001
Male sex, N (%)	2334 (78.1)	2300 (77.1)	0.33	3259 (79.4)	3203 (78.1)	0.15
Race, N (%)			<0.001			<0.001
Asian	316 (10.6)	240 (8.0)		402 (9.8)	308 (7.5)	
Black	234 (7.8)	249 (8.3)		290 (7.1)	266 (6.5)	
White	2238 (74.9)	2262 (75.8)		3159 (77.0)	3220 (78.5)	
Other	199 (6.7)	233 (8.2)		254 (6.2)	307 (7.5)	
Geographic region, N (%)			<0.001			<0.001
Asia	300 (10.0)	222 (7.4)		382 (9.3)	288 (7.0)	
Western Europe	587 (19.7)	718 (24.1)		827 (20.1)	1086 (26.5)	
Eastern Europe	972 (32.5)	818 (27.4)		1408 (34.3)	1273 (31.0)	
North America	586 (19.6)	542 (18.2)		757 (18.4)	611 (14.9)	
Latin America	542 (18.1)	684 (22.9)		731 (17.8)	843 (20.6)	
Randomized as an inpatient, N (%)	569 (19.0)	776 (26.0)	<0.001	871 (21.2)	1188 (29.0)	<0.001
Physiological measures						
Systolic blood pressure (mmHg), mean (SD)	119.0±14.8	115.0±15.9	<0.001	118.5±14.8	114.4±15.7	<0.001

Heart rate (bpm)	69.9±10.9	72.8±11.9	<0.001	70.8±11.4	73.9±12.7	<0.001
BMI (kg/m^2)	29.6±6.2	27.2±5.8	<0.001	29.6±6.3	27.3±5.8	<0.001
eGFR (mL/min/1.73m^2), mean (SD)	67.4±21.8	57.0±22.0	<0.001	66.0±21.4	54.9±21.0	<0.001
eGFR <60 mL/min/1.73m^2, N (%)	1163 (38.9)	1764 (59.1)	<0.001	1705 (41.5)	2599 (63.4)	<0.001
Ischemic etiology, N (%)	1624 (54.4)	1708 (57.2)	0.026	2185.0 (53.2)	2216.0 (54.0)	0.46
LVEF, mean (SD)	27.4±6.0	25.3±6.4	<0.001	27.4±6.0	25.7±6.4	<0.001
NYHA class, N (%)			<0.001			<0.001
II	1893 (63.4)	1454 (48.7)		2484 (60.5)	1875 (45.7)	
III	1045 (35.0)	1418 (47.5)		1539 (37.5)	2060 (50.2)	
IV	49 (1.6)	112 (3.8)		82 (2.0)	166 (4.0)	
KCCQ-TSS, mean (SD)	71.9±23.3	64.4±25.7	<0.001	70.7±23.8	62.3±25.7	<0.001
Atrial fibrillation/flutter*, N (%)	--	--	--	725 (17.7)	1510 (36.8)	
Medical history, N (%)						
Hypertension	2085 (69.8)	2038 (68.3)	0.21	2908 (70.8)	2854 (69.6)	0.22
Type 2 diabetes	1188 (39.8)	1288 (43.2)	0.008	1662.0 (40.5)	1702.0 (41.5)	p=0.35
Previous MI	1315 (44.0)	1361 (45.6)	0.22	1727 (42.1)	1696 (41.4)	0.51
Treatment, N (%)						
ACEI/ARB/ARNI	2752.0 (92.1)	2481.0 (83.1)	<0.001	3752.0 (91.4)	3388.0 (82.6)	<0.001
ARNI	629.0 (21.1)	536.0 (18.0)	0.003	862.0 (21.0)	728.0 (17.8)	<0.001
Beta-blocker	2865.0 (95.9)	2771.0 (92.9)	<0.001	3921.0 (95.5)	3819.0 (93.1)	<0.001
MRA	2377.0 (79.6)	2238.0 (75.0)	<0.001	3279.0 (79.9)	3101.0 (75.6)	<0.001
Diuretic	2541 (85.1)	2732 (91.6)	<0.001	3554 (86.6)	3801 (92.7)	<0.001
Digoxin	319 (10.7)	372 (12.5)	0.031	610 (14.9)	771 (18.8)	<0.001
ICD	893.0 (29.9)	1012.0 (33.9)	<0.001	1222.0 (29.8)	1380.0 (33.7)	<0.001
CRT-P/CRT-D	352.0 (11.8)	460.0 (15.4)	<0.001	480.0 (11.7)	672.0 (16.4)	<0.001

*Percentages may not total 100 because of rounding

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; CRT-P/D = cardiac resynchronization therapy with or without a defibrillator; GFR = glomerular filtration rate; ICD = implantable cardioverter-defibrillator; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire total symptom score - range from 0 to 100, with higher scores indicating fewer symptoms; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart association.

[0233] Compared to those with NT-proBNP level less than or equal to the median (≤ median), patients with a level greater than median (>median) were older, more often from Western Europe or Latin America, and less frequently from Asia. Participants with a NT-proBNP level greater than median had a lower mean body mass index, eGFR (and larger proportion of patients with eGFR <60 mL/min/1.73m^2) and systolic blood pressure, but higher heart rate and troponin I. They were also more likely to have a lower ejection fraction, and considerably worse NYHA functional class and KCCQ-TSS. These differences were seen both in participants without AF/F and in the overall population. Some differences were only seen in patients without AF/F and not in the overall population. Participants without AF/F, with a NT-proBNP level greater than median, were more likely to have

diabetes and an ischemic etiology, than those with a NT-proBNP less than or equal to the median (these differences were not significant in the overall population).

