CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

BRIEFING DOCUMENT

Omecamtiv Mecarbil
for
Chronic Heart Failure

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350 Oyster Point Boulevard
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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACEi	Angiotensin converting enzyme inhibitor
AE	Adverse event
AFF	Atrial fibrillation/flutter
ARB	Angiotensin receptor blocker
ARNi	Angiotensin receptor/neprilysin inhibitor
ARR	Absolute risk reduction
BID	Bis en die, twice daily
CI	Confidence interval
CK-MB	Creatine kinase-MB
C_{max}	Maximum plasma concentration
CO	Cardiac output
$C_{predose}$	Predose plasma concentration
CRT	Cardiac resynchronization therapy
CV	Cardiovascular
CYP	Cytochrome P450
dP/dt	Rate of pressure development
EC_{50}	Half maximal effective concentration
ECG	Electrocardiogram
ED	Emergency department
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
FS	Fractional shortening
GCP	Good Clinical Practice
GDMT	Guideline-directed medical therapy
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
ICD	Implantable cardioverter defibrillator
IP	Investigational product
IV	Intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire

Abbreviation	Definition
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
LS	Least squares
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic diameter
MCIE	Major cardiac ischemic events
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PK	Pharmacokinetic(s)
PD	Pharmacodynamic(s)
QTcF	QT interval corrected using Fridericia's formula
RRR	Relative risk reduction
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SET	Systolic ejection time
SGLT2	Sodium glucose cotransporter-2
SOC	System organ class
SV	Stroke volume
TSS	Total Symptom Score
US	United States

EXECUTIVE SUMMARY

Cytokinetics is seeking approval of omecamtiv mecarbil for the treatment of symptomatic chronic heart failure (HF) with reduced ejection fraction in patients with persistent or clinically worsening HF in whom the benefit of treatment is most evident, particularly in those patients with lower baseline left ventricular ejection fraction (LVEF). Oral dosing is individualized and guided by plasma concentrations of omecamtiv mecarbil to achieve a therapeutic range of 200 to 750 ng/mL. Cytokinetics recommends that the labelled indication reflect the patient population in which the benefit was observed to be highest, specifically in those patients with lower ejection fraction (EF) who, despite guideline directed medical therapy, continue to have persistent or worsening chronic HF.

At the time the research program for omecamtiv mecarbil was initiated over twenty years ago, patients with heart failure with reduced ejection fraction (HFrEF) had effective therapies (angiotensin converting enzyme inhibitors [ACEi], β-adrenergic blockers, and mineralocorticoid receptor antagonists [MRA]); however, the incidence of persistent HF and risk of clinical deterioration remained unacceptably high. Thus, new options were needed to further reduce the risk of HF related events especially for patients not adequately responding to best medical therapy. Unfortunately, this statement remains true today despite newer HF therapies such as angiotensin receptor/neprilysin inhibitors (ARNi) and sodium glucose cotransporter-2 (SGLT2) inhibitors.

Omecamtiv mecarbil is a first-in-class cardiac myosin activator that was designed to increase cardiac function without adverse effects on heart rate, blood pressure, cardiac rhythm, or renal function. It is the product of a drug discovery effort started over 20 years ago based on advanced biochemical and biophysical insights anchored to the central hypothesis that cardiac dysfunction is causal to heart failure. The extensive clinical development program for omecamtiv mecarbil has spanned 15 years, 33 clinical trials, and over 10,000 participants, culminating in the Phase 3 cardiovascular outcomes trial, Study 20110203 (GALACTIC-HF). Table 1 summarizes the more important trials in Phase 1 and 2 that were critical to understanding the exposure-response relationship and the safety of omecamtiv mecarbil, first in healthy participants, and then subsequently in patients with both acute and chronic HF. In total, these clinical trials provide strong mechanistic data consistent with the original therapeutic hypothesis that omecamtiv mecarbil improves cardiac function, decreases cardiac volumes, and reduces heart rate and N-terminal pro-B-type natriuretic peptide (NT-proBNP), all without adversely affecting blood pressure or renal function. The favorable effects of omecamtiv mecarbil on cardiac function, structure and biomarkers in the Phase 2 Study 20110151 (COSMIC-HF) supported the hypothesis that omecamtiv mecarbil could improve long-term HF outcomes in HFrEF patients, leading to the conduct of GALACTIC-HF, the Phase 3 clinical outcomes trial.

Table 1: Key Phase 1 and Phase 2 Clinical Trials in Development Program

Study No.	N	Form	Trial Objectives	Results
Healthy Participants (CY 1111)	34	IV	Safety and tolerability; PK/ PD	PK: Linear, Dose Proportional Echo: Dose and concentration dependent increases in cardiac function Safety: Well-tolerated up to MTD
Stable Heart Failure (CY 1121)	45	IV	Safety and tolerability; PK/ PD	PK: Linear, Dose Proportional Echo: Dose and concentration dependent increases in cardiac function Safety: Well-tolerated up to MTD
Acute Heart Failure (Study 20100754; ATOMIC-AHF)	613	IV	Safety and tolerability; PK/ PD	Well-tolerated in inpatients with acute heart failure
Stable Heart Failure (Study 20110151; COSMIC-HF)	544	Oral	Safety and tolerability; PK/ PD	PK: Consistent exposure over 20 weeks Echo: Sustained improvements in cardiac function over 20 weeks of dosing Safety: Well-tolerated in outpatients with HFrEF

GALACTIC-HF was designed with extensive regulatory input to be a single pivotal Phase 3 clinical trial intended to support the registration of omecamtiv mecarbil for the treatment of patients with chronic HFrEF. Over 8,000 participants were enrolled in this randomized, double blind, placebo-controlled trial from both inpatient and outpatient settings from 35 countries and over 900 clinical sites making it the second largest trial of patients with HFrEF ever conducted. In GALACTIC-HF, omecamtiv mecarbil, when added to standard of care, reduced the rate of the primary composite endpoint of time to the first HF event or cardiovascular death by 8% relative to placebo, a result that was statistically significant (p = 0.025) and robust to sensitivity analyses (Table 2). There was no observed effect, either positive or negative, on cardiovascular mortality. The adverse event (AE) profile of omecamtiv mecarbil was similar to that of the placebo comparator with respect to incidence, severity, and seriousness.

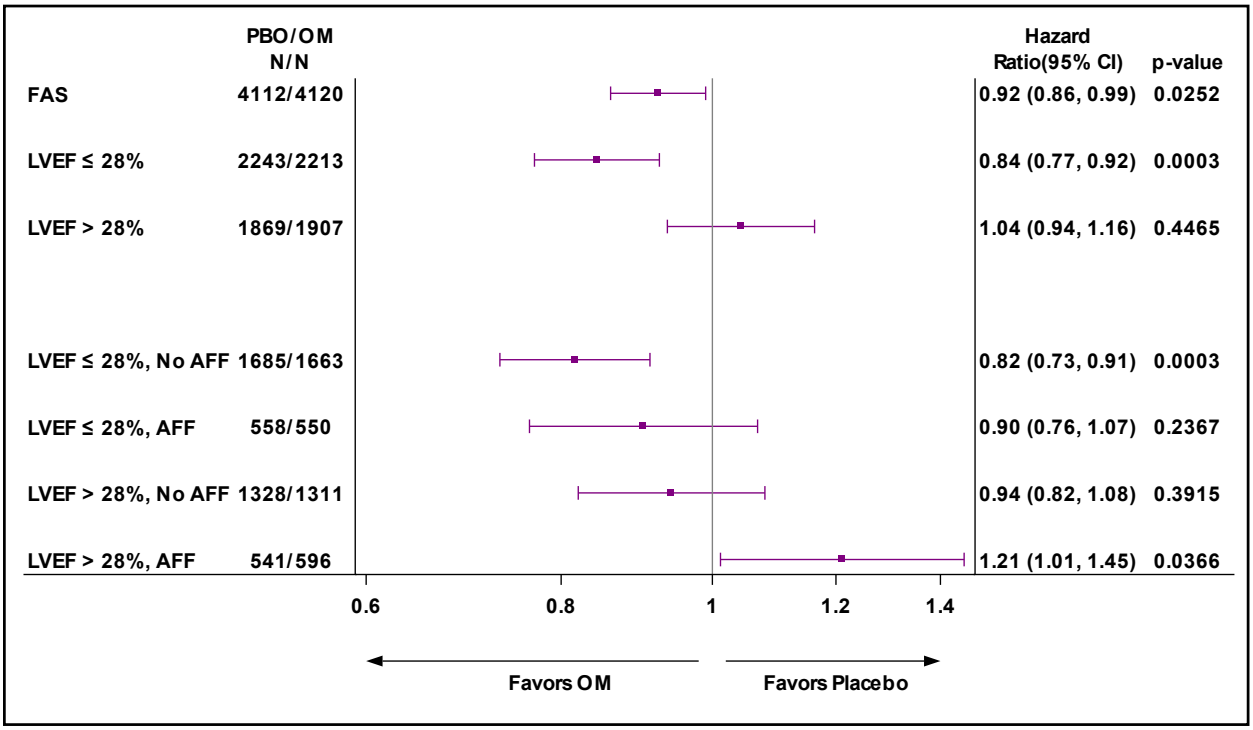
Table 2: Primary Endpoint and Additional Sensitivity Analyses

Clinical Outcomes	HR (95% CI) p value
Prespecified Analysis[a] of the Primary Composite Endpoint	0.92 (0.86, 0.99); p=0.025
Adjusting for Significant Pre-Specified Baseline Covariates	0.91 (0.85, 0.97); p=0.008
On Treatment, Primary Analysis Model[a]	0.90 (0.84, 0.97); p=0.007
Patients Receiving Highest Dose (50 mg), Primary Analysis Model[a]	0.87 (0.80, 0.96); p=0.003
Patients Receiving Highest Dose (50 mg), Adjusting for Significant Prespecified Baseline Covariates	0.89 (0.81, 0.97); p=0.009
Patients in the Therapeutic Range (200 - <750 ng/mL), Adjusting for Significant Prespecified Baseline Covariates	0.86 (0.79, 0.93); p <0.001
Using Investigator Reported Events, Primary Analysis Model[a]	0.93 (0.87, 0.99); p=0.03
Time to first cardiovascular death, HF event, myocardial infarction, hospitalization for unstable angina, coronary revascularization, or stroke	0.92 (0.86, 0.98); p=0.013

[a] Cox model stratified by randomization setting (inpatient or outpatient) and region and including terms for baseline eGFR and treatment group.

Prespecified subgroup analyses of GALACTIC-HF showed that LVEF at baseline was the strongest predictor of benefit for omecamtiv mecarbil (univariate interaction p-value = 0.003). This finding is also the most biologically plausible, given the mechanism of action of omecamtiv mecarbil which directly increases myocardial contractility and improves cardiac function. Participants with lower baseline LVEF were at higher risk and benefited more from omecamtiv mecarbil; there was a 16% reduction in the hazard rate and a 5.1% absolute risk reduction (ARR) in the primary composite endpoint ($p < 0.001$) for participants whose LVEF was below or equal to the median (28%) in the trial (Figure 1). The treatment interaction was statistically robust; a global test for heterogeneity of treatment effect across all the prespecified subgroups was highly statistically significant ($p = 0.008$) and in the multivariate analysis, LVEF emerged as the most significant treatment-by-covariate interaction term ($p = 0.005$). The presence of atrial fibrillation/flutter (AFF) also showed a highly statistically significant interaction in the multivariate analysis ($p = 0.006$) with a lack of benefit observed overall in participants with AFF. However, in participants with LVEF ≤ 28% at baseline, the point estimates for the treatment benefit of omecamtiv mecarbil were less than 1.0 in both the presence and absence of AFF (Figure 1).

Figure 1: Treatment Effects of Omecamtiv Mecarbil by LVEF and LVEF/AFF



The effects of omecamtiv mecarbil were also greater in participants with other higher risk features, such as lower blood pressure, higher NT-proBNP, worse New York Heart Association (NYHA) Class, or more recent HF hospitalization, without meaningful changes to its safety profile. In consideration of the unique profile of omecamtiv mecarbil, namely its increased effectiveness in higher risk participants as well as its lack of adverse hemodynamic or renal effects, Cytokinetics recommends that the labelled indication also reflect the patient population in which the benefit is greatest, specifically in patients with lower ejection fraction who, despite best tolerated guideline directed therapy, continue to have persistent or worsening chronic HF.

Pharmacokinetic-guided Dosing

Pharmacokinetic (PK) guided dosing was used in GALACTIC-HF as an intentionally conservative approach aimed to maximize the proportion of participants achieving therapeutic concentrations of omecamtiv mecarbil (200 to 750 ng/mL) while avoiding levels exceeding 1,200 ng/mL, a concentration which had been identified in early studies to be associated with a risk of acute myocardial ischemia or myocardial infarction (MI) in a few participants, likely due to an excess of the intended pharmacologic effect.

The PK-guided dose-selection strategy in GALACTIC-HF that was used to achieve therapeutic plasma concentrations of omecamtiv mecarbil was designed to do so by selecting the target dose in a single step, using a single PK sample collected after two weeks of dosing. Dosing was initiated at 25 mg twice daily (BID) with escalation directly to either 37.5 mg BID or 50 mg BID at Week 4 based on the plasma concentration of omecamtiv mecarbil at 2 weeks.

While there may be a potential advantage to this single titration approach that was used in GALACTIC-HF, Cytokinetics now believes that a simpler, sequential dose titration strategy, targeting the same plasma concentration range, will be more reliably implemented and equally safe and effective and recommends its description in labelling and its use after approval.

In sequential dose titration, omecamtiv mecarbil is started at 25 mg BID and increased to 37.5 mg BID only if the plasma concentration of omecamtiv mecarbil is < 300 ng/mL after 2 weeks of treatment. After 2 more weeks of treatment, the plasma concentration of omecamtiv mecarbil should be checked again and the dose increased to 50 mg BID if the plasma concentration of omecamtiv mecarbil remains < 300 ng/mL. If at any time, the omecamtiv mecarbil concentration is > 750 ng/mL, dose adjustment to the next lowest level should be implemented (Table 3).

Table 3: Omecamtiv Mecarbil Dose Selection

If plasma concentration is:	Adjust to:
< 300 ng/mL	Increase to next higher dose.
300-750 ng/mL	No change in dose.
> 750 ng/mL	Decrease to next lower dose.[a]

[a] If > 750 ng/mL on starting dose of 25 mg BID, then 25 mg QD may be appropriate.

This stepwise dose titration scheme to a target drug concentration range based on periodic testing will be familiar to cardiologists and other healthcare providers who commonly adjust medications based on blood tests (eg, warfarin, cholesterol lowering medications, renin angiotensin-aldosterone system [RAAS] blockers, digoxin) or physiological parameters (eg, blood pressure with antihypertensive medications, heart rate with beta blockers), and should not represent a significant barrier to achieving the appropriate dose.

Cytokinetics has established a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) assay, the benchmark standard methodology for measurement of small molecule drugs, in a large centralized national reference laboratory that is compliant with the latest guidance documents for the analysis of therapeutic drugs as outlined in CLSI C62, FDA Bioanalytical GLP guidance and the central laboratory's validation guidance criteria for quantitative methods (incorporating multiple CLSI guidance documents). This assay,

implemented as a laboratory test, will be widely available at the time of approval and performed in the same manner as other therapeutic drug monitoring assays used routinely in clinical practice.

Regulatory Framework

FDA bases its approval decisions, in part, on whether the data included in a new drug application provide substantial evidence of effectiveness (Food, Drug & Cosmetic Act section 505(d)). Generally, two adequate and well-controlled clinical trials are required to demonstrate substantial evidence of effectiveness; however, in December 2019, FDA issued a draft guidance (FDA 2019a), "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products," to describe other means of demonstrating substantial evidence of effectiveness. Although FDA's evidentiary standards have not changed, the guidance provides scenarios by which one adequate and well-controlled study plus confirmatory evidence may be used to establish substantial evidence of effectiveness. Factors FDA will consider when determining whether reliance on a single adequate and well-controlled clinical investigation plus confirmatory evidence is an appropriate basis for approval may include the seriousness of the disease, the existence of an unmet medical need, the persuasiveness of the single trial, and the robustness of the confirmatory evidence.

Despite the availability and utilization of a broad range of therapeutics, HFrEF is a serious disease, and with its substantial morbidity and mortality, there is clearly an unmet need for new therapies, as described above. FDA's guidance describes several features of a trial that may increase its persuasiveness, and GALACTIC-HF includes these characteristics. GALACTIC-HF was a large, multinational trial; in fact, it was the second largest HF trial ever conducted, enrolling 8256 participants from 35 countries, and it included the largest number of North American participants of any recent global HF trial. With broad entrance criteria, the study enrolled patients with a range of demographic characteristics, disease severities, and concomitant therapies, ensuring that the study results would be generalizable to the US HFrEF population. Study retention was excellent with only one patient lost to follow-up for vital status. No single trial site or geographic region drove the overall result. Results in North America were generally similar to the results in the overall trial. Multiple procedures were in place to ensure trial quality (eg, extensive use of site audits and risk-based monitoring). According to FDA guidance, use of a meaningful, objective endpoint is another characteristic that supports the persuasiveness of a single trial. In GALACTIC-HF, the primary endpoint was a composite of time to first cardiovascular death or HF event. These events were rigorously adjudicated by a central events committee and are clinically meaningful.

Omecamtiv mecarbil, when added to standard of care, reduced the rate of the primary composite endpoint by 8% relative to placebo; a result that was statistically significant ($p = 0.025$) and robust to numerous sensitivity analyses. The treatment effect observed in GALACTIC-HF was driven by HF events, with a neutral effect on mortality. Such HF events, including hospitalizations, are clinically meaningful, and not infrequently life-changing, resulting in loss of strength, mobility, and independence that can lead to severe or irreversible morbidity.

FDA recently recognized the importance of non-fatal HF events in its June 2019 draft guidance "Treatment for Heart Failure: Endpoints for Drug Development" (FDA 2019b). The guidance emphasizes the importance of endpoints that demonstrate a reduction in morbidity for regulatory

decision making, and clarified that demonstration of a mortality benefit is not a prerequisite for the approval of drugs for HF. In this guidance, the FDA recognizes heart failure hospitalization as a meaningful clinical endpoint and also clarifies the acceptance of outpatient interventions as a measure of clinically important worsening symptoms:

> "As heart failure treatment moves away from the inpatient setting, FDA will consider alternative endpoints that reflect clinically important worsening symptoms leading to an intervention (e.g., treatment in an emergency department, a same-day access clinic, or an infusion center) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic."

In keeping with FDA's 2019 guidance "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products," the evidentiary standard for approval can be met with one adequate and well-controlled clinical investigation plus confirmatory evidence. One example described in the guidance is "one adequate and well-controlled clinical investigation supported by data that provide strong mechanistic support." Mechanistic support can be provided by well-understood pharmacodynamic (PD) endpoints that, by themselves, are not accepted endpoints to establish substantial evidence of effectiveness.