[0234] With respect to heart failure treatment, patients with a NT-proBNP level greater than median were less often treated with renin-angiotensin system blockers (including sacubitril-valsartan), mineralocorticoid receptor antagonists and beta-blockers, but had more often prescribed a diuretic and digoxin (even in patients without AF/F) and were more likely to have an implanted cardiac device.

[0235] Generally, these differences were also observed whether patients were enrolled as an outpatient or an inpatient, and in patients with AF/F.

[0236] Hospitalization and mortality outcomes in relation to baseline concentration of NT-proBNP

[0237] Event rates were higher in patients with a NT-proBNP greater than the median, compared with less than or equal to the median, in participants without AF/F and in the overall population, as shown by comparison of the placebo groups in Table 16. When NT-proBNP was examined as a continuous variable, the rate of the primary endpoint rose steeply with increasing NT-proBNP concentration (**FIGURES 16A-16D and 17A-17D**). The same was observed whether patients were enrolled as an outpatient or an inpatient, and in patients with AF/F.

Effect of omecamtiv mecarbil on outcomes according to baseline concentration of NT-proBNP

[0238] Table 16 shows the effect of omecamtiv mecarbil on the prespecified morbidity and mortality endpoints, according to baseline NT-proBNP level divided at the median, as prespecified, in patients without AF/F and in the overall trial population. Additional analyses of the effect of omecamtiv mecarbil examining NT-proBNP as a continuous variable are shown in (**FIGURES 18A-18D and 19A-19D**).

Table 16. Outcomes according to baseline NT-proBNP level (less than or equal to the median or greater than the median) in relation to randomized treatment assignment in the prespecified analysis population (no atrial fibrillation/flutter at baseline) and in all patients randomized

	No AF/F (n=5971)						**All patients (n=8206)**					
	Placebo (n=3006)		**OM** (n=2965)		HR (95% CI)	P value	**Placebo** (n=4099)		**OM** (n=4107)		HR (95% CI)	P value
	n (%)	Rate[1]	n (%)	Rate[1]			n (%)	Rate[1]	n (%)	Rate[1]		
1° Outcome[2,3]												
≤ NTproBNP	352 (23)	13.42	328 (22)	12.42	0.94 (0.80, 1.09)	0.392	518 (25)	14.84	537 (26)	15.00	1.02 (0.90,1.15)	0.790
> NTproBNP	748 (50)	38.85	650 (44)	31.30	0.81 (0.73,0.90)	0.000	1080 (52)	41.59	981 (48)	36.52	0.88 (0.81,0.96)	0.003
Hospitalization[3,4]												
≤ NTproBNP	263 (17)	10.02	254 (17)	9.62	0.97 (0.82,1.15)	0.728	399 (20)	11.43	424 (20)	11.84	1.04 (0.91,1.19)	0.565
> NTproBNP	570 (38)	29.62	483 (32)	23.26	0.79 (0.70,0.89)	0.000	830 (40)	31.97	750 (37)	27.93	0.88 (0.79,0.97)	0.008
CV death[3]												
≤ NTproBNP	141 (9)	4.85	135 (9)	4.64	0.96 (0.76,1.22)	0.761	202 (10)	5.13	227 (11)	5.63	1.11 (0.92,1.34)	0.296
> NTproBNP	405 (27)	16.32	363 (24)	14.29	0.87 (0.75,1.00)	0.047	591 (29)	17.18	578 (28)	17.15	0.99 (0.88,1.11)	0.811
All-cause death												
≤ NTproBNP	205 (14)	7.05	196 (13)	6.74	0.96 (0.79,1.17)	0.715	292 (14)	7.42	327 (16)	8.11	1.10 (0.94,1.29)	0.223

> NTproBNP	530 (35)	21.35	474 (32)	18.67	0.86 (0.76,0.97)	0.017	766 (37)	22.27	737 (36)	21.87	0.97 (0.88,1.07)	0.544

[1]per 100 person-years
[2]a composite of time to heart failure hospitalization or cardiovascular death, whichever came first
[3]NTproBNP median values
[4]hospitalization for HF
AF/F = atrial fibrillation/flutter OM = omecamtiv mecarbil HF = heart failure
Numbers of patients in subgroups
No AF/F NTproBNP ≤ median: placebo = 1511/OM = 1476. NTproBNP > median: placebo = 1495/OM = 1489
All patients: NTproBNP ≤ median: placebo = 2032/OM = 2073 NTproBNP > median: placebo = 2067/OM = 2034

Primary composite outcome

[0239] Among patients without AF/F, compared to placebo, omecamtiv mecarbil had more benefit on the primary endpoint in participants with a NT-proBNP greater than the median (HR 0.81, 95% CI 0.73-0.90) than in patients with a NT-proBNP less than or equal to the median (HR 0.94, 0.80-1.09); P for interaction=0.035. A similar interaction was seen in the overall population: HR 0.88, 0.80-0.96 in patients with NT-proBNP >median and 1.01, 0.90-1.15 in participants with a NT-proBNP less than or equal to the median; P for interaction=0.095.

[0240] When NT-proBNP was examined as a continuous variable, the increasing beneficial effect of omecamtiv mecarbil with increasing NT-proBNP became clearer as shown in **FIGURES 18A-18D and 19A-19D**.