Omecamtiv mecarbil is a cardiac myosin activator that was developed to improve cardiac function. The drug has demonstrated improvements in cardiac function as measured by echocardiography in nonclinical models (Malik 2011), healthy humans (Teerlink 2011) and patients with HFrEF (Cleland 2011) using intravenous infusions up to 72 hours (Section 2.1, Section 3.1, Section 3.2). The Phase 2 trial, COSMIC-HF, studied chronic oral dosing with omecamtiv mecarbil for 20 weeks in 448 participants with HFrEF. As was observed with the intravenous studies, there were statistically significant improvements in all prespecified echocardiographic endpoints, indicative of improved cardiac function and structure. These parameters included systolic ejection time (SET), stroke volume (SV), left ventricular end-systolic diameter, and left ventricular end-diastolic diameter. Additionally, statistically significant improvements in exploratory endpoints such as left ventricular fractional shortening, left ventricular end-systolic volume, and cardiac output were also observed. Both heart rate and NT-proBNP decreased, each considered a favorable pharmacodynamic effect in heart failure. These are well-understood and widely accepted PD endpoints that provide strong mechanistic support as confirmatory evidence. The biological plausibility that an improvement in cardiac function results in an improvement in clinical outcomes is further strengthened if one considers that device-based cardiac resynchronization therapy, the only other chronic intervention known to directly improve cardiac function and structure, reduces the risk of death and non-fatal heart failure events (Moss 2009, Bristow 2004).

In summary, GALACTIC-HF is a large, global, high-quality clinical trial that met its prospectively-defined primary efficacy endpoint with a p-value of 0.025. The trial has the features of a single trial that could provide substantial evidence of effectiveness as the basis for a single-trial approval. The overall effect size was modest but the prespecified subgroup of LVEF had the most statistically significant interaction effect in both univariate and multivariate analyses and is a biologically plausible modifier of the treatment effect in patients with reduced cardiac function given the mechanism of action of omecamtiv mecarbil. COSMIC-HF, another adequate and well-controlled trial, provides strong mechanistic support for the clinical effect observed in GALACTIC-HF. This mechanistic support constitutes confirmatory evidence that,

together with the results of GALACTIC-HF, clearly provide substantial evidence of effectiveness for omecamtiv mecarbil for the treatment of HFrEF. With implementation of the planned dosing paradigm and judicious monitoring, the safety profile is acceptable; of note, much of the toxicities known to occur with other heart failure therapies (eg, hypotension, hyperkalemia, renal dysfunction) are not found with omecamtiv mecarbil.

Altogether, the totality of the data evaluated for concordance with the guidance indicates persuasiveness of the results demonstrating substantial evidence of effectiveness. Thus, Cytokinetics believes the NDA provides substantial evidence of effectiveness for omecamtiv mecarbil, and the benefit-risk profile is positive, such that the evidentiary standard has been met for the approval of omecamtiv mecarbil as a treatment of HFrEF.

Summary

The objective of this Advisory Committee meeting is to discuss the totality of evidence supporting the effectiveness and safety of omecamtiv mecarbil, the characteristics of the patients in whom the benefit-risk profile is acceptable, and the dosing of omecamtiv mecarbil as guided by its plasma concentrations.

This briefing document summarizes the key efficacy and safety data for omecamtiv mecarbil in support of the proposed indication, posology, and indicated patient population as below:

> *Omecamtiv mecarbil is a cardiac myosin activator indicated to reduce the risk of cardiovascular death and heart failure events in patients with symptomatic chronic heart failure with reduced ejection fraction. Benefits are increasingly evident the lower the left ventricular ejection fraction.*

Cytokinetics recommends that the labelled indication reflect the patient population in which the benefits of omecamtiv mecarbil have been observed to be greatest, specifically in those patients with lower EF who, despite guideline directed medical therapy, continue to have persistent or worsening chronic HF.

1. HEART FAILURE WITH REDUCED EJECTION FRACTION

1.1. Disease Background

Heart failure (HF) is a serious, chronic, progressive condition due to reduced or inadequate cardiac output and/or elevated intracardiac pressures with an inability to adequately perfuse organ systems throughout the body. Patients with heart failure with reduced ejection fraction (HFrEF) often exhibit a collection of signs (eg, edema, gallop, rales) and symptoms (eg, dyspnea, fatigue, exertional intolerance) that have a significant negative impact on their quality of life and sense of well-being. HF impacts approximately 64 million people worldwide (James 2018). In developed countries, approximately 1% to 2% of the adult population has HF, with the prevalence rising to > 10% among those 70 years of age or older (McDonagh 2021; Groenewegen 2020). In the United States (US) alone, an estimated 6.2 million people ≥ 20 years of age have HF, and the prevalence is predicted to increase by 46% by 2030 (Virani 2021). HF is the leading cause of hospitalizations in patients >65 years and accounts for 1–2% of all hospitalizations in the Western world (Savarese 2022). The American Heart Association reported patients with HF accounted for 3,267,000 office physician visits, 1,404,000 emergency room visits, and 1,250,000 hospitalizations with a primary diagnosis of HF in 2018, underscoring the need for better implementation of current therapies (Tsao 2022) as well as the need for new therapeutic options.

Approximately 50% of all HF cases are HFrEF (McDonagh 2021; Savarese 2017), which means that 32 million patients worldwide have HFrEF at present, based on current global prevalence estimates. HFrEF is a chronic, progressive condition characterized by impaired cardiac contractility. The signs and symptoms of HF are categorized according to the American College of Cardiology Foundation/American Heart Association Stages of HF and the New York Heart Association (NYHA) Functional Classification (Yancy 2013). The natural history of HFrEF is punctuated by frequent recurrent hospitalizations and, not infrequently, a cardiovascular (CV) death.

1.2. Classification of Heart Failure

In 2022, the American College of Cardiology, the American Heart Association, and the Heart Failure Society of America published a comprehensive guideline for the management of HF (Heidenreich 2022). It provides for a classification of HF based on left ventricular ejection fraction (LVEF) with HFrEF defined as those patients with LVEF ≤ 40%. It also includes a classification of HF into four stages (Figure 2 and Figure 3) as well as describing the trajectory of patients with Type C HF into those with (1) new onset or de novo HF, (2) resolution of symptoms, (3) persistent HF, and (4) worsening HF. Based on this framework, GALACTIC-HF enrolled HFrEF patients in Stage C with persistent or worsening HF and those in Stage D.

Figure 2: Stages of Heart Failure

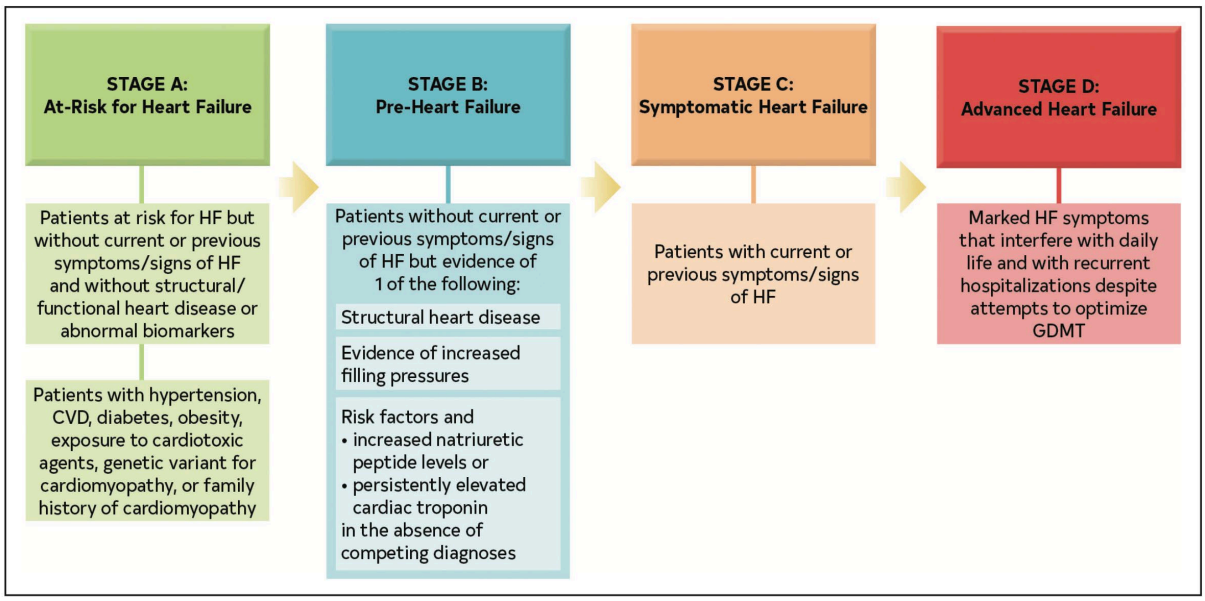
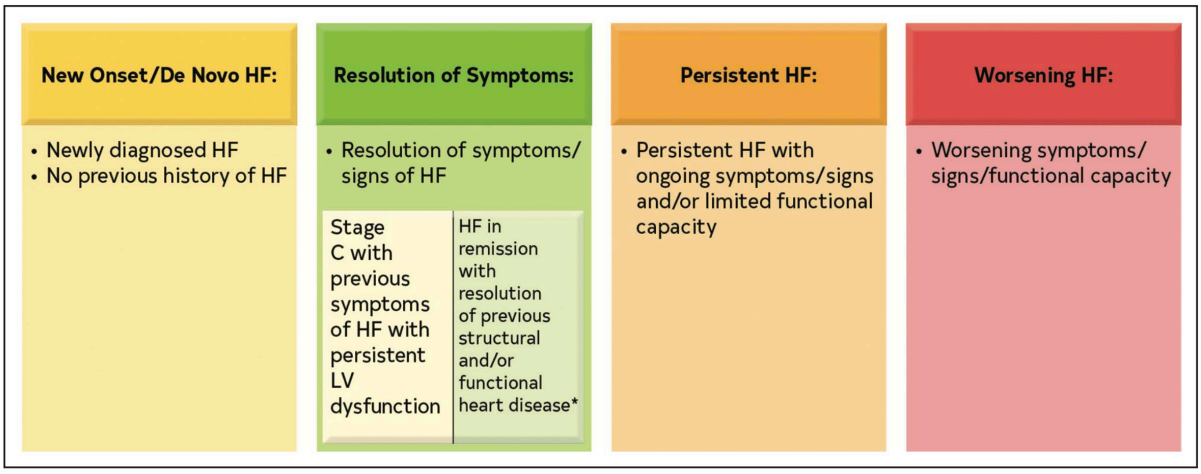


Figure 3: Trajectory of Stage C Heart Failure



1.3. Overview of Treatment of HFrEF and Unmet Medical Need

Long-term goals of HFrEF therapy include reducing CV death and hospital readmission rates (Yancy 2013; McMurray 2012). Several interventions have been shown to reduce the rate of HFrEF hospitalizations and improve mortality, including angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor/neprilysin inhibitors (ARNi), β-adrenergic blockers, and mineralocorticoid receptor antagonists (MRAs) (Yancy 2013; Zannad 2013), with the sodium glucose cotransporter-2 (SGLT2) inhibitors now joining the list of these foundational medical therapies (Packer 2020; McMurray 2019).

Despite the advent of these new therapies, a substantial residual risk of HF hospitalization and CV death remains, as illustrated by the results from recent, large, randomized, placebo-controlled CV outcomes studies. Results from four such recent interventional clinical trials in patients with HFrEF, one evaluating an ARNi (sacubitril-valsartan), two evaluating SGLT2 inhibitors

(dapagliflozin and empagliflozin), and one evaluating a soluble guanylate cyclase inhibitor (vericiguat), are presented in Table 4. Despite excellent background therapy in these trials (Teerlink 2020), the morbidity and mortality for HF patients remains high. For example, in the PARADIGM-HF trial, which had a median duration of follow-up of 27 months, the incidence of CV death or hospitalization for HF was 21.8%, the incidence of CV death was 13.3%, and the incidence of all-cause mortality was 17.0% in patients receiving valsartan sacubitril (McMurray 2014). In a population of worsening HF patients enrolled in the recently completed VICTORIA trial, the event rate for CV death or hospitalization for HF was 33.6 per 100 patient years and the event rate for CV death was 12.9 per 100 patient-years in patients receiving vericiguat (Armstrong 2020). For comparison, the rates of CV death in patients with atherosclerotic heart disease in trials such as FOURIER (PSCK-9, Sabatine 2017) and PARADISE (ARNi, Pfeffer 2015) were 0.8 and 2.6 per 100 patient-years. Thus, despite the availability of a number of guideline-directed medical therapies, the mortality rate in HFrEF remains similar to that of many common malignancies (Mamas 2017).

Table 4: Event Rates in Recent Clinical Trials in Patients with HFrEF

Trial (Publication year)	PARADIGM-HF (2014)	DAPA-HF (2019)	VICTORIA (2020)	EMPEROR-Reduced (2020)
Therapy	Sacubitril/valsartan	Dapagliflozin	Vericiguat	Empagliflozin
Annualized Event Rate (events per 100 patient-years at risk) in active arm				
Primary Composite Endpoint	10.5	11.6	33.6	15.8
CV Death	6.0	6.5	12.9	7.6
First HF Event[a]	6.2	7.1	25.9	10.7

CV = cardiovascular; HF = heart failure
[a] In VICTORIA and EMPEROR-Reduced, HF event refers to hospitalization for HF.
Primary Composite Endpoint: time to first of CV Death or HF Event (or Hospitalization)
Source: Armstrong 2020; Packer 2020; McMurray 2014; McMurray 2019

In patients with characteristics that portend higher risk such as lower LVEF, higher N-terminal pro-B-type natriuretic peptide (NT-proBNP), poor functional capacity (NYHA Class III/IV), low systolic blood pressure, intolerance of medical therapy, and recent hospitalization, the risk of HF hospitalization and death increases (Table 5). These higher-risk patients also account for a disproportionate number of HF events and thus also economic costs (Desai 2022).

Table 5: Placebo Event Rates in GALACTIC-HF - Patients with Higher Risk Features

	Overall population	LVEF ≤ 28%	HF Hosp < 3 months	NYHA Class III/IV	NT-proBNP > 2000 pg/mL	Systolic BP ≤ 100 mmHg	Intolerant to ACEi/ARB/ARNi
Annualized Event Rate (events per 100 patient-years at risk) in placebo arm							
PCE	26.3	31.2	31.2	35.2	41.6	43.2	43.7
CV Death	10.8	12.9	12.1	14.7	17.2	17.0	20.3
First HF Event	20.3	24.4	24.6	26.8	32.0	33.6	32.1

Primary Composite Endpoint (PCE): time to first of CV Death or HF Event

Additionally, optimal doses of standard of care therapies are often not well tolerated because of their side effects, most frequently in patients with high-risk features. For example, achieving target doses of neurohormonal blockers may be difficult in patients with baseline hypotension or renal insufficiency, and the availability of additional therapies with mechanisms that are complementary (and therefore potentially additive) may provide an opportunity to tailor therapy to address the specific needs of individual patients, and reduce their residual risk.

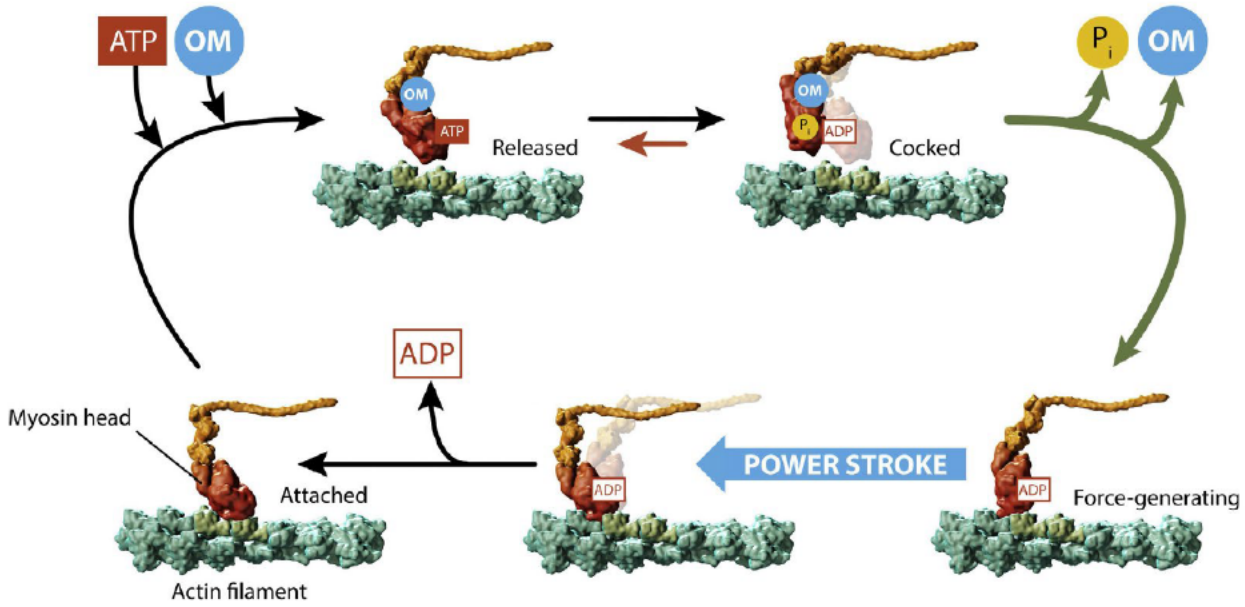
In sum, despite the application of state-of-the-art therapies in recent trials in HFrEF, event rates remain extraordinarily high, particularly in patients with easily identifiable traits that portend higher risk. The burden on these patients, their caregivers, and the healthcare system is significant; therefore, there remains a need for additional innovative therapeutic options in this large patient population.

2. BACKGROUND INFORMATION ON OMECAMTIV MECARBIL

2.1. Mechanism of Action

Omecamtiv mecarbil selectively binds to and activates the enzymatic domain of cardiac myosin by stabilizing its lever arm in a primed position, resulting in an accumulation of cardiac myosin heads in the pre-powerstroke state (Figure 4). This accelerates the transition rate from a weakly bound state into the tightly bound, force-generating state with actin, as evidenced by an increase in the rate of phosphate release from myosin (Planelles-Herrero 2017; Malik 2011). As a consequence, more force-generating myosin heads are recruited to interact with the actin filament during systole, improving cardiac contractility and increasing the duration of systole (Liu 2016; Shen 2010).

Figure 4: Mechanochemical Cycle of Myosin and the Effect of Omecamtiv Mecarbil



ADP = adenosine diphosphate; ATP = adenosine triphosphate; OM = omecamtiv mecarbil; Pi = inorganic phosphate.

Omecamtiv mecarbil demonstrates high selectivity for cardiac myosin relative to the other major muscle myosins (fast skeletal muscle myosin and smooth muscle myosin). In contrast to other positive inotropes such as β-adrenergic agonists, phosphodiesterase inhibitors, and cardiac glycosides, the pharmacological effect of omecamtiv mecarbil is independent of changes in cardiac myocyte intracellular calcium.

In a nonclinical model of HF (Shen 2010), omecamtiv mecarbil increased measures of cardiac function, such as stroke volume (SV), ejection fraction (EF), and cardiac output (CO) in the absence of changes in the rate of pressure development (dP/dt) or blood pressure while heart rate decreased. These effects on cardiac function did not produce a substantial change in coronary blood flow. Underlying these effects was an increase in the systolic ejection time (SET), a measure of the duration of systole and a highly sensitive measure of the pharmacodynamic (PD) effect of omecamtiv mecarbil. Additionally, omecamtiv mecarbil minimally impacted myocardial oxygen consumption and improved myocardial efficiency. Thus, the basic physiology of this contractile mechanism of action, acting directly on cardiac myosin, is distinct from other inotropes, which act indirectly through changes in cardiac myocyte calcium or second messenger pathways to increase dP/dt and myocardial oxygen consumption and shorten the SET (Banfor 2008). In contrast to these so-called calcitropes, omecamtiv mecarbil is a myotrope that directly activates cardiac myosin and appears to improve systolic function without the liabilities of calcitropes that increase mortality, such as proarrhythmia and increased myocardial oxygen consumption.

2.2. Nonclinical Program

Consistent with applicable regulatory guidance, most notably ICH M3(R2), a comprehensive series of pharmacology, pharmacokinetic (PK) and toxicology studies was conducted to characterize the nonclinical efficacy and safety profile of omecamtiv mecarbil.

There is no identified secondary pharmacology in other tissues, and no evidence of off-target effects at therapeutically relevant concentrations. There were no effects on QTc interval or on the human Ether-a-go-go Related Gene (hERG), Nav1.2 or Cav1.5 channels at relevant concentrations. Omecamtiv mecarbil also did not prolong action potential duration in isolated canine Purkinje fibers. Therefore, omecamtiv mecarbil presents a low risk for QT prolongation and arrhythmias, consistent with clinical observations in healthy participants and participants with chronic HF.

Forced titration to intolerance in a dog hemodynamic model showed that at plasma concentrations much greater than those required for maximum pharmacological effect, the systolic ejection period becomes excessively prolonged at the expense of diastole likely leading to impaired coronary blood flow, cardiac ischemia, reduced ventricular filling and cardiac output.

Nonclinical repeat dose toxicity studies demonstrated that the dose-limiting toxicity of omecamtiv mecarbil was myocardial necrosis or degeneration with fibrosis; the lesions were related to maximum exposure (C_{max}) and were not progressive with chronic dosing. This myocardial injury occurred at higher plasma drug concentrations than the therapeutic levels targeted in humans, and the findings were consistent with the effects of excessive pharmacology.

Additionally, omecamtiv mecarbil is not genotoxic, does not affect male or female fertility or demonstrate teratogenicity, and is not carcinogenic in the 6-month Tg.rasH2 mouse carcinogenicity study or in a 2-year rat carcinogenicity study.

2.3. Clinical Pharmacology

The clinical pharmacology of omecamtiv mecarbil has been comprehensively characterized during the clinical development program through an extensive battery of in vitro studies and clinical studies in humans.

2.3.1. ADME

Comparison of the PK of omecamtiv mecarbil following oral tablet and intravenous (IV) formulations indicates near-complete bioavailability of the oral tablet. Omecamtiv mecarbil clearance is primarily by metabolism, with renal clearance contributing less than 10% (1 L/h) of the total clearance (12.1 L/h). The major metabolic pathway is decarbamylation of omecamtiv mecarbil to M3 followed by further biotransformation to M4 and other metabolites, all of which are inactive at their circulating concentrations.

2.3.2. Pharmacokinetic Profile

Omecamtiv mecarbil exhibits generally linear and time-independent PK across the clinically relevant dose range (25 to 50 mg) and the $t_{½}$ in patients with HF is ~27 hours. Steady state concentrations occur by 14 days, which supports potential dose adjustments in 2-week increments in patients with chronic HF. There is a modest food effect with C_{max} and area under the curve (AUC_{inf}) increased by approximately 33% to 41% and 13% to 25%, respectively, following administration with a high-fat meal compared to fasted state. Considering the PK-guided dosing strategy, these results supported administration of omecamtiv mecarbil without regard to food in the pivotal Phase 3 trial.

2.3.3. Drug-Drug Interactions

The results of the DDI evaluations did not suggest any substantial drug interactions with the exception of strong inhibition of CYP3A4, and support administration of omecamtiv mecarbil with inhibitors of CYP3A, CYP2D6, P-gp and BCRP or substrates of CYP2C8, CYP3A4, P-gp and BCRP particularly in the setting of PK-guided dosing.

2.3.4. Effect of Demographics and Organ Impairment

The effects of demographic factors including sex, race, body weight, age, disease status and hepatic (mild and moderate) or renal (mild, moderate, severe and end-stage renal disease [on and off hemodialysis]) impairment on the PK of omecamtiv mecarbil were evaluated in Phase 1 clinical studies, and/or using population PK analyses and post-hoc comparisons of PK data in Phase 3 participants with chronic HF.

Demographic factors, hepatic and renal impairment did not have a clinically relevant effect on the PK of omecamtiv mecarbil.

2.4. Overview of the Clinical Development Program

The clinical development program for omecamtiv mecarbil comprises 33 completed clinical studies, enrolling approximately 10,500 participants, evaluating healthy participants, participants with chronic HF, participants with acute HF, and participants with other conditions such as renal and hepatic impairment. In these studies, the PK, PD, efficacy, safety, and tolerability of omecamtiv mecarbil have been evaluated with IV infusions up to 72 hours and oral dosing up to 43 months.

The PK, PD, and safety and tolerability profile of omecamtiv mecarbil were first evaluated in healthy participants and then in participants with HF using an IV formulation with infusions up to 72 hours in duration. The effects of chronic oral dosing with omecamtiv mecarbil and the implementation of a PK-guided dose selection strategy, both informing the transition into Phase 3, were evaluated in the Phase 2 Study 20110151 (COSMIC-HF, Expansion Phase, n = 448 randomized, 445 treated).

The clinical efficacy and safety profile of omecamtiv mecarbil in support of the proposed indication in participants with chronic HFrEF is based primarily on data from the completed Phase 3 CV outcomes study, 20110203 (GALACTIC-HF). The primary endpoint in this trial was a composite of time to CV death or first HF event, whichever occurred.

3. EFFICACY

3.1. Effects on Cardiac Function in Early Clinical Studies

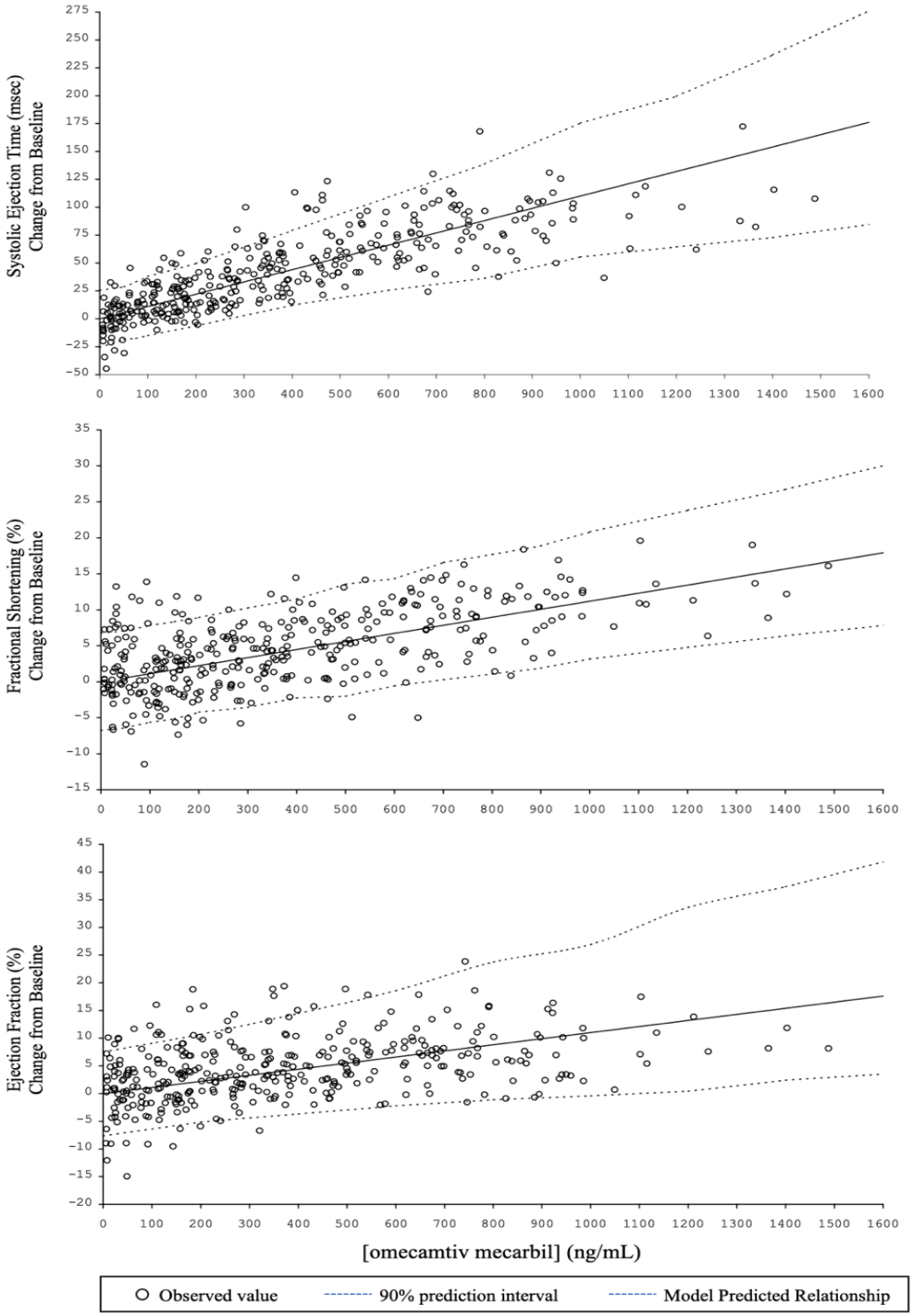
Echocardiography was the primary modality employed to assess the PD of omecamtiv mecarbil in healthy participants and participants with HF. Key metrics of cardiac function assessed included SET (the most sensitive echocardiographic measure of the effect of omecamtiv mecarbil), SV, CO, fractional shortening (FS), LVEF, and left ventricular dimensions and volumes. Short-term administration of an IV formulation of omecamtiv mecarbil increased cardiac function in a dose- and concentration-related manner in both healthy participants (CY 1111) and participants with HF (CY 1121). These PD effects were sustained with chronic oral dosing up to 20 weeks (COSMIC-HF).

3.1.1. Pharmacodynamic Effects in Healthy Participants

The first-in-human study, CY 1111, sought to identify in healthy participants (n = 35) a maximum tolerated dose of omecamtiv mecarbil administered IV as a 6-hour infusion once each week for 4 weeks in double-blind fashion. Each sequence consisted of 3 ascending doses of omecamtiv mecarbil (ranging from 0.005 to 1.0 mg/kg/hr) with a placebo infusion randomized into the sequence. Omecamtiv mecarbil produced significant concentration-related increases in SET associated with increases in FS and LVEF (Figure 5) with a half maximal effective concentration (EC_{50}) of approximately 400 ng/mL for SET and EF. Omecamtiv mecarbil increased atrial contractile function, and there were no clinically relevant changes in diastolic function. The dose-limiting toxicity was myocardial ischemia occurring at plasma concentrations exceeding 1,200 ng/mL in some but not all individuals, likely due to excessive prolongation of the SET (by more than 110 msec in each case), and reduction of time during diastole for

coronary perfusion (Teerlink 2011). Across the full development program, 6 of 16 participants experienced ischemic events in conjunction with plasma concentrations exceeding 1,200 ng/mL.

Figure 5: Pharmacokinetic/Pharmacodynamic Relationship for SET, FS, and LVEF in Healthy Participants



FS = fractional shortening; LVEF = left ventricular ejection fraction by 2D method of discs; SET = systolic ejection time (also abbreviated as aortic valve ejection time).

3.1.2. Pharmacodynamics in Patients with Chronic HFrEF

The PD of omecamtiv mecarbil in participants with HFrEF (n = 45) were first explored in CY 1121, a double-blind, placebo-controlled, dose-ranging, cross-over clinical trial investigating the effects of omecamtiv mecarbil given IV for 2, 24, or 72 hours to participants with stable HF and left ventricular systolic dysfunction receiving guideline-indicated therapy.

Placebo-corrected, concentration-dependent improvements in SET, SV, CO, FS, and LVEF were observed (Table 6), associated with a modest decline in heart rate. Higher plasma concentrations were also associated with reductions in end-systolic and diastolic volumes that may have been more pronounced with longer-term infusion. As in healthy participants, cardiac ischemia emerged at plasma concentrations exceeding 1,200 ng/mL in some but not all individuals (Cleland 2011). In this study, the PD response across most PD markers, in particular LVEF and CO, was statistically significant at plasma concentrations of omecamtiv mecarbil above 300 ng/mL.

Table 6: PK/PD Relationship for Omecamtiv Mecarbil

Parameter	Baseline (Mean, SD)	Omecamtiv Mecarbil Concentration (ng/mL) Least Squares Mean Difference from Baseline (SEM) (test-placebo)						p-value for Correlation
		>0-100	>100-200	>200-300	>300-400	>400-500	>500	
SET (msec)	316 (41)	0.6 (4)	18 (4)	47 (5)	58 (6)	59 (6)	80 (5)	< 0.0001
	p-value	0.88	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	
SV (mL)	69 (23)	-0.3 (2)	0.7 (2)	5.4 (2)	11 (3)	9.0 (3)	9.7 (2)	< 0.0001
	p-value	0.85	0.70	0.010	< 0.0001	0.0013	<0.0001	
CO (mL/min)	4,423 (1,623)	-32 (116)	52 (123)	180 (141)	408 (173)	400 (189)	330 (142)	0.0005
	p-value	0.78	0.67	0.20	0.019	0.034	0.020	
FS (%)	18 (7)	0.6 (1)	1.5 (1)	2.9 (1)	2.6 (1)	2.4 (1)	4.6 (1)	< 0.0001
	p-value	0.037	0.036	0.0004	0.0086	0.032	< 0.0001	
LVEF (%)	32 (16)	0.2 (1)	1.2 (1)	2.7 (2)	7.9 (2)	6.8 (2)	10 (1)	< 0.0001
	p-value	0.83	0.35	0.074	< 0.0001	0.0009	< 0.0001	
LVESV (mL)	168 (72)	0.8 (4)	3.4 (4)	-5.0 (5)	-11 (6)	-13 (7)	-15 (5)	< 0.0001
	p-value	0.84	0.43	0.30	0.077	0.056	0.0026	
LVEDV (mL)	243 (85)	0.8 (5)	5.3 (5)	-1.7 (6)	-14 (8)	-15 (8)	-16 (6)	0.0005
	p-value	0.87	0.33	0.79	0.066	0.068	0.0096	

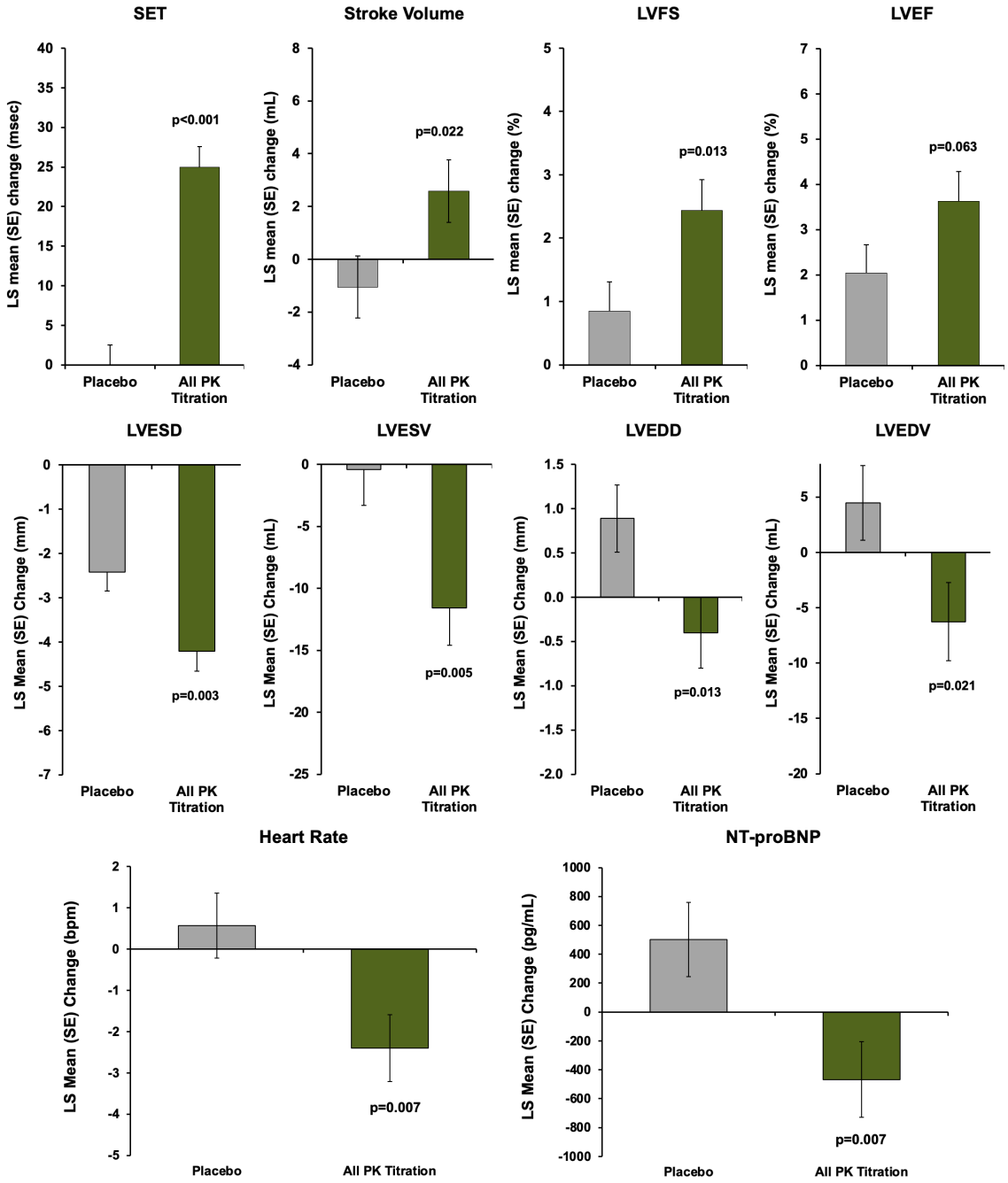
SD = Standard deviation; SEM = standard error of the mean

3.2. Phase 2 Trial 20110151 (COSMIC-HF)

The PD effects of omecamtiv mecarbil with chronic oral dosing (20 weeks) in participants with HFrEF (n = 448) were explored in the Expansion Phase of COSMIC-HF, a randomized, double-blind trial in participants with stable, symptomatic chronic HF and LVEF 40% or lower. Participants were randomly assigned equally to receive 25 mg oral omecamtiv mecarbil twice

daily (BID) (fixed dose group), 25 mg BID titrated to 50 mg BID guided by PK (PK-titration group), or placebo for 20 weeks. The dose in the PK-titration group was increased from 25 to 50 mg BID if the plasma concentration of omecamtiv mecarbil was < 200 ng/mL at steady state.

Figure 6: Pharmacodynamic Efficacy Endpoints following 20 Weeks of Dosing with Omecamtiv Mecarbil (Placebo, N = 149; PK Titration, N = 149)



SET = Systolic Ejection Time; LV = Left ventricular; LVFS = LV fractional shortening; LVEF = LV ejection fraction; LVESD = LV end-systolic diameter; LVESV = LV end-systolic volume; LVEDD = LV end-diastolic diameter; LVESV = LV end-diastolic volume; NT-proBNP = N-terminal pro-B-type natriuretic peptide; Least squares mean (SE) changes from baseline to 20 weeks. The p-values are for comparisons with the placebo group.

The mean (SD) pre-dose concentration of omecamtiv mecarbil in the PK titration group at Week 20 was 239 (118) ng/mL. Nominally, statistically significant improvements were observed for all the prespecified efficacy endpoints of SET, SV, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, heart rate, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) over 20 weeks of oral dosing with omecamtiv mecarbil (Figure 6), with larger apparent effects in the PK titration group.