[0241] Qualitatively similar findings were seen in participants enrolled in both the outpatient and inpatient setting. A completely different pattern was observed in patients with AF/F at baseline, with a higher event rate in the omecamtiv mecarbil groups, compared with the placebo group, especially in patients with a NT-proBNP less than or equal to the median.

Secondary outcomes

[0242] Examination of the secondary hospitalization and mortality outcomes in patients without AF/F suggested the interaction between baseline NT-proBNP level and the effect of omecamtiv mecarbil was more evident for heart failure hospitalization than for cardiovascular or all-cause death (Table 16 and **FIGURES 18A-18D and 19A-19D**). While both hospitalization and mortality were reduced by omecamtiv mecarbil in participants without AF/F and a NT-proBNP greater than the median, the mortality benefits were lost when the overall population was analyzed, because of the absence of an effect of omecamtiv mecarbil in patients with AF/F. Even the larger benefit of omecamtiv mecarbil on heart failure hospitalization was attenuated by the addition of patients with AF/F in the overall population.

[0243] Table 17 shows the effect of omecamtiv mecarbil on physiologic measures and on plasma biomarkers according to baseline NT-proBNP level divided at the median, in patients without AF/F and in the overall trial population.

Table 17. Change from baseline to 24 weeks in physiologic measures and biomarkers according to baseline NT-proBNP level (≤median or >median) in relation to randomized treatment assignment in the prespecified analysis population (no atrial fibrillation/flutter at baseline) and in all patients randomized.

No AF/F (n=5971)	All patients (n=8206)

	Placebo (n=3006)		OM (n=2965)		Δ/ Ratio	P valu e	Placebo (n=4099)		OM (n=4107)		Δ / Ratio	P value
	t_0	24 wks	t_0	24 wks			t_0	24 wks	t_0	24 wks		
SBP (mmHg)												
≤ NT proBNP	119 (15)	122 (18)	119 (15)	120 (16)	-1.0 (-2.1, 0.1)	0.06	119 (14)	121 (17)	118 (15)	120 (16)	-0.8 (-1.7, 0.2)	0.11
> NT proBNP	115 (16)	117 (19)	117 (18)	120 (16)	0.3 (-0.8, 1.4)	0.59	114 (16)	116 (18)	114 (16)	116 (17)	-0.1 (-1.0, 0.9	0.88
HR (bpm)												
≤ NT proBNP	70 (11)	70 (11)	70 (11)	69 (11)	-1.5 (-2.2, -0.8)	<0.0 01	71 (12)	71 (12)	71 (11)	70 (11)	-1.5 (-2.2, -0.09)	<0.001
> NT proBNP	73 (12)	71 (11)	73 (12)	70 (12)	-1.7 (-2.5, -0.9)	<0.0 01	74 (12)	72 (12)	74 (13)	70 (12)	-1.6 (-2.3, -0.8)	<0.001
Creatine (mg/dL)												
≤ NT proBNP	1.19 (0.40)	1.18 (0.40)	1.16 (0.36)	1.17 (0.42)	0.02 (0.00, 0.04)	0.07	1.20 (0.40)	1.20 (0.39)	1.19 (0.37)	1.21 (0.43)	0.02 (0.00, 0.04)	0.019
> NT proBNP	1.37 (0.50)	1.40 (0.56)	1.39 (0.52)	1.37 (0.50)	-0.01 (-0.03, 0.02)	0.66	1.40 (0.49)	1.43 (0.57)	1.42 (0.52)	1.43 (0.56)	-0.01 (-0.03, 0.02)	0.54
NT-proBNP (pg/mL)												
≤ NTproBNP	829 (535, 1174)	691 (332, 1150)	791 (506, 1176)	614 (332, 1150)	0.95 (0.88, 1.01)	0.11	914 (610, 1444)	818 (410, 1480)	992 (592, 1469)	772 (385, 1472)	0.95 (0.90, 1.01)	0.10
> NTproBNP	3574 (2387, 6312)	2754 (1424, 5241)	3586 (2364, 6353)	2302 (1146, 4689)	0.83 (0.76,0. 90)	<0.0 01	4065 (2798, 6952)	3207 (1766, 5774)	4100 (2732, 6972)	2809 (1474, 5145)	0.84 (0.78,0 .89)	<0.001
Troponin I (ng/L)												
≤ NTproBNP	19 (10, 37)	16 (10, 35)	18 (10, 35)	16 (10, 35)	1.25 (1.18, 1.31)	<0.0 01	20 (10,39)	18 (10,37)	19 (10,38)	24 (10,50)	1.28 (1.22, 1.34)	<0.001
> NTproBNP	33 (18, 61)	31 (16, 56)	36 (18, 67)	40 (20, 78)	1.23 (1.16, 1.31)	<0.0 01	35 (19,64)	34 (17,62)	37 (19,67)	44 (22,81)	1.23 (1.17, 1.29)	<0.001

AF/F = atrial fibrillation/flutter BP = blood pressure BPM = beats per minute OM = omecamtiv mecarbil NT-proBNP = N-terminal pro-B-type natriuretic peptide

[0244] Changes from baseline (t_0) to the 24-week visit are provided. Omecamtiv mecarbil did not have a significant effect on systolic blood pressure in any subgroup but did reduce heart rate, significantly, by 1-2 beats per minute in in all 4 patient subgroups. Omecamtiv mecarbil also increased troponin I, significantly, and by a similar proportional amount, in all 4 patient subgroups. By contrast, omecamtiv mecarbil reduced NT-proBNP only in patients with a baseline value NT-proBNP greater than the median at baseline, as shown in more detail in Figures 20A-F.

Safety outcomes

[0245] The occurrence of adverse events according to treatment assignment according to NT-proBNP category is shown Table 18.

Table 18. Adverse events according to baseline NT-proBNP level (less than or equal to the median or greater than the median) in relation to randomized treatment assignment in the prespecified analysis population (no atrial fibrillation/flutter at baseline) and in all patients randomized.

	No AF/F (n=5971)				All patients (n=8206)			
	Placebo (n=3006)	**OM** (n=2965)	RR	P value	**Placebo** (n=4099)	**OM** (n=4107)	RR	P value
Ventricular tachyarrhythmia								
≤ median NT-proBNP	104 (8.1)	84 (6.7)	0.82 (0.62,1.09)	0.17	142 (8.2)	130 (7.3)	0.89 (0.71,1.12)	0.32
> median NT-proBNP	112 (8.2)	115 (8.6)	1.05 (0.82,1.35)	0.69	161 (8.4)	160 (8.7)	1.03 (0.83,1.27)	0.79
Torsade/QT prolongation								
≤ median NT-proBNP	57 (4.4)	47 (3.7)	0.84 (0.58,1.23)	0.37	86 (4.9)	78 (4.4)	0.88 (0.65,1.19)	0.41
> median NT-proBNP	72 (5.2)	71 (5.3)	1.01 (0.73,1.39)	0.95	108 (5.6)	98 (5.3)	0.94 (0.72,1.23)	0.64
Ventricular tachyarrhythmia leading to treatment								
≤ median NT-proBNP	44 (2.9)	29 (2.0)	0.67 (0.42,1.07)	0.09	58 (2.9)	51 (2.5)	0.86 (0.59,1.25)	0.43
> median NT-proBNP	43 (2.9)	49 (3.3)	1.15 (0.77,1.72)	0.51	68 (3.3)	68 (3.4)	1.02 (0.73,1.42)	0.91
Major cardiac ischemic events								
≤ median NT-proBNP	76 (5.0)	86 (5.8)	1.16 (0.86,1.56)	0.34	101 (5.0)	114 (5.5)	1.10 (0.85,1.43)	0.46
> median NT-proBNP	77 (5.2)	83 (5.6)	1.08 (0.80,1.47)	0.60	87 (4.2)	85 (4.2)	0.99 (0.74,1.33)	0.97
Stroke								
≤ median NT-proBNP	31 (2.1)	25 (1.7)	0.83 (0.49,1.39)	0.47	52 (2.6)	36 (1.7)	0.68 (0.44,1.03)	0.07
> median NT-proBNP	40 (2.7)	29 (2.0)	0.73 (0.45,1.17)	0.19	59 (2.9)	40 (2.0)	0.69 (0.46,1.03)	0.07

AF/F = atrial fibrillation/flutter OM = omecamtiv mecarbil Torsade = Torsade de pointes ventricular tachycardia
Numbers of patients in subgroups
No AF/F NTproBNP ≤ median: placebo = 1511/OM = 1476. NTproBNP >median: placebo = 1495/OM = 1489
All patients NTproBNP ≤ median: placebo = 2032/OM = 2073 NTproBNP >median: placebo = 2067/OM = 2034
Rate is per 100 person-years

[0246] Comparison of the placebo groups showed no substantial difference in any adverse event in patients with a baseline NT-proBNP concentration greater than the median compared to less than or equal to the median. Similarly, there was no strong or consistent evidence that any adverse event was more common with omecamtiv mecarbil, compared to placebo, in any of the 4 subgroups of patients.

[0247] In GALACTIC-HF, the benefit of omecamtiv mecarbil appeared to be larger in patients with higher baseline NT-proBNP levels, especially in patients without AF/F.

Effect of OM by baseline Atrial Fibrillation/Flutter (AF/F)

[0248] Atrial fibrillation is common in patients with heart failure and contributes to morbidity and mortality. Atrial fibrillation has not modified the treatment effect of renin-angiotensin-aldosterone inhibitors that have proven beneficial in heart failure, but may modify the treatment effect of beta-blockers. Here we report the effect of

omecamtiv mecarbil according to baseline status of in patients either without AF/F or with AF/F. Further exploration of digoxin use within the two subpopulations was also assessed.

Results

[0249] A determination of AF/F at baseline was available the 8232 patients randomized. Of these, 5987 patients did not have AF/F on their baseline ECG. Baseline characteristics according to median baseline AF/F status are presented in Table 19 for participants without AF/F and with AF/F.

Table 19. Baseline characteristics of patients according to pre-randomization atrial fibrillation/flutter status (no atrial fibrillation/flutter at baseline or having atrial fibrillation/flutter at baseline) in all patients randomized.