These data overall provide strong mechanistic support and confirmatory evidence given the impact of omecamtiv mecarbil on well-understood pharmacodynamic endpoints relevant to HFrEF.

3.3. Phase 3 Trial 20110203 (GALACTIC-HF)

3.3.1. Study Design

GALACTIC-HF was a randomized, placebo-controlled, double-blind, parallel-group, multicenter, multinational study that enrolled 8,256 participants with HFrEF, including participants who were either hospitalized for HF at time of enrollment or had a hospitalization or emergency department visit for HF within 1 year of screening. Eligible participants were adults with LVEF ≤ 35%, NYHA Class II-IV, elevated NT-proBNP, and a history of chronic HF, defined as receiving treatment for HF for a minimum of 30 days before randomization, who were being managed with HF standard of care therapies consistent with regional clinical practice guidelines according to investigator judgment.

PK-guided dose selection was employed to attain target steady-state plasma concentrations of omecamtiv mecarbil (300 to 750 ng/mL) while reducing the risks associated with excessive omecamtiv mecarbil concentrations (> 1,200 ng/mL). Participants randomized to omecamtiv mecarbil were started at the lowest dose (25 mg BID). The dose was increased from 25 mg BID to 37.5 or 50 mg BID only in participants who were both adherent to the regimen and whose plasma concentrations of omecamtiv mecarbil were below the target range after steady state had been achieved (2 weeks). Investigators were blinded to the results of PK assessments throughout the study. To further maintain the blind, participants randomized to placebo received placebo throughout the study but underwent identical PK assessments and investigational product resupply procedures as those receiving omecamtiv mecarbil.

The primary endpoint was a composite of time to CV death or first HF event, whichever occurred first. A death was defined as a CV death endpoint if the death was positively adjudicated as a CV death, presumed CV death, or presumed sudden death. An HF event was defined as an urgent, unscheduled clinic/office/emergency department (ED) visit, or hospital admission, with a primary diagnosis of HF, where the patient exhibited new or worsening symptoms of HF on presentation, had objective evidence of new or worsening HF, and received initiation or intensification of treatment specifically for HF. Changes to oral diuretic therapy did not qualify as initiation or intensification of treatment.

The study concluded when approximately 1,590 CV death events had been reported. All deaths, HF events, major cardiac ischemic events (MCIE; myocardial infarction [MI], unstable angina hospitalization, and coronary revascularization), and strokes were adjudicated by an independent external Clinical Events Classification Committee using standardized definitions (Hicks 2015) developed in consultation with the FDA. An external independent Data Monitoring Committee

formally reviewed the accumulating unblinded data throughout the study. Participants who experienced a nonfatal primary endpoint did not end study participation and continued treatment and follow-up procedures until the study ended. All participants were followed from randomization through the date of study termination unless the participant withdrew consent, irrespective of whether the participant continued to receive study treatment.

3.3.2. Statistical Methodology

It was determined that enrollment of approximately 8,000 participants with a target of approximately 1,590 CV deaths would provide a power of 90% to detect a hazard ratio of 0.8 for CV death in the group receiving omecamtiv mecarbil. Assuming the rates for experiencing either a heart failure event or CV death were double those for CV death alone, the primary composite endpoint was expected to have > 99% power when the primary analysis was triggered. The overall type I error was 0.05 for 2-sided testing across primary and secondary outcomes. Control for multiple comparisons was achieved by means of the following testing algorithm: if the primary outcome met the p-value threshold of 0.05, a Bonferroni split would be used where 0.96α was allocated to testing the time to CV death and 0.04α was allocated to testing change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ TSS).

On the basis of a 1-sided alpha level of 0.0005, an interim efficacy analysis was conducted after approximately two-thirds of the targeted number of CV deaths had occurred. If the study had been terminated early for superiority, the interim analysis hypothesis test results would have been used as the primary hypothesis test results. Since the study continued, the full alpha error of 0.05 was used in the final analysis.

The efficacy analysis was performed on the full analysis set which included all participants who had undergone randomization except for 24 participants from a single site who were excluded on the basis of Good Clinical Practice (GCP) violations. The decision to exclude these participants was made prior to the end of the study before the database lock. Time-to-event data were evaluated using Kaplan Meier estimates and Cox proportional-hazards models stratifying for the randomization setting (inpatient or outpatient) and geographic region and with terms of treatment group and the baseline estimated glomerular filtration rate (eGFR). The mean differences in the change in the KCCQ TSS from baseline to Week 24 were estimated with the use of mixed models fit within the randomization setting, with each model containing fixed effects for the baseline total symptom score, geographic region, baseline eGFR, scheduled visit (Week 12 or Week 24), trial group, and the interaction between trial group and scheduled visit and an unstructured covariance matrix for repeated measures across visits. A joint omnibus F-test of a treatment difference within at least 1 subset of trial participants (inpatients or outpatients) was used to test the treatment effect for the KCCQ TSS.

The prespecified safety analyses included serious adverse events (SAEs), AEs associated with the discontinuation of omecamtiv mecarbil or placebo, and adverse events of special interest (ie, AEs of ventricular arrhythmias, adjudicated MCIE [MI, hospitalization for unstable angina, and coronary revascularization], and adjudicated strokes). The safety analyses were performed for randomized participants who had received at least 1 dose of omecamtiv mecarbil or placebo, with the exclusion of the 24 participants from the site that had been excluded from the full analysis set.

To evaluate baseline covariates and covariates by treatment interactions, post-hoc analyses were performed using a Cox model stratified by randomization setting and region fit with prespecified baseline subgroup covariates and covariates by treatment group interaction terms for the primary endpoint. Variables measured as continuous were included in the model as continuous covariates. A global test of the prespecified covariates by treatment group interaction terms was obtained via Wald test and hazard ratios (HRs) evaluating individual covariates by treatment interactions were provided. In addition to prespecified subgroup analyses, post hoc analyses were conducted for additional efficacy and safety outcomes. The primary composite event incidence rate per 100 patient years as a function of baseline LVEF was modeled using a Poisson distribution with terms of treatment group and baseline LVEF expressed using restricted cubic splines by treatment. Incidence rates and the treatment effect ratio were plotted over the baseline LVEF to display the relationship between baseline LVEF and treatment effect. Post-hoc dose- and concentration-response analyses were also conducted for the primary composite endpoint, secondary endpoints, and safety events of special interest.

3.3.3. Demographics and Baseline Characteristics

The study population in GALACTIC-HF included 8,256 participants who were randomized at 944 sites in 35 countries. Overall, the participant population enrolled in this study is representative of the US population with chronic HFrEF. Key baseline characteristics by treatment arm and randomization setting are presented in Table 7.

The study population included 1,749 women (21.2%) and 6,483 men (78.8%). The mean (standard deviation [SD]) age of participants was 64.5 (11.4) years, and 54.5% of participants were ≥ 65 years of age. The majority of the participants were white (77.7%), 8.6% were Asian, and 6. 8% were Black or African American; 21.5% of participants were of Hispanic/Latino ethnicity. Approximately one-sixth of participants were enrolled from North America with 1220 participants enrolled in the United States. Demographic and other baseline characteristics were generally similar between the treatment groups, and in both outpatient and inpatient subgroups.

A total of 2,084 (25.3%) participants were enrolled as inpatients after stabilization during a hospitalization for HF. Cardiac arrhythmias, chronic kidney disease, diabetes mellitus, cerebrovascular disease, and hypertension (omecamtiv mecarbil group only) were more common among inpatient participants compared with outpatient participants. Overall, 62.3% of participants had a history of coronary artery disease, 70.3% had hypertension, and 55.0% had a history of cardiac arrhythmias. Other medical comorbidities were common in patients with HF, and well-balanced between the treatment groups.

Vital sign parameters at baseline were similar between the omecamtiv mecarbil and placebo groups. Mean (SD) systolic blood pressure (SBP) was 116.5 (15.3) mm Hg, diastolic blood pressure was 71.5 (10.3) mm Hg, and heart rate was 72.4 (12.1) bpm; inpatient participants had slightly lower blood pressure compared with the outpatient participants.

Participants were well-treated with guideline-recommended HF therapies at baseline, with 87% receiving an ACEi/angiotensin receptor blocker (ARB)/ARNi, 94% a beta blocker, and 78% an MRA. Approximately two-thirds of participants received triple therapy (ACEi/ARB/ARNi + beta blocker + MRA). Almost 32% of participants had an implantable cardioverter defibrillator

(ICD), and 14% had cardiac resynchronization therapy (CRT) at baseline. Of note, SGLT2 inhibitors were not approved for use in HFrEF at the time of study conduct.

Table 7: Summary of Key Baseline Demographics and Disease Characteristics

Characteristic	Omecamtiv Mecarbil (N = 4120)	Placebo (N = 4112)
Age, years	64.5 ± 11.3	64.5 ± 11.4
Female sex, n (%)	875 (21.2)	874 (21.3)
Race or ethnic group, n (%)[a]		
White	3196 (77.6)	3201 (77.8)
Asian	355 (8.6)	355 (8.6)
Black	285 (6.9)	277 (6.7)
Other	284 (6.9)	279 (6.8)
Geographic region, n (%)		
Eastern Europe or Russia	1344 (32.6)	1337 (32.5)
Western Europe, South Africa, or Australasia	961 (23.3)	960 (23.3)
Latin America	787 (19.1)	787 (19.1)
United States or Canada	693 (16.8)	693 (16.9)
Asia	335 (8.1)	335 (8.1)
Inpatient setting, n (%)	1044 (25.3)	1040 (25.3)
Clinical features		
Atrial fibrillation or flutter, n (%)	1146 (27.8)	1099 (26.7)
Type 2 diabetes mellitus, n (%)	1652 (40.1)	1657 (40.3)
Ischemic heart failure, n (%)	2193 (53.2)	2222 (54.0)
Left ventricular ejection fraction, %	26.6±6.3	26.5±6.3
NYHA Classification, n (%)		
II	2195 (53.3)	2173 (52.8)
III	1801 (43.7)	1815 (44.1)
IV	124 (3.0)	124 (3.0)
Median KCCQ Total Symptom Score (IQR)[b]	68.8 (49.0–87.5)	68.8 (49.0–87.5)
Outpatient	74.0 (54.2–90.6)	75.0 (56.3–91.7)
Inpatient	54.2 (34.4–72.9)	52.1 (31.3–69.8)
Systolic blood pressure, mmHg	116.3 ± 15.4	116.6 ± 15.3
Heart rate, beats/min	72.4 ± 12.2	72.3 ± 12.1
Median NT-proBNP (IQR), pg/mL	1977 (980–4061)	2025 (1000–4105)
Median cardiac troponin I (IQR), ng/L	27 (14–51)	26 (14–51)

Table 7: Summary of Key Baseline Demographics and Disease Characteristics (Continued)

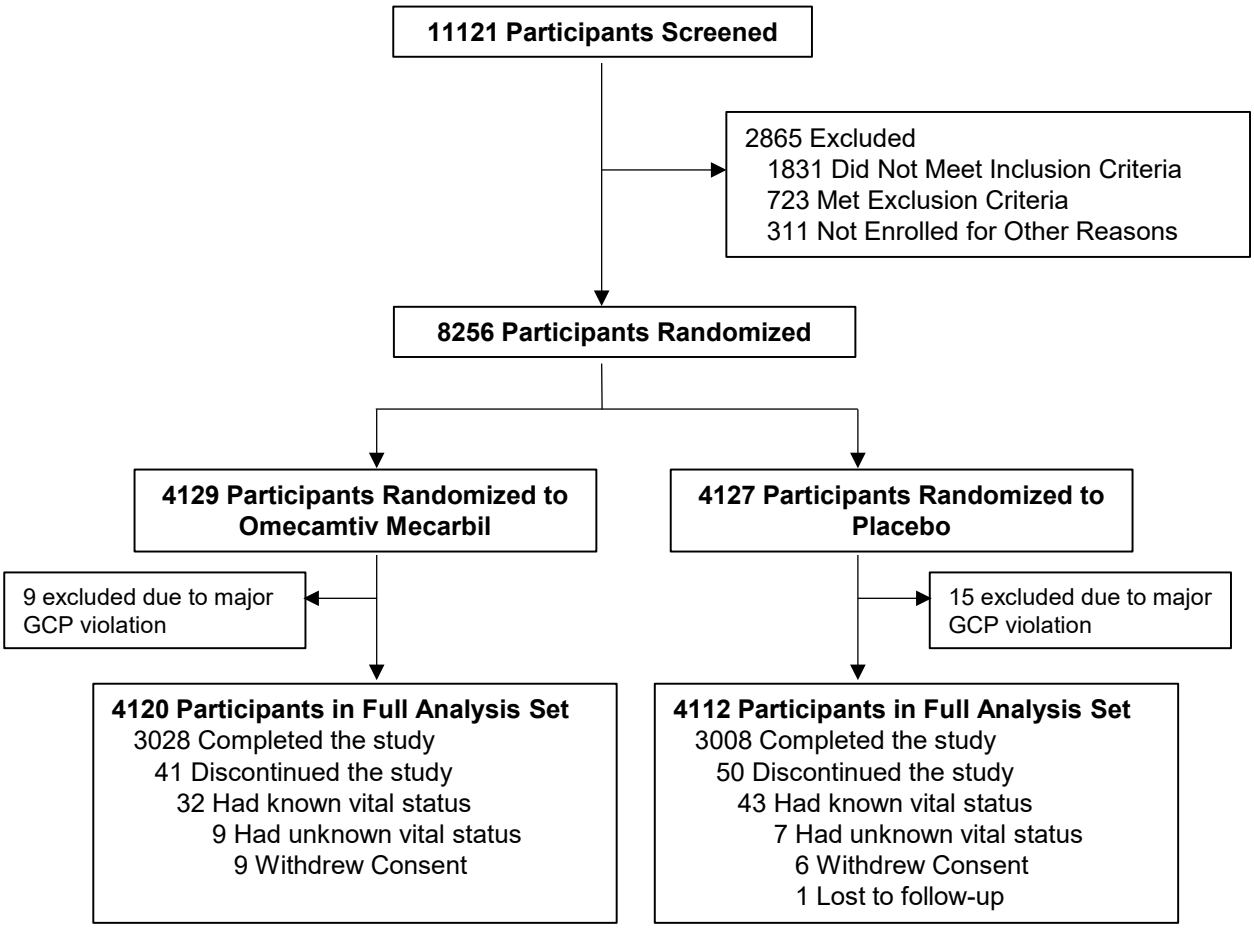
Characteristic	Omecamtiv Mecarbil (N = 4120)	Placebo (N = 4112)
Median eGFR (IQR), mL/min/1.73 m^2	58.8 (44.3–74.3)	58.7 (43.8–73.7)
Heart-failure therapy, n (%)		
ACE inhibitor, ARB, or ARN inhibitor	3583 (87.0)	3576 (87.0)
ARN inhibitor	819 (19.9)	782 (19.0)
Beta-blocker	3881 (94.2)	3883 (94.4)
Mineralocorticoid-receptor antagonist	3199 (77.6)	3198 (77.8)
SGLT2 inhibitor	104 (2.5)	114 (2.8)
Cardiac-resynchronization therapy	592 (14.4)	566 (13.8)
Implantable cardioverter–defibrillator	1326 (32.2)	1288 (31.3)

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; ARN = angiotensin receptor–neprilysin; eGFR = estimated glomerular filtration rate; IQR = interquartile range; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; SGLT2 = sodium–glucose cotransporter 2
Plus–minus values are means ±SD.
Percentages may not total 100 because of rounding.
[a] Race or ethnic group was reported by the participants. The category of Other includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or multiple participant-identified races or ethnic groups.
[b] Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100, with higher scores indicating a lower frequency and severity of symptoms.

3.3.4. Disposition

A total of 8,256 participants were randomized in GALACTIC-HF. All participants, except for 24 participants at a single site excluded because of GCP violations, were included in the final analyses of the study. As a result, a total of 8,232 participants, comprised of 2,084 participants who were hospitalized for HF at the time of enrollment and 6,148 participants who had a hospitalization or ED visit for HF within 1 year of screening, were included in the efficacy and safety analyses as defined in the statistical analysis plan (SAP) before database lock. Of these, 4,120 participants received omecamtiv mecarbil and 4,112 participants received placebo. At the end of the trial, 99.8% of the participants had known vital status; 16 participants had unknown vital status (omecamtiv mecarbil: 9 participants withdrew consent; placebo: 6 participants withdrew consent and 1 participant lost to follow-up). The overall median duration of follow-up was 21.8 months. An overview of participant disposition is presented in Figure 7.

Figure 7: Participant Disposition in GALACTIC-HF



3.3.5. Dosing

A PK-guided dosing strategy was used to maximize participant exposure to omecamtiv mecarbil in the target plasma concentration range (300 to 750 ng/mL), while minimizing the frequency of concentrations > 1,200 ng/mL. The dose titration algorithm was designed to achieve the target concentration range and dose in a single step following a single plasma concentration check after 2 weeks of dosing. All participants in the omecamtiv mecarbil group (N = 4,120) were assigned to start on an initial dose of 25 mg BID. Plasma concentrations of omecamtiv mecarbil were then measured at Week 2. Ten participants randomized to omecamtiv mecarbil treatment were never dosed. The target doses of omecamtiv mecarbil (25, 37.5, or 50 mg BID) were dispensed at Week 4 based on Week 2 plasma concentrations, at which time 24.1%, 15.4%, and 52.7% of participants were given 25, 37.5, and 50 mg BID, respectively (of the remaining participants, 3.2% discontinued investigational product [IP], 1.2% had no IP box dispensed, and for 3.3%, the visit did not occur).

A substantial proportion of participants remained on 25 mg BID and were not up-titrated due to conservative measures that were incorporated into the dosing strategy. If plasma concentration results were not available in time for any dose titration visit or if participant compliance with dosing was not affirmatively documented by the investigator, the dose of omecamtiv mecarbil remained at or was reduced to 25 mg BID.

At Week 6, omecamtiv mecarbil plasma concentrations were measured to determine whether the selected doses resulted in exposures above the therapeutic range (ie, omecamtiv mecarbil concentrations above 750 ng/mL) with plans to adjust the dose accordingly, as needed, at the next visit (Week 8). At the Week 8 visit, 3.0% of participants had their doses adjusted from 50 to 25 mg BID and 1.1% from 37.5 to 25 mg BID. Only 9 participants were down-titrated at Week 8 due to plasma concentrations >750 ng/mL; otherwise, down-titrations were due to either a missing omecamtiv mecarbil plasma concentration (laboratory value not available in time or PK sample not obtained) or failure to confirm participant compliance. At the end of the dose titration (Week 8), 28.6% of participants were on 25 mg BID, which was higher than the anticipated proportion (4.1%) based on the population PK modeling that informed the dosing strategy. In participants who completed the dosing algorithm as intended and were titrated to 37.5 or 50 mg BID, mean omecamtiv mecarbil plasma concentrations were higher than those in the 25 mg BID dose group, as expected. Overall, the proportions of participants receiving each of the omecamtiv mecarbil doses remained generally consistent over time.

3.4. Overall Efficacy in Patients with HFrEF

3.4.1. Primary Endpoint

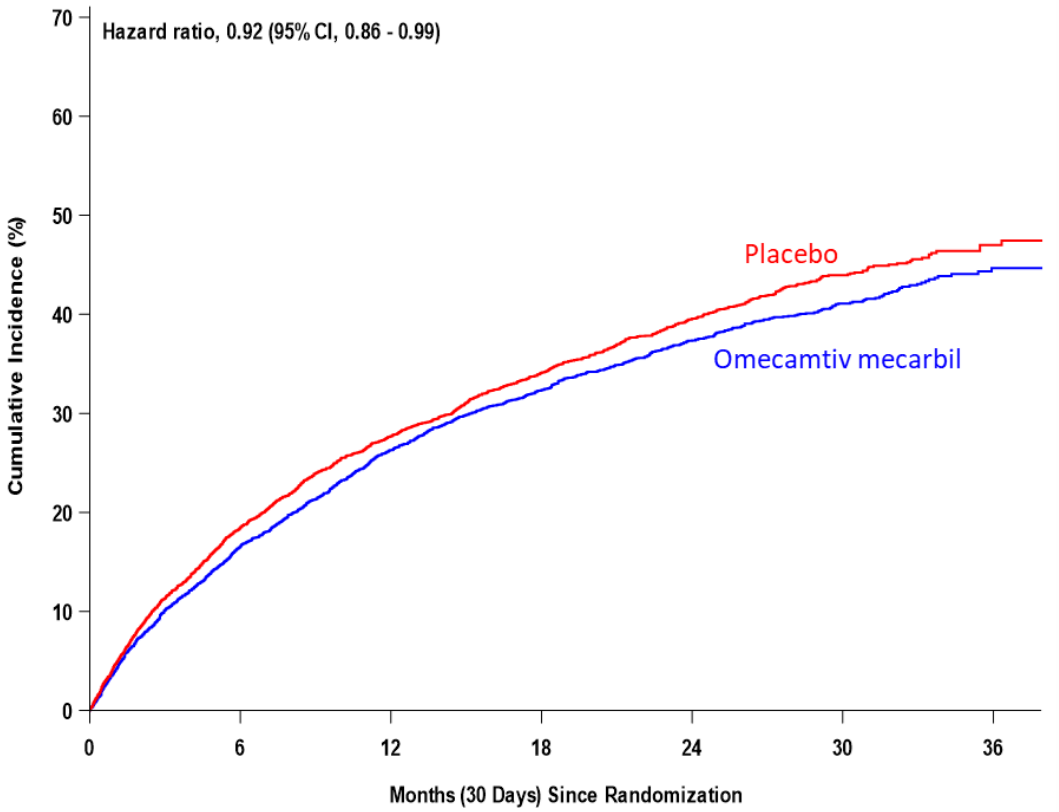
In the pivotal trial GALACTIC-HF, overall, 37.0% participants in the omecamtiv mecarbil group had a positively adjudicated primary composite endpoint event, compared with 39.1% participants in the placebo group (Table 8). The Kaplan-Meier curve for time to the primary composite endpoint for the overall population is provided in Figure 8 (HR [95% confidence interval; CI]: 0.92 [0.86, 0.99]; p = 0.0252). Although both components of the primary endpoint numerically favored omecamtiv mecarbil, the benefit was driven primarily by a decrease in the rates of HF events.

Table 8: Treatment Effect for the Primary Composite Endpoint of Cardiovascular Death and Heart Failure Events

	Omecamtiv Mecarbil (N=4,120)		Placebo (N=4,112)		Treatment Comparison		
	n (%)	Event Rate per 100 pt-yrs	n (%)	Event Rate per 100 pt-yrs)	Hazard Ratio (95% CI)[c]	p-value	ARR[d]
Primary endpoint							
Composite of cardiovascular death or heart failure events	1,523 (37.0)	24.2	1,607 (39.1)	26.3	0.92 (0.86, 0.99)	0.025	2.1
Cardiovascular death	346 (8.4)		371 (9.0)				
Heart failure events	1,177(28.6)		1,236 (30.1)				

ARR = absolute risk reduction; CI = confidence interval; N = Number of participants in Full Analysis Set; n = Number of participants with an event.

Figure 8: Cumulative Incidence Estimates for Time to the Primary Composite Endpoint



Placebo	4112	3310	2889	2102	1349	647	141
Omecamtiv mecarbil	4120	3391	2953	2158	1430	700	164

CI = confidence interval.

3.4.1.1. Prespecified and Ad hoc Sensitivity Analyses of the Primary Endpoint

There were three prespecified sensitivity analyses of the primary endpoint including a stratified log-rank test (eliminating eGFR from the primary analysis model), a repeat of the Cox model including events only up to the minimum of the last nonfatal potential endpoint collection, end-of-study, or analysis cut-off, and a tipping point analysis.

Eliminating eGFR from the primary analysis model and conducting a stratified log-rank test by randomization setting and region resulted in a p-value of 0.021.

Inclusion of CV deaths only up to the earliest of the last nonfatal potential endpoint collection, end-of-study, or analysis cut-off for the mortality component, as opposed to the earlier of last confirmed survival status date or analysis cut-off date, was done for the primary analysis and was intended to avoid counting a CV death when non-fatal endpoint might have occurred first. This analysis only eliminated 0.4% of the endpoints captured in the primary analysis and the result (HR [95% confidence interval; CI]: 0.92 [0.86, 0.99]; p = 0.0245) was nearly identical to the primary analysis (HR [95% confidence interval; CI]: 0.92 [0.86, 0.99]; p = 0.0252).

In the planned tipping point sensitivity analysis, participants who discontinued the study early (not ending the study due to death or COVID-19) had randomly drawn exponentially distributed time-to-event variables multiply imputed with specified HRs to determine the HR that would result in a p-value that is greater than or equal to 0.05. For the participants that discontinued the trial for reasons other than death or COVID-19 a HR of 5.1 for those on omecamtiv mecarbil relative to those on placebo endpoint was necessary to overturn the primary endpoint to $p \geq 0.05$ with a HR (95% CI) 0.93 (0.87, 1.00). The tipping point analysis indicates that the treatment effect was insensitive to missing data.

Additional ad hoc analyses were performed to support the robustness of the primary endpoint analysis. These included adjusting for all significant prespecified subgroup covariates, confining the analysis to participants on treatment, at the highest dose, or in the therapeutic range of plasma concentrations, and including investigator reported events as opposed to only adjudicated events. A prespecified exploratory endpoint of time to first CV death, HF event, myocardial infarction (MI), hospitalization for unstable angina, coronary revascularization, or stroke captured the hazard for both intended benefits and competing risks. The results of these analyses are summarized in Table 9.

Table 9: Additional Sensitivity Analyses of the Primary Endpoint

Clinical Outcomes	HR (95% CI) p value
Prespecified Analysis[a] of the Primary Composite Endpoint	0.92 (0.86, 0.99); p=0.025
Adjusting for Significant Pre-Specified Baseline Covariates	0.91(0.85, 0.97); p=0.008
On Treatment, Primary Analysis Modela	0.90 (0.84, 0.97); p=0.007
Patients Receiving Highest Dose (50 mg), Primary Analysis Modela	0.87 (0.80, 0.96); p=0.003
Patients Receiving Highest Dose (50 mg), Adjusting for Significant Prespecified Baseline Covariates	0.89 (0.81, 0.97); p=0.009
Patients in the Therapeutic Range (200 - <750 ng/mL), Adjusting for Significant Prespecified Baseline Covariates	0.86 (0.79, 0.93); p <0.001
Using Investigator Reported Events, Primary Analysis Model[a]	0.93 (0.87, 0.99); p=0.03
Time to first cardiovascular death, HF event, myocardial infarction, hospitalization for unstable angina, coronary revascularization, or stroke	0.92 (0.86, 0.98); p=0.013

[a] Cox model stratified by randomization setting (inpatient or outpatient) and region and including terms for baseline eGFR and treatment group.

3.4.2. Secondary Endpoints

The results of the analyses of the secondary endpoints in the overall population are summarized in Table 10. The time to positively adjudicated CV death, time to first HF hospitalization, and time to all-cause death were not significantly different between the omecamtiv mecarbil and placebo treatment groups.

The least squares (LS) mean (standard error [SE]) change from baseline to Week 24 in KCCQ TSS numerically favored omecamtiv mecarbil compared to placebo groups and was driven mainly by the inpatient participants whose baseline KCCQ scores were substantially worse than the outpatients; however, the hypothesis test was not statistically significant when adjusting for

multiplicity according to the prespecified rules for the apportionment of alpha error set forth in the protocol and the SAP.

Table 10: Summary of Secondary Efficacy Endpoints

Secondary Efficacy Endpoints	Omecamtiv Mecarbil (N=4,120) n (%)	Placebo (N=4,112) n (%)	Hazard Ratio[a]/ Mean Difference[b] (95% CI)	p-value[a] (Significance)
Time to cardiovascular death	808 (19.6)	798 (19.4)	1.01 (0.92, 1.11)	0.856 (non-sig)
KCCQ TSS change from baseline to Week 24, LS mean (SE)[c]				0.028 (non-sig)
Inpatient participants	23.65 (0.7)	21.15 (0.7)	2.50 (0.54, 4.46)	
Outpatient participants	5.83 (0.3)	6.29 (0.3)	-0.46 (-1.40, 0.48)	
Time to first HF hospitalization	1,142 (27.7)	1,179 (28.7)	0.95 (0.87, 1.03)	0.190 (non-sig)
Time to all-cause death	1,067 (25.9)	1,065 (25.9)	1.00 (0.92, 1.09)	0.963 (non-sig)

CI = confidence interval; eGFR = estimated glomerular filtration rate; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; KCCQ TSS = Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LS = least squares; N = number of participants in the analysis set; n = number of participants with observed data; non sig = non-significant; OM = omecamtiv mecarbil; SE = standard error; SOC = system organ class.

[a] Based on a stratified Cox model with treatment group and baseline eGFR as the independent variables and stratified by randomization setting and region.

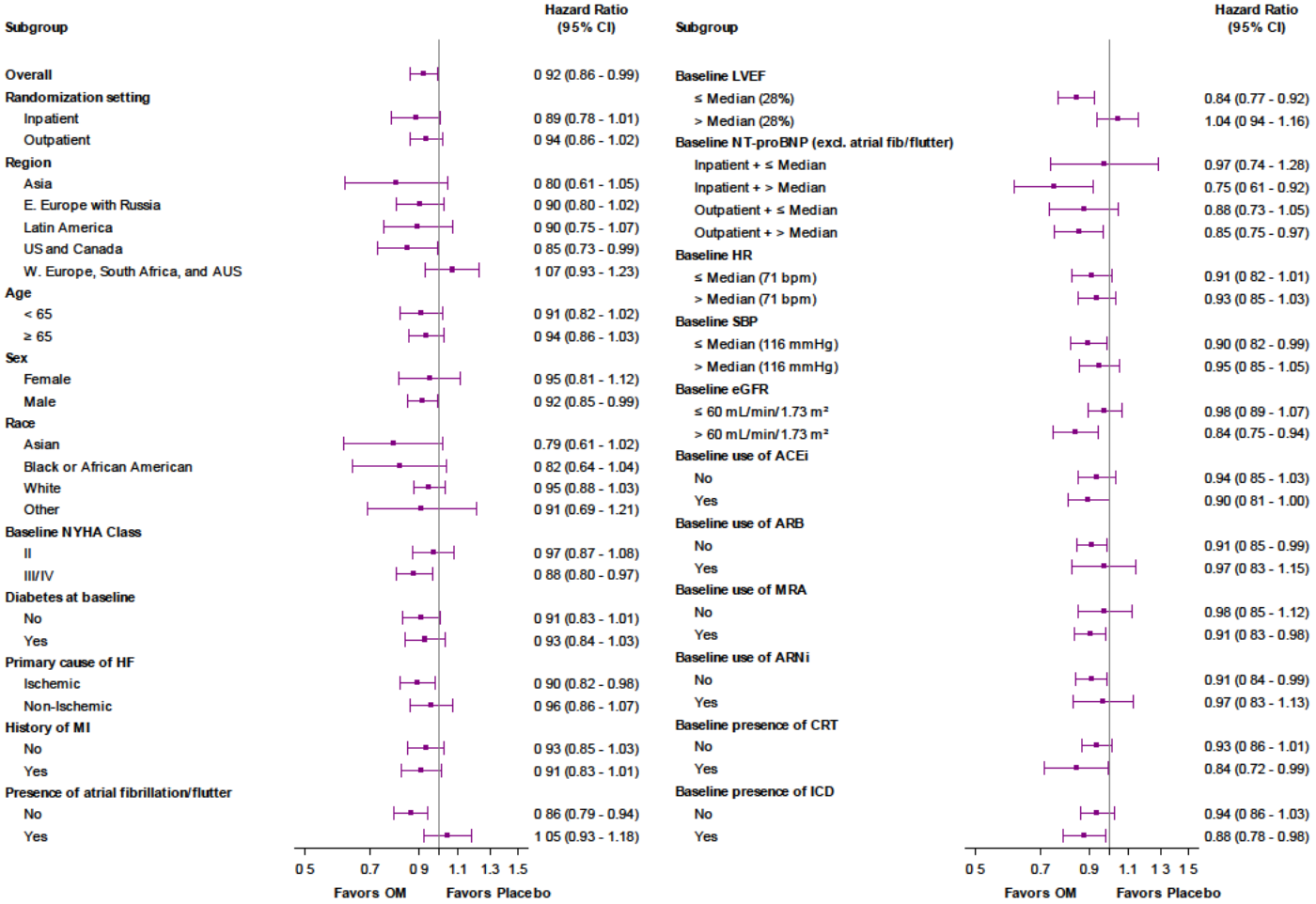
[b] For KCCQ, within each randomization setting subgroup, LS mean is from the mixed model which includes baseline total symptom score value, region, baseline eGFR, scheduled visit, treatment group, and interaction of treatment with scheduled visit as covariates. The LS mean (SE) treatment difference is using placebo as the reference.

[c] Positive changes represent improvements in symptoms. Per statistical testing hierarchy, $p < 0.002$ considered significant.

3.5. Efficacy Analyses by Prespecified Subgroups

Prespecified subgroup analyses of the primary composite endpoint generally demonstrated treatment effects for most subgroups that were broadly consistent with those observed in the overall study population (Figure 9).

Figure 9: Forest Plot of the Primary Composite Endpoint in the Prespecified Subgroups



ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor blocker/neprilysin inhibitor; CI = confidence interval; CRT = cardiac resynchronization therapy, eGFR = estimated glomerular filtration rate; HF = heart failure; HR = hazard ratio; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction, MI = myocardial infarction; MRA = mineralocorticoid receptor antagonists; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OM = omecamtiv mecarbil; SBP = systolic blood pressure; SE = standard error; SOC = system organ class.

3.5.1. Multivariable Interaction Analysis

The study met its primary endpoint with a statistically significant 2-sided p-value of 0.0252 in the full analysis set. In order to assess for a heterogeneous treatment effect among the prespecified subgroups, a simultaneous test of all interaction terms (global test for heterogeneity) was done and provided statistical evidence for a heterogeneous treatment effect among prespecified subgroups with a p-value of 0.008 as shown in Table 11, suggesting that the study population was heterogeneous with respect to the response to omecamtiv mecarbil relative to placebo. This analysis included all the treatment-by-prespecified baseline subgrouping covariate interactions in a global interaction test. The multivariate analysis further explained that the heterogeneity of the treatment effect was mainly driven by LVEF (p = 0.005) and AFF (p=0.006); these two covariates are discussed in detail below (LVEF in Section 3.5.2; AFF in Section 4.3.2).

Table 11: Multivariable Interaction Analysis of the Primary Endpoint

Treatment-Covariate Interaction	p-value (Global p = 0.008 [28 covariates])
LVEF (per 10%)	0.005
Atrial Fib / Flutter	0.006
MRA use	0.03
NT-proBNP (per log unit)	0.1
Ischemic etiology	0.12
eGFR	0.22
History of MI	0.23
NYHA Class II (vs III/IV)	0.25
Age	0.30
CRT	0.34
ARNi use	0.43
Ethnicity	0.49
Region (ref = E. Europe and Russia)	0.53
US/Canada	
W. Europe / SA / Australia	
Latin America	
Asia	
ACE use	0.63
Heart Rate	0.64
ARB use	0.67
ICD use	0.71

Table 11: Multivariable Interaction Analysis of the Primary Endpoint (Continued)

Treatment-Covariate Interaction (n=8202)	p-value (Global p = 0.008 [28 covariates])
SBP	0.74
Diabetes Mellitus	0.81
Race (ref = White)	0.83
Asian	
Black	
Other	
Inpatient/Outpatient Status	0.86
Gender	0.88
Weight	0.94

3.5.2. Ejection Fraction

Based on the prespecified subgroups in GALACTIC-HF, baseline LVEF was observed to have the strongest univariate treatment-covariate interaction for the primary composite endpoint (p = 0.0034) (Section 3.4.1). Participants with LVEF ≤ median (28%) (n = 4456; 54.1%) experienced greater risk reduction of the primary endpoint with omecamtiv mecarbil versus placebo than participants with LVEF > median (HR = 0.84 [95% CI: 0.77, 0.92] versus HR = 1.04 [95% CI: 0.94, 1.16], respectively).

Baseline characteristics for LVEF ≤ 28% and > 28% indicated that within each subgroup, there were no meaningful differences between the placebo and omecamtiv mecarbil groups as was observed in the overall study population. Compared to the LVEF > 28% group, the LVEF ≤ 28% participants were younger and had higher NT-proBNP, lower SBP, a lower incidence of AFF, a lower incidence of ischemic etiology for HF, and were less commonly from Eastern Europe and Russia (Table 12).

Table 12: Baseline Characteristics of LVEF Subgroups

	Baseline LVEF ≤Median (n=4,456)	**Baseline LVEF >Median (n=3,776)**
Demographics		
Age - yr (Mean ± SD)	63.3 ± 11.73	66.0 ± 10.72
Female Sex, n (%)	873 (19.6)	876 (23.2)
Race or ethnic group, n (%)[a]		
White	3,300 (74.1)	3,097 (82.0)
Asian	395 (8.9)	315 (8.3)
Black	399 (9.0)	163 (4.3)
Other	362 (8.1)	201 (5.3)
Geographic Region, n (%)		
Eastern Europe/Russia	1,093 (24.5)	1,588 (42.1)
Western Europe/South Africa/Australasia	1,133 (25.4)	788 (20.9)
Latin America	942 (21.1)	632 (16.7)
US And Canada	922 (20.7)	464 (12.3)
Asia	366 (8.2)	304 (8.1)
Inpatient setting, n (%)	1,144 (25.7)	940 (24.9)
Clinical Features		
Atrial fibrillation or flutter, n (%)	1,108 (24.9)	1,137 (30.1)
Type 2 diabetes mellitus, n (%)	1,749 (39.3)	1,560 (41.3)
Ischemic heart failure, n (%)	2,186 (49.1)	2,229 (59.0)
Left ventricular ejection fraction, % (Mean ± SD)	21.8 ± 4.41	32.2 ± 2.13
NYHA Classification, n (%)		
Class II	2,324 (52.2)	2,044 (54.1)
Class III	1,975 (44.3)	1,641 (43.5)
Class IV	157 (3.5)	91 (2.4)
Median KCCQ Total Symptom Score (IQR) [b]	68.8 (47.9 – 87.5)	69.8 (50.0 – 87.5)
Outpatient	75.0 (55.2 – 91.7)	74.0 (55.2 – 89.6)
Inpatient	52.1 (31.25 – 70.8)	54.2 (34.4 – 72.9)

Table 12: Baseline Characteristics of LVEF Subgroups (Continued)

	Baseline LVEF ≤Median (n=4,456)	Baseline LVEF >Median (n=3,776)
Systolic blood pressure, mmHg (Mean ± SD)	113.6 ± 15.13	119.9 ± 14.89
Heart rate, beats/min (Mean ± SD)	72.9 ± 12.2	71.7 ± 12.1
Median NT-proBNP (IQR), pg/mL	2277 (1152 – 4710)	1743 (834 – 3437)
Median cardiac troponin I (IQR), ng/L	30 (15 – 56)	24 (12 – 46)
Median eGFR (IQR), mL/min/1.73m^2	58.8 (44.0 – 74.2)	58.7 (44.3 – 73.9)
Heart Failure Therapy, n (%)		
ACE inhibitor, ARB, or ARN inhibitor	3,836 (86.1)	3,329 (88.2)
ARN inhibitor	1,002 (22.5)	599 (15.9)
Beta-blocker	4,186 (93.9)	3,577 (94.7)
Mineralocorticoid-receptor antagonist	3,507 (78.7)	2,890 (76.5)
SGLT2 inhibitor	131 (2.9)	87 (2.3)
Cardiac resynchronization therapy	775 (17.4)	383 (10.1)
Implantable cardioverter defibrillator	1,717 (38.5)	897 (23.8)

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; ARN = angiotensin receptor–neprilysin; eGFR = estimated glomerular filtration rate; IQR = interquartile range; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SGLT2 = sodium–glucose cotransporter 2
Plus–minus values are means ±SD.
Percentages may not total 100 because of rounding.
[a] Race or ethnic group was reported by the participants.
[b] Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100, with higher scores indicating a lower frequency and severity of symptoms.