Clinical Characteristics	No AF/Flutter at baseline	AF/Flutter at baseline	P-value
	n=5987	n=2245	
Demographics			
Age - yr	63.3 ± 11.6	67.9 ± 9.9	p<0.001
Sex, Female	1340 (22.4%)	409 (18.2%)	p<0.001
Race			p<0.001
Asian	556 (9.3 %)	154 (6.9 %)	
Black	487 (8.1 %)	75 (3.3 %)	
Other	433 (7.2 %)	130 (5.8 %)	
White	4511 (75.3%)	1886 (84.0%)	
Geographic Region			P<0.001
Asia	522 (8.7 %)	148 (6.6 %)	
Eastern Europe/Russia	1790 (29.9%)	891 (39.7%)	
Latin America	1226 (20.5%)	348 (15.5%)	
US And Canada	1138 (19.0%)	248 (11.0%)	
Western Europe/South Africa/Australasia	1311 (21.9%)	610 (27.2%)	
Randomization Setting: In-patient	1361 (22.7%)	723 (32.2%)	p<0.001
Hypertension Hx	4136 (69.1%)	1648 (73.4%)	P < 0.001
Type 2 diabetes mellitus	2431 (40.6%)	878 (39.1%)	P = 0.22
History of stroke	497 (8.3 %)	257 (11.4%)	P < 0.001
Ischemic heart failure etiology	3341 (55.8%)	1074 (47.8%)	P < 0.001
LVEF - %	26.4 ± 6.3	27.1 ± 6.1	P < 0.001
NYHA Classification			P < 0.001

Class II	3353 (56.0%)	1015 (45.2%)	
Class III	2473 (41.3%)	1143 (50.9%)	
Class IV	161 (2.7 %)	87 (3.9 %)	
SBP — mmHg	117.0 ± 15.5	115.1 ± 14.8	P < 0.001
Heart rate — beats/min	71.3 ± 11.5	75.1 ± 13.4	P < 0.001
NT-proBNP — pg/mL	1675 [812 , 3579]	2873 [1699 , 5294]	P < 0.001
Cardiac Troponin I — ng/L	25 [13 , 48]	31 [16 , 59]	P < 0.001
eGFR — mL/min/1.73m2	60.6 [45.7 , 76.1]	53.4 [40.4 , 68.1]	P < 0.001
Heart Failure Therapies			
ACEi, ARB or ARNi	5246 (87.6%)	1913 (85.2%)	P = 0.004
BB	5650 (94.4%)	2113 (94.1%)	P = 0.66
MRA	4627 (77.3%)	1770 (78.8%)	P = 0.13
Digoxin	693 (11.6%)	692 (30.8%)	P < 0.001
Cardiac Resynchronization Therapy	815 (13.6%)	343 (15.3%)	P = 0.05
Implantable Cardioverter Defibrillator	1913 (32.0%)	701 (31.2%)	P = 0.53

[0250] **Figure 21A** depicts the frequency of AFF in patients having LVEF ≤35%. AFF was observed to coincide with higher LVEF (but less than 35%).

[0251] The influence of AFF on the effectiveness of OM on the primary and secondary outcome in patients who were or were not receiving digoxin was evaluated. In one of 24 prespecified subgroups, patients with AFF (n = 2245, 27%) were older, more likely to be randomized as an inpatient, less likely to have a history of ischemic etiology or myocardial infarction, had a worse NYHA class, worse quality of life, lower eGFR, and higher NT-proBNP at baseline. AFF at baseline was associated with a modestly increased adjusted risk of cardiovascular death or heart failure events (HR 1.17, 95% CI 1.09, 1.27). Using a multivariable covariate-interaction model, the treatment effect of OM appeared to be modified by AFF (interaction p = 0.012), with patients without AFF deriving greater benefit (**Figure 21B**, top panel). As further shown in **Figure 21B**, the presence of AFF was also found to modify the treatment effect of omecamtiv mecarbil as considered for cardiovascular (CV) death (interaction p =0.002), all-cause death (interaction p < 0.001), with patients without AFF deriving greater benefit. However, as illustrated in **Figure 21E**, treatment with omecamtiv mecarbil led to a significant reduction in serious adverse events for patients having atrial fibrillation/flutter at baseline (interaction p = 0.046), with the omecamtiv mecarbil treatment arm having 55 events per 2974 patients and the placebo arm having 78 events per 3013 patients over the course of the study. The treatment effect modification by AFF was significantly more

pronounced in digoxin users than in non-users (p=0.004), with strong evidence of effect modification in digoxin users in AFF (p=0.001) and minimal evidence of effect modification in non-users (p=0.52) or digoxin users not in AFF (Figure 21B, bottom panel). In **Figure 21D**, the effect of digoxin use (digoxin or no digoxin) in tandem with omecamtiv mecarbil for patients with AFF and without AFF is shown for cardiovascular death, all-cause death and heart failure hospitalization.

[0252] Atrial fibrillation or flutter at baseline modified the treatment effect of omecamtiv mecarbil, even after multivariable adjustment, with greater benefit observed in patients not in AFF. The treatment effect modification by AFF was concentrated in patients using digoxin in AFF with minimal evidence of effect modification in non-users in AFF. Digoxin did not modify the treatment effect of omecamtiv mecarbil in patients not in AFF.

[0253] At 6 weeks, omecamtiv mecarbil PK values were similar in those taking and those not taking digoxin (median 286 vs. 280 ng/ml, p = 0.78). In patients in whom digoxin doses were known, digoxin doses were similar in both treatment arms (0.12 mg vs. 0.12mg, p = 0.85) and similar in patients with and without AFF at baseline (.12 mg vs .12 mg, p = 0.44). In patients in AFF at baseline taking omecamtiv mecarbil, there was less troponin I increase at 6 weeks in those taking digoxin (+29%, +21% to +38%) vs those not taking digoxin (+45%, +38% to 53%) (p=0.026).

[0254] **Figures 21F** and **21G** depict data from a study evaluating any drug-drug interaction between digoxin and omecamtiv mecarbil, showing PK values for digoxin.

[0255] Patients in atrial fibrillation/flutter at baseline were less likely to benefit from OM than patients without AFF, although this effect modification appeared to be driven by digoxin use in those patients, and suggests that the when considering OM, the combination of AFF and digoxin is a potential risk factor.

[0256] Among patients with EF ≤ 30%, without AFF, and without taking digoxin at baseline, OM led to significant clinical benefits and reductions in resource utilization, as presented in Table 21.

Table 21. Outcomes and resources used in the prespecified analysis population (EF ≤ 30%, no AFF, and no digoxin).

Resource Use	**OM (n=2674)**	**Pbo (n=2695)**		
Time to first HFE	18.9 / 100 pt yrs	22.7 /100 pt yrs	HR 0.85, 0.77-0.93, p<0.001	ARR 3.8 /100 pt yrs NNT 26.5
Frequency of HFE (all events)	31.2 / 100 pt yrs	38.0 / 100 pt yrs	HR 0.85, CI 0.75-0.96	ARR 6.7 / 100 pt yrs NNT 14.9
Cumulative rate of HFEs at 36 months	81.8 /100 pts	102.4 /100 pts	Rate Ratio 0.799	increasing treatment effect over time

Resource Intensity	/100 pt yrs	/100 pt yrs	
Total days in hospital	524.1	652.2	Rate Ratio 0.80, CI 0.79-0.82
IV Diuretics /Inotropes /Vasodilators	35.7	42.3	Rate Ratio 0.84, CI 0.79-0.90
Mechanical circulatory support during HF hospitalizations	2.2	2.4	n/a
Mechanical fluid removal during HF hospitalizations	0.8	0.9	n/a

ARR= absolute risk reduction. CI= 95% confidence interval. HFE= heart failure event. NNT=number needed to treat. OM= omecamtiv mecarbil + standard care. Pbo= placebo + standard care.

Effect of OM by baseline Systolic Blood Pressure (SBP)

[0257] Systolic blood pressure (SBP) is a major predictor of outcomes in patients with heart failure and reduced ejection fraction (HFrEF). Omecamtiv mecarbil directly improves cardiac function and reduced the primary composite endpoint of an episode of worsening HF (urgent clinic visit, emergency department visit, or hospitalization) or cardiovascular death in the Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure trial (GALACTIC-HF). This trial provided data on the efficacy and tolerability of omecamtiv mecarbil according to baseline SBP values. In contrast to other HFrEF therapies, which may not be tolerated in patients with low baseline blood pressure (*e.g.*, <100 mmHg), the present study was able to enroll patients with SBP at baseline of 85 mmHg or greater.

Results

[0258] The 8232 randomized patients were subdivided according to SBP at baseline: <100 mmHg (n = 1473), 101-110 mmHg (n = 1734), 111-120 mmHg (n = 1824), 121-130 mmHg (n = 1627), and >130 mmHg (n = 1574). Significant differences between these subgroups were found with respect of multiple baseline characteristics. The primary composite endpoint occurred in 715 (48.5%), 682 (39.3%), 679 (37.2%), 556 (34.2%), and 498 (31.6%) patients in each SBP subgroup, respectively. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the treatment effect on the primary outcome were of 0.81, 0.70-0.94; 0.88, 0.76-1.03; 1.03, 0.88-1.19; 0.87, 0.73-1.03; and 1.07, 0.90-1.28 in each SBP subgroup, respectively. When examined as a continuous variable, baseline SBP had a linear inverse relation with the primary event rate and a linear direct relation with the treatment effect (**Figures 23A** and **23B**). No significant change in SBP and no difference in adverse events with omecamtiv mecarbil, compared with placebo, occurred during follow-up in each subgroup.

[0259] Omecamtiv mecarbil did not change SBP from baseline and was well tolerated independently from SBP at baseline, including in patients having low baseline blood pressure (<100 mmHg) for whom the use of other HFrEF therapies cannot be tolerated or may be associated with the added cost of increased averse events or worsening renal function. Omecamtiv mecarbil tended to have a larger effect on the primary outcome, compared with placebo, in the patients with lower SBP at baseline (≤100 mmHg).

Effect of food

[0260] Administration of OM with a high-fat, high-calorie meal in healthy subjects had no clinically significant effect on its systemic exposure.

Distribution

[0261] OM was observed to be moderately bound to plasma proteins (81.5%) and the protein binding was independent of drug concentration up to 4000 ng/mL. After a single 35 mg dose of radiolabeled OM to healthy subjects, the blood to plasma ratio of total radioactivity was approximately 0.4, indicating that radioactivity did not disproportionately partition into blood components. The volume of distribution at steady state was approximately 4.8-6.6 L/kg.

Elimination

[0262] Clearance of OM after oral administration was primarily through metabolism in the liver. The total systemic clearance was found to be 11.7 L/hr with mean renal clearance of 1 L/hr, accounting for less than 10% of the systemic clearance. The median half-life of OM was found to be approximately 23-32 hours in patients with heart failure. OM was observed to be extensively metabolized in the liver by multiple metabolic pathways, including CYP3A4 and CYP2D6. Following oral administration of radiolabeled OM to healthy subjects, approximately 49% of the dose was excreted in urine (primarily as metabolites with 8% of parent compound recovered) and 38% in feces (primarily as unchanged drug).

Patients with Hepatic Impairment

[0263] The pharmacokinetics of a single dose of OM 25 mg were evaluated in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. The pharmacokinetics (Cmax and AUC) of OM in patients with mild or moderate hepatic impairment were similar to those in patients with normal hepatic function.