3.5.2.1. Primary Endpoint

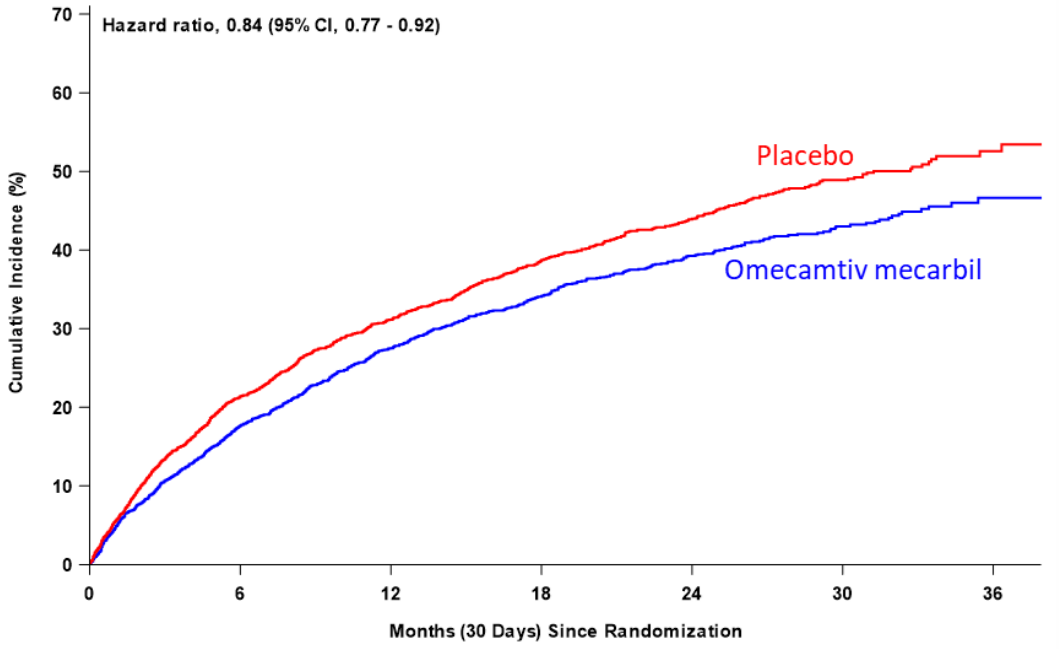
Analyses of time to first event for the primary composite endpoint, HF event, CV death, and all-cause death indicated that participants in the low LVEF subgroup experienced greater treatment benefit than those in the high LVEF subgroup (Table 13 and Figure 10). In the low LVEF subgroup, nominally significant risk reductions were observed with omecamtiv mecarbil versus placebo for time to first event in the primary composite endpoint (HR=0.84; 95% CI 0.77, 0.92) and for time to the first HF event (HR=0.83; 95% CI 0.75, 0.92). In the high LVEF subgroup, analyses of the primary composite endpoint and individual component analyses did not indicate an overall treatment benefit.

Table 13: Clinical Outcomes in LVEF Subgroups

LVEF ≤ 28% (N = 4456)	**Omecamtiv Mecarbil (N = 2213)**	**Placebo (N = 2243)**	**HR (95% CI)**	**ARR**
	# Events		**p value**	**(per 100 pt yrs)**
Primary Outcome	850	971	0.84 (0.77, 0.92); p<0.001	5.1
CV Death	195	212		
HF Hosp	614	700		
Urgent Outpatient Visit	41	59		
CV Death	459	500	0.92 (0.81, 1.05); p=0.21	1.0
Heart Failure Hospitalization	635	727	0.84 (0.76, 0.94); p=0.002	3.7
All-cause Death	607	650	0.94 (0.84, 1.05); p=0.27	1.1
First HF event	655	759	0.83 (0.75, 0.92); p<0.001	4.3
LVEF > 28% (N = 3776)	**Omecamtiv Mecarbil (N = 1907)**	**Placebo (N = 1869)**	**HR (95% CI)**	**ARR**
	# Events		**p value**	**(per 100 pt yrs)**
Primary Outcome	673	636	1.04 (0.94, 1.16); p=0.45	-0.9
CV Death	151	159		
HF Hosp	493	433		
Urgent Outpatient Visit	29	44		
CV Death	349	298	1.15 (0.98, 1.34); p=0.08	-1.3
Heart Failure Hospitalization	507	452	1.11 (0.98, 1.26); p=0.11	-1.7
All-cause Death	460	415	1.09 (0.95, 1.24); p=0.23	-1.1
First HF event	522	477	1.08 (0.95, 1.22); p=0.24	-1.3

ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; N = number of participants.

Figure 10: Cumulative Incidence Estimates for Primary Composite Endpoint in the Prespecified Baseline LVEF ≤28% Subgroup

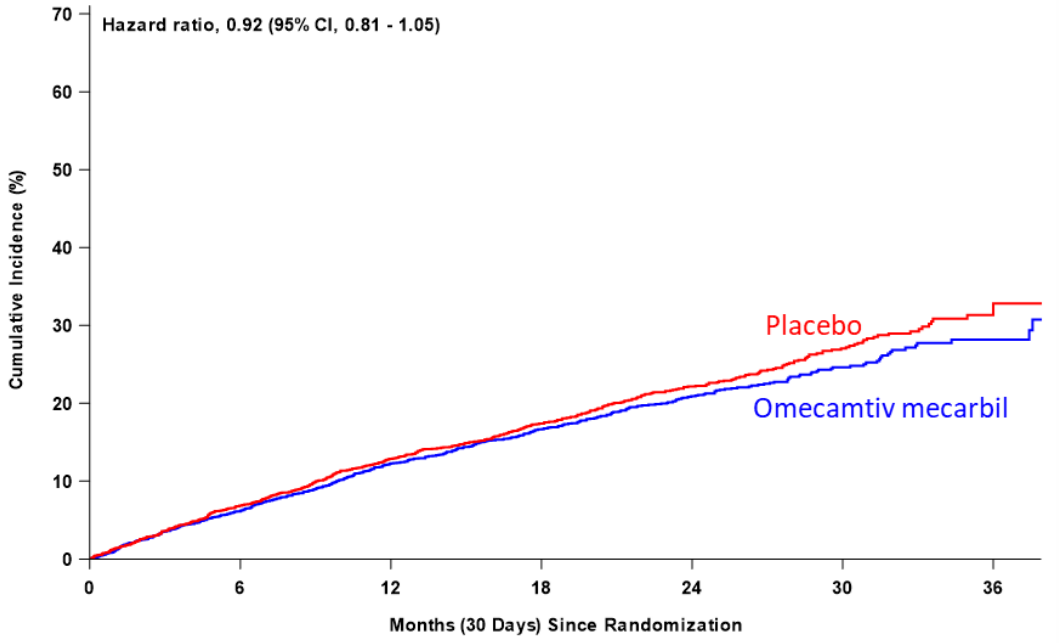


Placebo	2243	1735	1492	1035	649	295	64
Omecamtiv mecarbil	2213	1799	1557	1100	711	314	76

3.5.2.2. Cardiovascular Death

Comparing omecamtiv mecarbil to placebo in participants with LVEF ≤ 28%, a total of 459 (20.7%) participants in the omecamtiv mecarbil group and 500 (22.3%) in the placebo group had an outcome of CV death. The HR (95% CI) was 0.92 (0.81, 1.05). The cumulative incidence estimates of CV death for the participants with LVEF ≤ 28% is presented in Figure 11.

Figure 11: Cumulative Incidence Estimates for Cardiovascular Death in the Prespecified Baseline LVEF ≤ 28% Subgroup

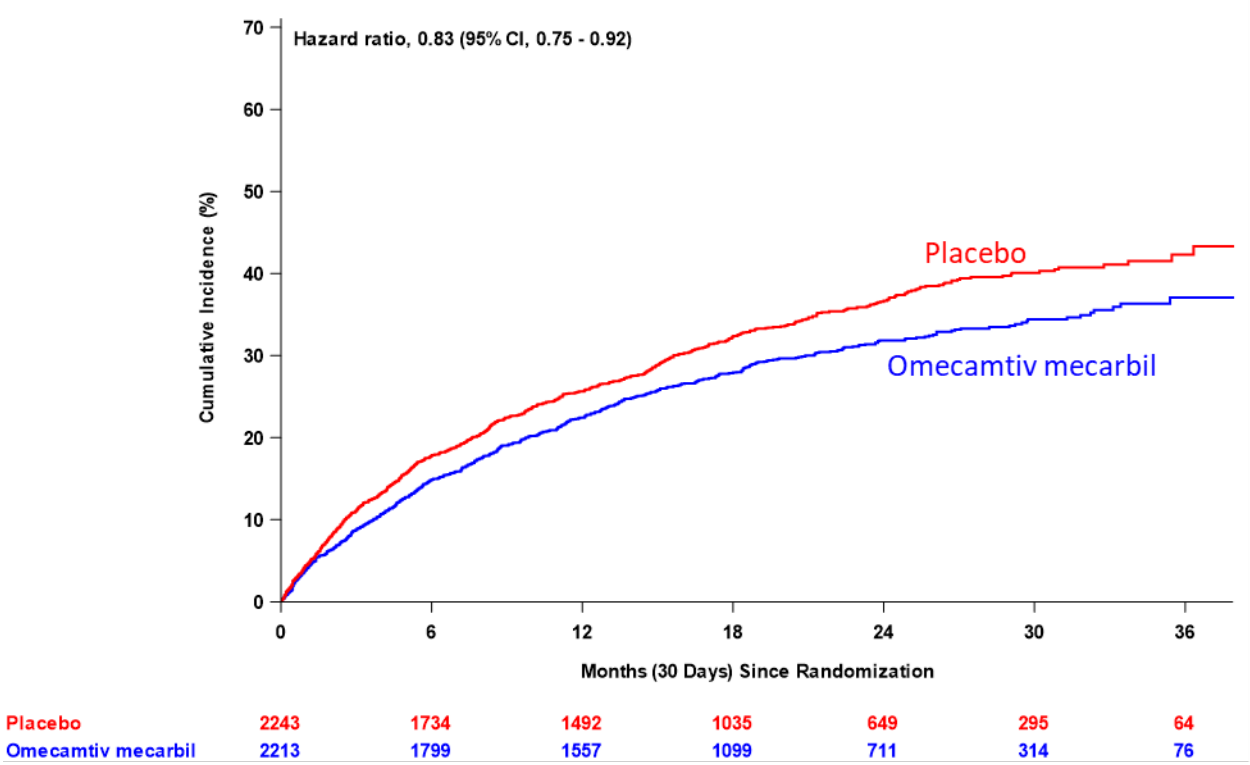


Placebo	2243	2055	1888	1390	894	431	98
Omecamtiv mecarbil	2213	2050	1875	1393	920	414	106

3.5.2.3. Heart Failure Events

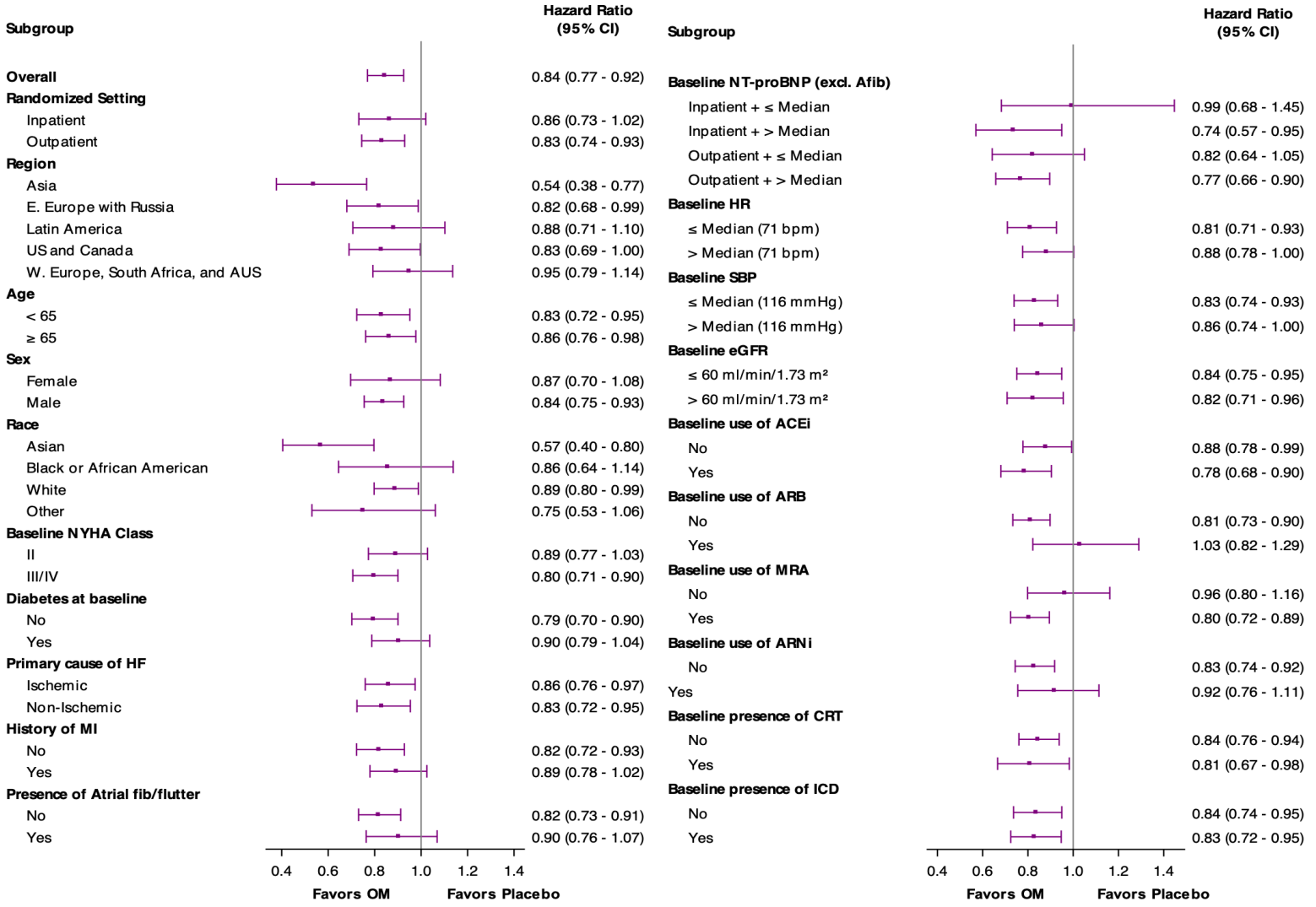
Comparing omecamtiv mecarbil to placebo in participants with LVEF ≤ 28%, 655 (29.6%) participants in the omecamtiv mecarbil group and 759 (33.8%) in the placebo group had a HF event including HF hospitalization. Participants in the omecamtiv mecarbil group had a nominally significant lower risk compared with the placebo group (HR=0.83 (0.75, 0.92); p<0.001; absolute risk reduction [ARR]=4.3%). In the overall population, the HR (95% CI) was 0.93 (0.86, 1.00). The cumulative incidence estimates of heart failure event for the participants with LVEF ≤ 28% is presented in Figure 12. The cumulative event curves begin to separate at approximately 2 months in favor of the omecamtiv mecarbil group.

Figure 12: Cumulative Incidence Estimates for Heart Failure Event in the Baseline LVEF ≤ 28% Subgroup



Analyses of the primary composite endpoint for the prespecified subgroups in participants with LVEF ≤ 28% generally demonstrated positive treatment effects that were consistent with those observed in the overall LVEF ≤ 28% group. Nearly all point estimates for the primary endpoint were less than unity favoring omecamtiv mecarbil compared with placebo. HR (95% CI) estimates for the treatment difference between groups in the primary composite endpoint for all subgroups are depicted in Figure 13.

Figure 13: Forest Plot of the Primary Composite Endpoint in the Prespecified Subgroups for Participants with Baseline LVEF ≤ 28%



CI = confidence interval; NYHA = New York Heart Association; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; N = number of participants; NT-proBNP = N terminal prohormone B-type natriuretic peptide; SBP = systolic blood pressure.

3.5.2.4. Treatment Effect as a Function of Baseline LVEF as a Continuous Variable

As the treatment effect was strongly modified by baseline LVEF, the relationship between LVEF evaluated as a continuous variable and risk for the primary composite endpoint was further examined. As baseline LVEF decreased, the incidence of the primary composite endpoint increased in both the omecamtiv mecarbil and placebo groups, as expected; however, the incidence rate increased to a lesser extent in the omecamtiv mecarbil group, resulting in increasingly greater absolute risk reductions (Figure 14A). Similarly, treatment with omecamtiv mecarbil was associated with increasingly greater risk reductions with decreasing baseline LVEF (Figure 14B). Thus, there were greater benefits with omecamtiv mecarbil treatment versus placebo associated with lower LVEF at baseline. This finding has strong biological plausibility, given that omecamtiv mecarbil directly increases myocardial contractility and improves cardiac function consistent with its mechanism of action. Patients with worse left ventricular function might be expected to benefit more from omecamtiv mecarbil because of its effect on increasing cardiac contractility and SV.

Figure 14: Incidence Rate (A) and Treatment Effect (B) for the Primary Endpoint as a Function of Left Ventricular Ejection Fraction

A. Incidence Rate per 100 Patient Years (95% CI)

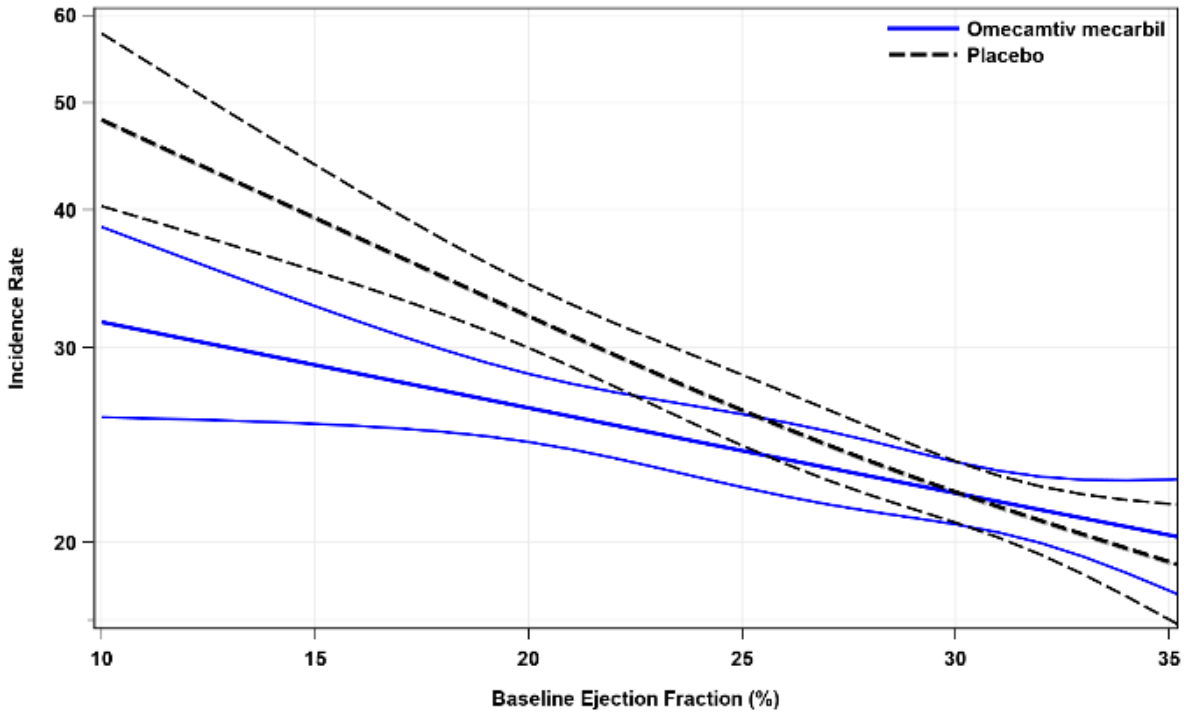
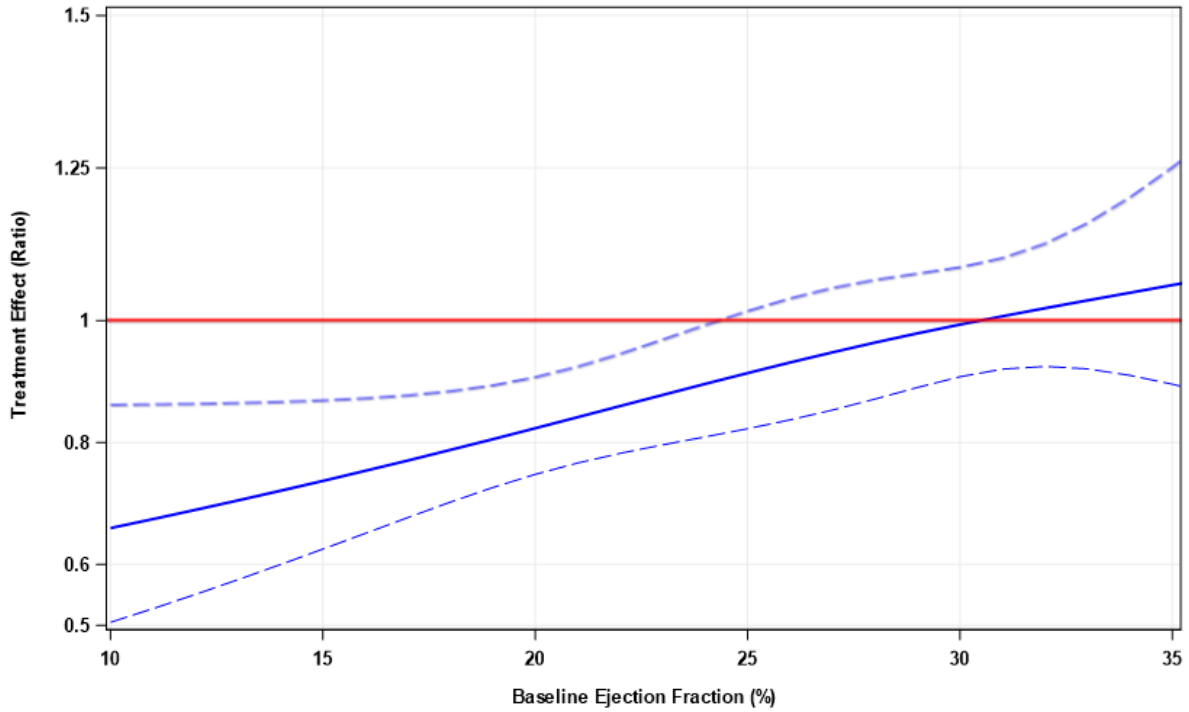


Figure 14: Incidence Rate (A) and Treatment Effect (B) for the Primary Endpoint as a Function of Left Ventricular Ejection Fraction (Continued)

B. Treatment Effect Ratio (95% CI)



3.5.2.5. Treatment Effect of Omecamtiv Mecarbil by Baseline LVEF in Combination with Other Measures of Higher Risk Patients

It is important that new therapies address the greatest needs of patients with heart failure and so we undertook an analysis of the treatment effect of omecamtiv mecarbil in participants with LVEF ≤ 28% and common clinical markers of higher risk such as higher NT-proBNP, poor functional capacity (NYHA Class III/IV), low SBP, and recent HF hospitalization. As one can see in Table 14, these patients have inordinately high event rates that are positively impacted by omecamtiv mecarbil with highly nominally significant hazard rate reductions and absolute risk reductions that grow commensurately as patient risk increases. These patients represent some of the most difficult to treat and for whom additional treatment options are sorely needed.

Table 14: Treatment Effect of Omecamtiv Mecarbil in Participants with LVEF ≤ 28% and Other Common Clinical Markers of Higher Risk

	Omecamtiv Mecarbil	Placebo	HR (95% CI), p value	ARR (per 100 pt yrs)
	Event Rate Incidence (per 100 pt yrs)			
Primary Outcome				
LVEF ≤ 28% (n = 4456)	26.1	31.2	0.84 (0.77, 0.92); p<0.001	5.1
LVEF ≤ 28% + HF Hosp < 3 mo (n = 2692)	30.2	36.2	0.83 (0.74, 0.93); p=0.002	6.0
LVEF ≤ 28% + SBP < 110 mmHg (n = 1820)	31.7	39.7	0.81 (0.70, 0.92); p=0.002	8.0
LVEF ≤ 28% + NYHA III/IV (n = 2132)	33.6	42.7	0.80 (0.71, 0.90); p<0.001	9.1
LVEF ≤ 28% + NT-proBNP > 2000 pg/mL (n = 2431)	36.0	47.3	0.77 (0.69, 0.87); p<0.001	11.3

3.5.3. Heart Rate and NT-proBNP

Echocardiography was not performed in GALACTIC-HF, however two pharmacodynamic measures, NT-proBNP and heart rate, were assessed and behaved similarly as observed in the Phase 2 trial, COSMIC-HF (Table 15), providing supportive confirmatory mechanistic evidence for the intended pharmacodynamic effect in GALACTIC-HF.

Table 15: Change in NT-proBNP and Heart Rate at 24 and 48 Weeks

	Overall Population	
	Omecamtiv Mecarbil	Placebo
NT-proBNP, median (IQR), ng/mL		
Week 24	–251 (–1180, 295)	–180 (–915, 441)
Geometric Mean Ratio (95% CI)	0.90 (0.86, 0.94)	
Week 48	-306 (-1315, 280)	-207 (-1026, 491)
Geometric Mean Ratio (95% CI)	0.87 (0.83, 0.92)	
Heart Rate (bpm), mean ± SD		
Week 24	–2.1 ± 12.6	–0.5 ± 12.8
Difference (95% CI)	–1.6 (–2.2, –1.0)	
Week 48	–2.0 ± 13.1	–0.2 ± 13.2
Difference (95% CI)	–1.7 (–2.4, –1.1)	

3.6. Summary of Efficacy

GALACTIC-HF was a large, pivotal, Phase 3, randomized, placebo-controlled, double-blind, parallel group, multicenter trial designed to evaluate the effect of omecamtiv mecarbil, when administered with optimized standard of care HF therapies, on CV outcomes in high-risk participants with HFrEF, including participants currently hospitalized for HF or with a history of HF hospitalization or ED visit within 1 year prior to enrollment. Treatment with omecamtiv mecarbil when compared to placebo resulted in the following:

- Statistically significant and clinically meaningful risk reduction of the primary composite endpoint of time to CV death or HF event (HR [95% CI] = 0.92 [0.86, 0.99]); both components contributed to the time to first event analysis.
- The primary endpoint remained statistically significant across a range of prespecified and ad hoc sensitivity analyses.
- No effect on risk of CV death or all-cause death in the overall study population.
- Evidence for global heterogeneity of effect ($p = 0.008$) in the prespecified subgroups with the LVEF as the most significant modifier of treatment effect ($p = 0.005$) with HR (95% CI) = 0.84 (0.77, 0.92); $p < 0.001$ for the prespecified LVEF subgroup of ≤ median (28%).
- When lower LVEF was combined with other clinical features of higher risk, greater apparent clinical benefit was observed.

In conclusion, the primary composite endpoint of this trial was met, and omecamtiv mecarbil compared to placebo significantly reduced the risk of time to first HF event or CV death, a finding driven primarily by the reduction in HF events. While the overall treatment effect was modest, it was robust to a number of sensitivity analyses. Per prespecified analyses, participants with lower baseline LVEF had a greater, and more clinically meaningful, risk reduction of the primary endpoint. This finding was sustained and the absolute treatment effect larger when combined with other common clinical characteristics that portend patients at higher risk. Altogether, the totality of the data evaluated for concordance with the guidance (FDA 2019a), indicates persuasiveness of the results demonstrating substantial evidence of effectiveness.

4. SAFETY

The overall omecamtiv mecarbil clinical development safety database comprises data from approximately 10,500 participants in 33 completed studies. The clinical safety profile of omecamtiv mecarbil is based on safety data from a total of 5,637 participants who received at least 1 dose of omecamtiv mecarbil across the 33 completed clinical studies.

4.1. Safety in Early Phase Studies

The dose-limiting effects and exposures of omecamtiv mecarbil were established in Phase 1 and Phase 2a studies of healthy participants and participants with HF using both IV and oral routes of dosing. In total, 269 participants received at least 1 dose of omecamtiv mecarbil. In these studies, there were 15 participants who had omecamtiv mecarbil plasma concentrations > 1,200 ng/mL and of these, 5 participants undergoing IV infusions of omecamtiv mecarbil had clinically

evident signs and symptoms of cardiac ischemia or troponin I > upper reference limit; the peak creatine kinase-MB was 12 IU/L or less in all cases. In each case, symptoms of cardiac ischemia were self-limiting following discontinuation of omecamtiv mecarbil and no other long-term sequalae or lasting impact on cardiac function were evident.

In the Dose Escalation Phase of COSMIC-HF, fixed dosing of omecamtiv mecarbil (ie, 25 mg BID or 50 mg BID × 7 days) was first explored and was generally well tolerated. However, one participant receiving 50 mg BID achieved a concentration of omecamtiv mecarbil exceeding 1,200 ng/mL (C_{max} on Day 7: 1,320 ng/mL), which was substantially outside the range of the other participants. The participant experienced a positively adjudicated MI, developing angina and a modest rise in troponin. In order to maximize participant exposure of omecamtiv mecarbil in the therapeutic plasma concentration range (200 to 750 ng/mL) and minimize the incidence of excessive plasma concentrations, a PK-guided dose escalation strategy was implemented in the Expansion Phase of COSMIC-HF. Following the implementation of PK-guided dosing, no participants in COSMIC-HF were found to have plasma concentrations of omecamtiv mecarbil >1,000 ng/mL.

4.2. Overall Safety in Patients with HFrEF

Overall, the AE profile of omecamtiv mecarbil was similar to that of placebo with respect to incidence, severity, and seriousness for the studies included in this submission. Acute myocardial ischemia and MI were acknowledged as important identified risks associated with excessive concentrations of omecamtiv mecarbil in early studies. In GALACTIC-HF, the incidences of myocardial ischemic events and MI were similar in the omecamtiv mecarbil and placebo groups. Furthermore, there were no clinically meaningful differences in the incidences of other AEs of special interest, including ventricular arrhythmias, sudden cardiac death, or all-cause mortality between the omecamtiv mecarbil and placebo groups. A lower incidence of adjudicated stroke was observed in the omecamtiv mecarbil group compared with placebo. As expected in this study population, the most common SAEs were events associated with chronic HF (ie, HF events or known complications of chronic HF).

4.2.1. General Adverse Event Profile

In GALACTIC-HF, the incidence, nature, and severity of AEs, fatal AEs, SAEs, and AEs leading to investigational product (IP) discontinuation were similar between the omecamtiv mecarbil and placebo groups (Table 16).

Table 16: Summary of Participant Incidence of Adverse Events in GALACTIC-HF

	Omecamtiv Mecarbil (N=4,110) n (%)	Placebo (N=4,101) n (%)
All treatment-emergent adverse events	3,594 (87.4)	3,622 (88.3)
Grade ≥ 2	3,268 (79.5)	3,324 (81.1)
Grade ≥ 3	2,553 (62.1)	2,609 (63.6)
Grade ≥ 4	1,299 (31.6)	1,333 (32.5)
Serious adverse events	2,373 (57.7)	2,435 (59.4)
Adverse events leading to withdrawal of IP	432 (10.5)	447 (10.9)
Serious	332 (8.1)	337 (8.2)
Nonserious	110 (2.7)	112 (2.7)
Fatal adverse events	837 (20.4)	823 (20.1)

IP = Investigational product; N = number of participants randomized excluding study center 29002 and who received at least 1 dose of investigational product, n = number of participants with observed data.
Note: Percentages are based on N.

4.2.2. Common Adverse Events

Cardiac failure was the most frequently reported AE in GALACTIC-HF, consistent with the risk profile of the study population; the incidence of adverse events of cardiac failure (as a preferred MedDRA term) trended lower with omecamtiv mecarbil compared to placebo (Table 17). The incidences of other commonly reported AEs were similar between omecamtiv mecarbil and placebo, with small differences consistent with a play of chance.

Table 17: Adverse Events ≥5% in Either Treatment Group in GALACTIC-HF

Preferred Term	Omecamtiv Mecarbil (N=4,110) n (%)	Placebo (N=4,101) n (%)
Cardiac failure	1132 (27.5)	1203 (29.3)
Hypotension	309 (7.5)	271 (6.6)
Dyspnea	273 (6.6)	277 (6.8)
Pneumonia	259(6.3)	292 (7.1)
Dizziness	237 (5.8)	189 (4.6)
Atrial fibrillation	236 (5.7)	263 (6.4)
Acute kidney injury	230 (5.6)	225 (5.5)
Cardiac failure acute	221 (5.4)	263 (6.4)
Hyperkalemia	216 (5.3)	230 (5.6)
Cardiac failure chronic	204 (5.0)	210 (5.1)
Hypertension	198 (4.8)	229 (5.6)

N = Number of participants randomized excluding study center 29002 and who received at least 1 dose of investigational product, n = number of participants with observed data.
Note: Percentages are based on N.

4.2.3. Serious Adverse Events

In GALACTIC-HF, the overall incidence of SAEs was similar between the omecamtiv mecarbil (57.7%) and placebo (59.4%) groups (Table 18). There were no notable differences in the types or incidence of SAEs between the omecamtiv mecarbil and placebo groups by system organ class (SOC). The incidence of the most frequently reported SAE of cardiac failure trended lower with omecamtiv mecarbil compared with placebo. No individual SAE term was reported with ≥1% higher incidence in the omecamtiv mecarbil group relative to the placebo group.

Table 18: Serious Adverse Events ≥5% in Either Treatment Group in GALACTIC-HF

Preferred Term	Omecamtiv Mecarbil (N=4,110) n (%)	Placebo (N=4,101) n (%)
Number of participants with at least one SAE	2373 (57.7)	2435 (59.4)
Cardiac failure	988 (24.0)	1045 (25.5)
Cardiac failure acute	212 (5.2)	251 (6.1)

N = Number of participants randomized excluding study center 29002 and who received at least 1 dose of investigational product, n = number of participants with observed data.
Note: Percentages are based on N.

4.2.4. Deaths

In GALACTIC-HF, mortality rates were not different between omecamtiv mecarbil and placebo in the overall study population. Treatment-emergent all-cause death occurred in 25.9% (n = 1,067) of participants in the omecamtiv mecarbil group and in 25.9% (n = 1,065) of participants in the placebo group. Treatment-emergent CV death occurred in 19.6% (n = 808) of participants in the omecamtiv mecarbil group and in 19.4% (n = 798) of participants in the placebo group.

4.2.5. Adverse Events Leading to Withdrawal of Investigational Product

In GALACTIC-HF, the incidence of AEs that led to withdrawal of IP was similar between the omecamtiv mecarbil group (10.5%) and the placebo group (10.9%). Most AEs leading to IP withdrawal occurred in the SOC Cardiac disorders for omecamtiv mecarbil (5.3%) and placebo (5.5%) treatment groups. The only AE leading to withdrawal of IP in ≥ 2% of participants in either treatment group was cardiac failure (2.3% omecamtiv mecarbil, 2.0% placebo).

4.2.6. Adverse Events of Interest

Adjudicated AEs of interest, including MCIE (MI, unstable angina hospitalization, and coronary revascularization) and strokes, and AEs related to ventricular arrhythmias in GALACTIC-HF, are presented in Table 19. There were no clinically meaningful differences in adjudicated MI or ventricular arrhythmias. A nominally significant reduction in stroke was observed with omecamtiv mecarbil (1.8%) compared to placebo (2.7%), consistent with improved cardiac contractility and reduced risk of thromboembolism.

Table 19: Adverse Events of Interest in GALACTIC-HF

	Omecamtiv Mecarbil (N=4,110) n (%)	Placebo (N=4,101) n (%)	Relative Risk (95% CI)
Adverse Event of Interest			
Ventricular tachyarrhythmia	290 (7.1)	304 (7.4)	0.95 (0.82 – 1.11)
Torsade de pointes or QT prolongation	176 (4.3)	195 (4.8)	0.90 (0.74 – 1.10)
Serious adverse ventricular arrhythmia leading to treatment	119 (2.9)	127 (3.1)	0.94 (0.73 – 1.20)
Adjudicated major cardiac ischemic event	200 (4.9)	188 (4.6)	1.06 (0.87 – 1.29)
Myocardial infarction	122 (3.0)	118 (2.9)	–
Hospitalization for unstable angina	25 (0.6)	12 (0.3)	–
Coronary revascularization	115 (2.8)	117 (2.9)	–
Adjudicated stroke	76 (1.8)	112 (2.7)	0.68 (0.51 – 0.91)

CI = confidence interval; HF = heart failure; N = number of participants in the safety analysis set.

4.2.7. Other Safety Evaluations

No safety concerns were identified from the evaluation of vital signs and clinical laboratory abnormalities. No patterns indicative of clinically important treatment-related laboratory abnormalities were observed in hepatic tests or renal function tests.

In GALACTIC-HF, there were no clinically meaningful differences in blood pressure between treatment groups. The median baseline values were similar between the omecamtiv mecarbil and placebo groups for both systolic (116.0 and 117.0 mm Hg, respectively) and diastolic (70.0 and 71.0 mm Hg, respectively) blood pressure. Overall, the changes from baseline in systolic and diastolic blood pressure were balanced between groups and consistent over time.

In GALACTIC-HF, a small decrease in heart rate (pulse) was observed in the omecamtiv mecarbil group compared with the placebo group, consistent with improved cardiac function. The median changes from baseline in heart rate across time points ranged from -2.0 to 0.0 bpm in the omecamtiv mecarbil group and from 0.0 to 2.0 bpm in the placebo group.