Drug Interactions--Effects of Other Drugs on the Pharmacokinetics of OM

[0264] OM was found to be metabolized in vitro by multiple CYP enzymes including CYP3A4 and CYP2D6 and is a substrate of P-gp and BCRP. OM may be administered with drugs that are inhibitors or inducers of CYP3A4, CYP2D6, P-gp or BCRP. The effect of co-administered drugs on OM plasma exposures is presented in Table 22.

Table 22: Change in OM Pharmacokinetics in the Presence of Co-administered Drugs

Co-administered Drug	Dose of Co-administered Drug	OM Dose	N	% Change and Mean Ratio of OM Pharmacokinetic Parameters (90% CI)[a]	
				Cmax	AUC
P-gp Inhibitor: Amiodarone	600 mg SD	50 mg SD	14	↔ 1.08 (0.96-1.22)	↑ 21% 1.21 (1.08-1.36)
Moderate CYP3A Inhibitor: Diltiazem	240 mg QD X 8 days	10 mg SD	8	↓ 21% 0.79 (0.60-1.04)	↔ 1.08 (0.97-1.22)
Strong CYP3A and P-gp Inhibitor: Ketoconazole	200 mg BID X 8 days	10 mg SD	8	↔ 1.03 (0.76-1.40)	↑ 51% 1.51 (1.20-1.91)
CYP2D6 Genotype: PM versus EM[b]	NA	NA	8, 16[b]	↓ 18% 0.82 (0.63-1.07)	↑ 30% 1.30 (0.93-1.82)
pH Modifying Agent: Omeprazole	40 mg QD X 6 days	50 mg SD	12	↔ 1.01 (0.95-1.07)	↔ 0.95 (0.82-1.09)

↔ = no change; ↑ =increase; ↓=decrease; CI: Confidence Interval; NA: not applicable; SD: single dose

[a] Ratios for Cmax and AUC compare co-administration of the drug with OM versus administration of OM alone.

[b] PM (N=8): poor CYP2D6 metabolizer; EM (N=16): extensive CYP2D6 metabolizer.

CYP2D6 metabolic genotype had no clinically relevant effect on the pharmacokinetics of OM, indicating that inhibitors of CYP2D6 have no clinically relevant effect on OM exposures.

Drug Interactions--Effects of OM on the Pharmacokinetics of Other Drugs

[0265] In vitro, OM was found to be an inhibitor of P-gp, BCRP, MATE1, MATE 2-K, CYP2C8 and an inducer of CYP3A4. Clinical studies and the results of physiologically based pharmacokinetic modeling indicate that OM is a weak inhibitor of CYP2C8 and BCRP, and a weak inducer of CYP3A4. OM may be administered with drugs that are substrates of CYP3A4, CYP2C8, P-gp or BCRP. A summary of results from clinical studies is provided in Table 23.

Table 23: Change in Pharmacokinetics Co-administered Drugs in the Presence of OM

Co-administered Drug	Dose of Co-administered Drug	OM Dose	N	% Change and Mean Ratio of Co-administered Drug Pharmacokinetic Parameters (90% CI)[a]	
				Cmax	AUC
Sensitive CYP3A Substrate: Midazolam	5 mg SD	25 mg BID	14	↓ 10% 0.90 (0.75-1.08)	↓ 18% 0.82 (0.71-0.94)

Co-administered Drug	Dose of Co-administered Drug	OM Dose	N	% Change and Mean Ratio of Co-administered Drug Pharmacokinetic Parameters (90% CI)[a]	
				Cmax	AUC
Sensitive P-gp Substrate: Digoxin	0.5 mg SD	50 mg SD	15	↑ 8% 1.08 (0.92-1.26)	↔ 1.06 (0.99-1.14)
Sensitive BCRP Substrate: Rosuvastatin	10 mg SD	50 mg SD	14	↑ 45% 1.54 (1.33-1.79)	↑ 27% 1.27 (1.14-1.42)
Sensitive MATE 1/ 2K Substrate Metformin	850 mg SD	25 mg BID	14	↔ 1.10 (1.01-1.21)	↔ 0.99 (0.92-1.05)

↔ = no change; ↑ =increase; ↓=decrease; BID = twice daily; CI: Confidence Interval; NA: not applicable; SD: single dose

[a] Ratios for Cmax and AUC compare co-administration of the drug with OM versus administration of OM alone.

[0266] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[0267] The use of the terms "a" and "an" and "the" and "at least one" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The use of the term "at least one" followed by a list of one or more items (for example, "at least one of A and B") is to be construed to mean one item selected from the listed items (A or B) or any combination of two or more of the listed items (A and B), unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (for example, "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

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What is Claimed:

1. A method of treating heart failure in a patient having a left ventricular ejection fraction (LVEF) of less than 35% comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

2. The method of claim 1, wherein the patient has a LVEF of less than 30%.

3. The method of claim 1, wherein the patient has a LVEF of less than 28%.

4. The method of claim 1, wherein the patient has a LVEF of less than 25%.

5. The method of claim 1, wherein the patient has a LVEF of less than 22%.

6. A method of treating heart failure in a patient who does not exhibit atrial fibrillation or atrial flutter comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

7. The method of claim 6, wherein the patient has a LVEF of less than 35%.

8. The method of claim 6, wherein the patient has a LVEF of less than 30%.

9. The method of claim 6, wherein the patient has a LVEF of less than 28%.

10. The method of claim 6, wherein the patient has a LVEF of less than 25%.

11. The method of claim 6, wherein the patient has a LVEF of less than 22%.

12. A method of treating heart failure in a patient having heart failure classified as Class III or IV as determined using the New York Heart Association (NYHA) classification comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

13. A method of treating heart failure in a patient having advanced heart failure comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

14. The method of claim 13, wherein the patient has heart failure classified as Class III or IV as determined using the New York Heart Association (NYHA) classification.

15. The method of claim 13 or 14, wherein the patient has a LVEF of less than 30%.

16. The method of any one of claims 13-15, wherein the patient has had at least one heart failure hospitalization within 6 months prior to the treatment.

17. The method of any one of claims 13-16, wherein the patient does not exhibit atrial fibrillation or atrial flutter.

18. A method of treating ischemic heart failure in a patient comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

19. A method of treating heart failure in a patient who has had a myocardial infarction comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

20. A method of treating heart failure in a patient who has a pretreatment level of NT-proBNP of at least 2,000 pg/mL comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

21. The method of claim 20, wherein the patient has a LVEF of less than 35%.

22. The method of claim 20, wherein the patient has a LVEF of less than 30%.

23. The method of claim 20, wherein the patient has a LVEF of less than 28%.

24. The method of claim 20, wherein the patient has a LVEF of less than 25%.

25. The method of claim 20, wherein the patient has a LVEF of less than 22%.

26. The method of any one of claims 20-25, wherein the patient does not exhibit atrial fibrillation or atrial flutter.

27. A method of treating heart failure in a patient who has low blood pressure, symptomatic hypotension, impaired renal function, or bradycardia comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

28. The method of claim 27, wherein the patient has not previously been treated with one or more of an angiotensin-converting enzyme inhibitor, an angiotensin II receptor blocker, a beta blocker, a diuretic, an aldosterone antagonist, an inotrope, neprilysin inhibitors, digitalis, and digoxin.

29. A method of treating heart failure in a patient who is unable to tolerate one or more of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, diuretics, aldosterone

antagonists, inotropes, neprilysin inhibitors, digitalis, and digoxin comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

30. The method of claim 29, wherein the patient has low blood pressure, symptomatic hypotension, impaired renal function, or bradycardia.

31. A method of preventing stroke in a patient suffering from heart failure with reduced ejection fraction (HFrEF) comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

32. The method of claim 31, wherein the stroke is non-fatal.

33. The method of claim 31, wherein the stroke is fatal.

34. The method of any one of claim 31 to 33, wherein the stroke is ischemic.

35. The method of any one of claim 31 to 33, wherein the stroke is ischemic with hemorrhagic transformation.

36. The method of any one of claim 31 to 33, wherein the stroke is hemorrhagic.

37. A method of reducing the risk of heart failure events or death from cardiovascular causes in a heart failure patient comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof.

38. The method of claim 37, wherein the method reduces the risk of heart failure events in the patient.

39. The method of claim 37 or 38, wherein the patient has chronic heart failure with reduced ejection fraction.

40. The method of any one of claims 37-39, wherein the heart failure events are an urgent clinic visit, emergency department visit or hospitalization for worsening heart failure leading to treatment intensification beyond changed oral diuretic therapy.

41. The method of any one of claims 37-40, wherein the patient has a LVEF of less than 30%.

42. The method of any one of claims 37-40, wherein the patient has a LVEF of less than 28%.

43. The method of any one of claims 37-40, wherein the patient has a LVEF of less than 25%.

44. The method of any one of claims 37-40, wherein the patient has a LVEF of less than 22%.

45. The method of any one of claims 37-44, wherein the patient does not exhibit atrial fibrillation or atrial flutter.

46. The method of any one of claims 37-45, wherein the patient has advanced heart failure.

47. The method of any one of claims 37-46, wherein the patient has heart failure classified as Class III or IV as determined using the New York Heart Association (NYHA) classification.

48. The method of any one of claims 37-47, wherein the patient has had at least one heart failure hospitalization within 6 months prior to the treatment.

49. The method of any one of claims 1-48, wherein the patient is an inpatient.

50. The method of any one of claims 1-48, wherein the patient is an outpatient.

51. The method of any one of claims 1-50, wherein omecamtiv mecarbil is administered orally.

52. The method of claim 51, wherein omecamtiv mecarbil is administered as a tablet.

53. The method of any one of claims 1-52, comprising administering to the patient a therapeutically effective amount of omecamtiv mecarbil dihydrochloride hydrate.

54. The method of any one of claims 1-53, wherein omecamtiv mecarbil, or a hydrate, a salt, or a salt of a hydrate thereof is administered as a modified release matrix tablet.

55. The method of any one of claims 1-54, wherein omecamtiv mecarbil is administered twice daily.

56. The method of claim 55, wherein omecamtiv mecarbil is administered in a dosage of 25 mg twice daily.

57. The method of claim 55, wherein omecamtiv mecarbil is administered in a dosage of 37.5 mg twice daily.

58. The method of claim 55, wherein omecamtiv mecarbil is administered in a dosage of 50 mg twice daily.

59. The method of any one of claims 1-58, wherein the patient has undergone cardiac resynchronization therapy (CRT) prior to treatment.

60. The method of any one of claims 1-59, wherein the patient has an implantable cardioverter defibrillator (ICD) device.

61. The method of any one of claims 1-60, further comprising administering to the patient a therapeutically effective amount of an angiotensin-converting enzyme inhibitor.

62. The method of any one of claims 1-61, further comprising administering to the patient a therapeutically effective amount of a mineralocorticoid receptor antagonist.