Consistent with results of the modified QT study, there were no notable differences between treatment groups with respect to electrocardiogram (ECG) assessments in GALACTIC-HF, including no differences in corrected QT interval using Fridericia's formula (QTcF). In the analysis set of centrally read ECGs, the incidence of baseline and new post-baseline QTcF values (omecamtiv mecarbil, placebo) > 450 msec (7.3%, 7.7%), > 480 msec (2.8%, 3.1%) and > 500 msec (1.2%, 1.4%) were balanced between treatment groups. Maximum post-baseline increases (omecamtiv mecarbil, placebo) in QTcF > 30 msec (1.5%, 2.0%), and > 60 msec (0.3%, 0.3%) were also similar between the omecamtiv mecarbil and placebo groups. Participant incidences of baseline and new post-baseline ECG abnormalities in the omecamtiv mecarbil group were similar to those observed in the placebo group.

In GALACTIC-HF, the overall median baseline value for troponin I was 0.027 ng/mL in both the omecamtiv mecarbil and placebo groups. There was a small median increase from baseline to Week 24 in troponin I (0.004 ng/mL) in the omecamtiv mecarbil group compared with no change in the placebo group, but there was poor correlation between omecamtiv mecarbil plasma concentrations and maximum change from baseline in troponin I ($r^2 = 0.00$). Importantly, there was no imbalance in adjudicated MI by continuous or categorical analyses of maximal troponin excursion, indicating no clinically important adverse treatment effect related to threshold-defined troponin levels.

In GALACTIC-HF, there were no changes in creatinine or potassium in the omecamtiv mecarbil group compared with the placebo group. At Weeks 24 and 48, respectively, the mean change (± SD) from baseline in creatinine was 0.03 ± 0.33 and 0.06 ± 0.39 in the omecamtiv mecarbil group and 0.02 ± 0.32 and 0.05 ± 0.38 in the placebo group. At Weeks 24 and 48, respectively, the mean change (± SD) from baseline in potassium was -0.01 ± 0.57 and -0.03 ± 0.59 in the omecamtiv mecarbil group and -0.01 ± 0.57 and -0.02 ± 0.58 in the placebo group.

4.3. Safety Analyses by Key Subgroups

4.3.1. Baseline Ejection Fraction

The greater treatment benefits of omecamtiv mecarbil in the prespecified LVEF ≤28% (median) subgroup described in Table 20 were not associated with worse safety or tolerability. The incidences of SAEs overall, SAEs of ventricular arrhythmias, and adjudicated MCIE were similar between omecamtiv mecarbil and placebo in both the LVEF ≤28% and LVEF >28% subgroups (Table 20). Notably, the incidence of adjudicated stroke was lower with omecamtiv mecarbil versus placebo in both the LVEF ≤28% and LVEF >28% subgroups.

Table 20: Safety Outcomes in Prespecified LVEF Subgroups

LVEF ≤28%	Omecamtiv Mecarbil (N=2,208)	Placebo (N=2,236)
Any treatment-emergent SAE	1,299 (58.8)	1,385 (61.9)
AE: Ventricular tachyarrhythmia	177 (8.0)	184 (8.2)
AE: Torsade de Pointes or QT prolongation	114 (5.2)	129 (5.8)
Serious adverse ventricular arrhythmia leading to treatment	76 (3.4)	81 (3.6)
Adjudicated major cardiac ischemic event	101 (4.6)	94 (4.2)
Myocardial infarction	66 (3.0)	64 (2.9)
Hospitalization for unstable angina	8 (0.4)	4 (0.2)
Coronary revascularization	58 (2.6)	56 (2.5)
Adjudicated stroke	36 (1.6)	63 (2.8)

Table 20: Safety Outcomes in Prespecified LVEF Subgroups (Continued)

LVEF >28%	Omecamtiv Mecarbil (N=1,902)	Placebo (N=1,865)
Any treatment-emergent SAE	1,074 (56.5)	1,050 (56.3)
AE: Ventricular tachyarrhythmia	113 (5.9)	120 (6.4)
AE: Torsade de Pointes or QT prolongation	62 (3.3)	66 (3.5)
Serious adverse ventricular arrhythmia leading to treatment	43 (2.3)	46 (2.5)
Adjudicated major cardiac ischemic event	99 (5.2)	94 (5.0)
Myocardial infarction	56 (2.9)	54 (2.9)
Hospitalization for unstable angina	17 (0.9)	8 (0.4)
Coronary revascularization	57 (3.0)	61 (3.3)
Adjudicated stroke	40 (2.1)	49 (2.6)

AE = adverse event; LVEF = left ventricular ejection fraction; N = number of participants; n = number of participants with observed data; SAE = serious adverse event.

4.3.2. Baseline Atrial Fibrillation/Flutter

The presence or absence of AFF at baseline was observed to have one of the strongest prespecified univariate ($p = 0.012$) and post hoc multivariate treatment-covariate interactions for the primary composite endpoint ($p = 0.006$). Further analyses were conducted sequentially to better characterize and understand this observation.

4.3.2.1. Summary of Efficacy Outcomes in Patients with Atrial Fibrillation/Flutter

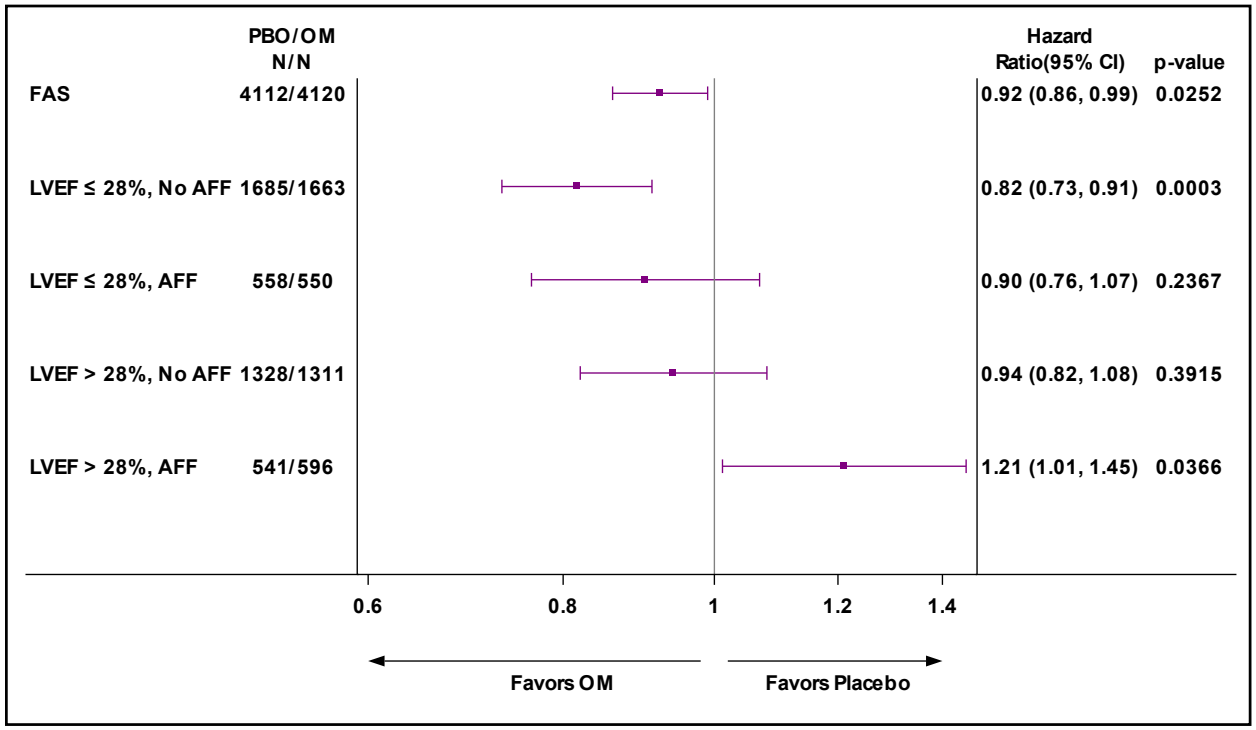
Baseline characteristics indicated that participants with AFF were older, had a higher incidence of inpatient status at randomization, were more likely to be NYHA Class III/IV, had more frequent digoxin and anticoagulant use, had higher NT-proBNP, and had lower eGFR.

Analyses of time to first event for the primary composite endpoint indicated that the subgroup of participants without AFF at baseline experienced greater treatment benefit with omecamtiv mecarbil than the subgroup of participants with AFF at baseline (Table 21). Consistent with the treatment effect modification by LVEF observed in the overall study population, participants with baseline AFF and LVEF ≤ median experienced treatment benefit for the primary composite endpoint compared to participants with baseline AFF and LVEF > median (Figure 15).

Table 21: Primary Composite Endpoint in Subgroups with and without Atrial Fibrillation/Flutter

Omecamtiv Mecarbil		Placebo		HR (95% CI); p-value	ARR (per 100 pt yrs)
n/N (%)	Rate (per 100 pt yrs)	n/N (%)	Rate (per 100 pt yrs)		
No Atrial Fibrillation/Flutter					
981/2,974 (33)	20.7	1,103/3,013 (37)	24.2	0.86 (0.79, 0.94); p < 0.001	3.5
Atrial Fibrillation/Flutter					
542/1,146 (47)	34.8	504/1,099 (46)	32.7	1.05 (0.93, 1.18); p = 0.47	-2.1

Figure 15: Primary Composite Endpoint by Atrial Fibrillation/Flutter and LVEF Subgroups

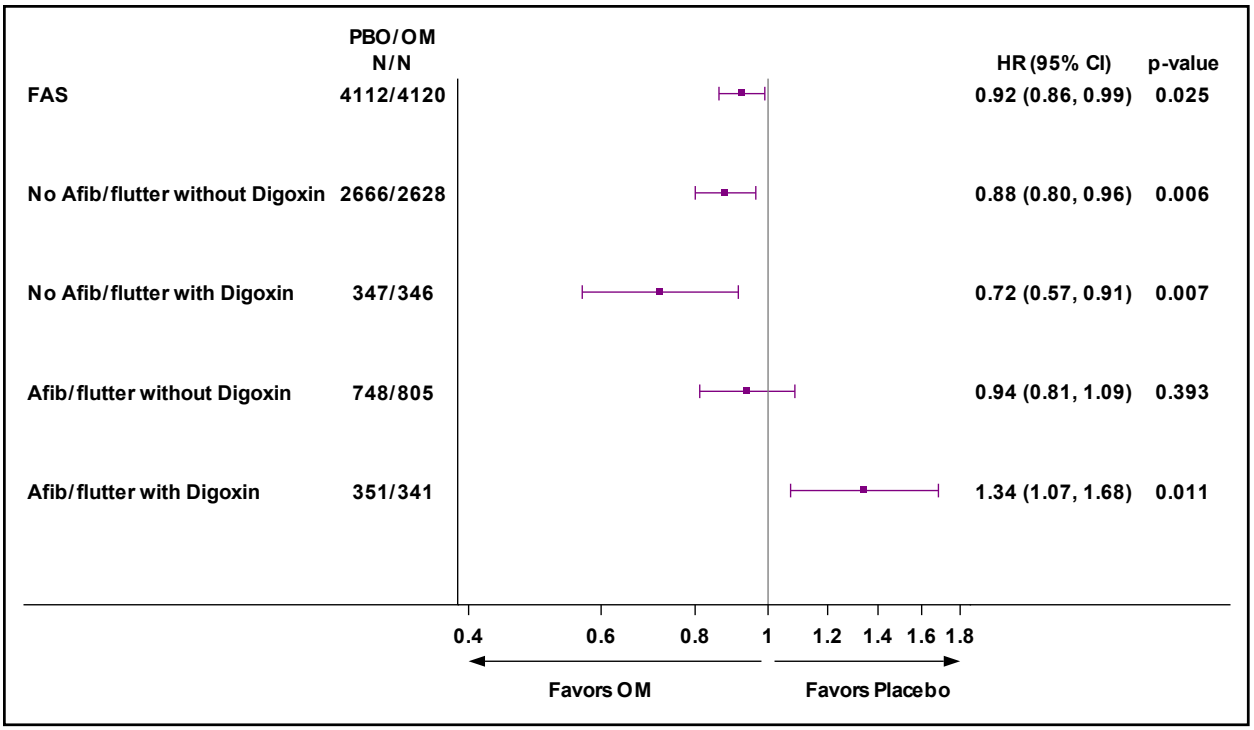


AFF = Atrial fibrillation/flutter; FAS = full analysis set; LVEF = left ventricular ejection fraction; OM = omecamtiv mecarbil; PBO = placebo

The potential etiology for the difference in clinical outcomes between AFF subgroups was explored; however, no responsible factor was definitively identified. As expected, digoxin use was higher in the participants with baseline AFF compared with participants without baseline AFF (30.9% vs 11.5%) and likely represents the use of digoxin for ventricular rate control. Analysis of AFF with and without digoxin use in the multivariable treatment-covariate model revealed a statistically significant treatment covariate interaction (p = 0.003). In participants with atrial fibrillation/flutter who received digoxin, the hazard ratio favored placebo and was nominally statistically significant (Figure 16). Although this finding might suggest a deleterious

interaction between omecamtiv mecarbil and digoxin, participants taking digoxin who were not in atrial fibrillation/flutter had a hazard ratio that was nominally statistically significant in favor of omecamtiv mecarbil. These directionally opposite results are difficult to interpret, and do not help to identify a causative mechanism.

Figure 16: Primary Composite Endpoint with or without Atrial Fibrillation/Flutter and Digoxin Use at Baseline



FAS = full analysis set; OM = omecamtiv mecarbil; PBO = placebo

4.3.2.2. Summary of Safety Outcomes in Patients by Atrial Fibrillation/Flutter

The safety outcomes in the subgroup by baseline AFF are summarized in Table 22. There was no increased incidence of MI, ventricular arrhythmias, or sudden cardiac death with omecamtiv mecarbil versus placebo. There was a higher incidence of HF as an adjudicated cause of CV death in participants with AFF who were treated with omecamtiv mecarbil compared with placebo. The incidence of stroke was decreased with omecamtiv mecarbil versus placebo in both participants with and without AFF at baseline.

Table 22: Safety Outcomes in Participants with and without Atrial Fibrillation/Flutter at Baseline

Variable, n (%)	No Atrial Fibrillation/Flutter		Atrial Fibrillation/Flutter	
	Omecamtiv Mecarbil (n=2,965)	Placebo (N=3,005)	Omecamtiv Mecarbil (n=1,145)	Placebo (N=1,096)
Any treatment-emergent serious adverse event	1,621 (54.7)	1,733 (57.7)	752 (65.7)	702 (64.1)
AE: Ventricular tachyarrhythmia	199 (6.7)	217 (7.2)	91 (7.9)	87 (7.9)
AE: Torsade de Pointes or QT prolongation[a]	118 (4.0)	130 (4.3)	58 (5.1)	65 (5.9)
Serious adverse ventricular arrhythmia leading to treatment	78 (2.6)	88 (2.9)	41 (3.6)	39 (3.6)
Adjudicated major cardiac ischemic event	169 (5.7)	153 (5.1)	31 (2.7)	35 (3.2)
Myocardial infarction	104 (3.5)	99 (3.3)	18 (1.6)	19 (1.7)
Hospitalization for unstable angina	20 (0.7)	9 (0.3)	5 (0.4)	3 (0.3)
Coronary revascularization	95 (3.2)	90 (3.0)	20 (1.7)	27 (2.5)
Adjudicated stroke	54 (1.8)	71 (2.4)	22 (1.9)	41 (3.7)
Adjudicated CV death	499 (16.8)	548 (18.2)	307 (26.8)	249 (22.7)
Acute myocardial infarction	14 (0.5)	13 (0.4)	4 (0.3)	2 (0.2)
Heart failure	226 (7.6)	266 (8.9)	187 (16.3)	123 (11.2)
Sudden cardiac	120 (4.0)	132 (4.4)	52 (4.5)	58 (5.3)

AE = adverse event; CV = cardiovascular; N = number of participants; n = number of participants with observed data.

[a] As defined by narrow standardized MedDRA query (SMQ).

5. DOSING & ADMINISTRATION

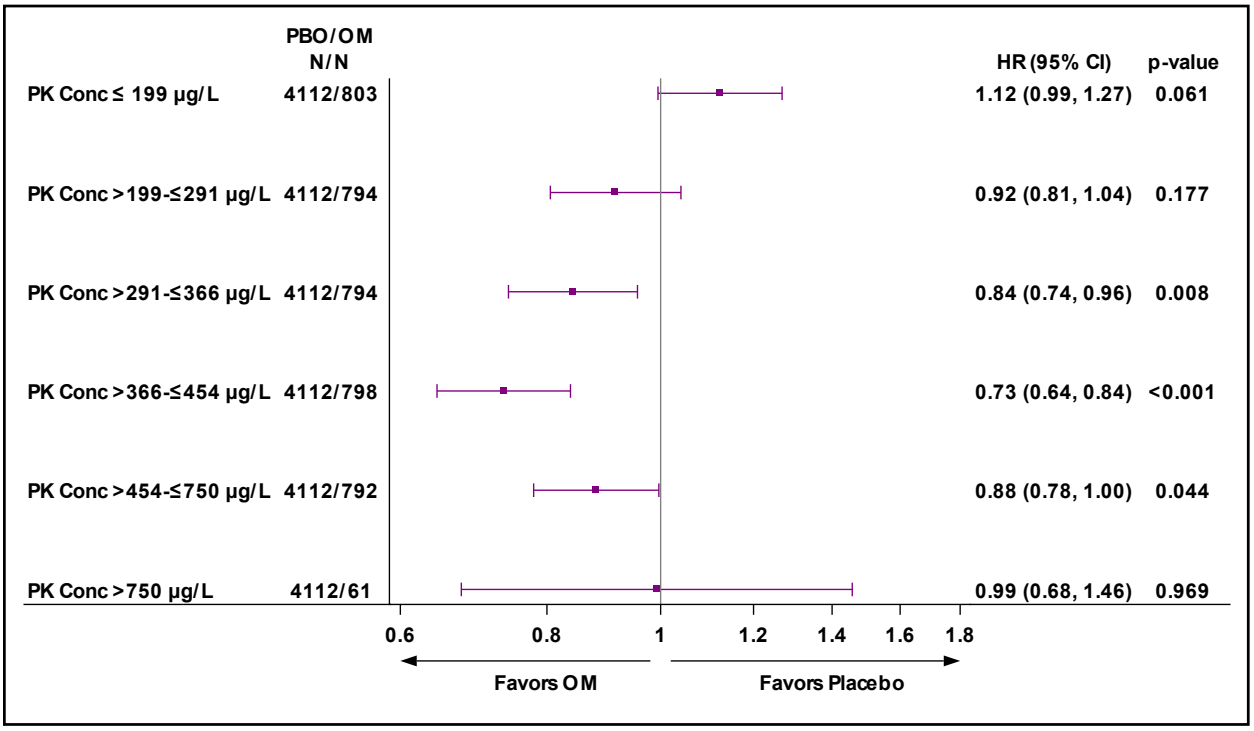
5.1. Dosing Regimen in Clinical Trials

The PK-guided dose titration strategy for the pivotal Phase 3 trial GALACTIC-HF was adapted from the Expansion Phase of COSMIC-HF (Section 4.1). All participants started at 25 mg BID and escalated to 50 mg BID if the predose plasma concentration ($C_{predose}$) was < 200 ng/mL as in COSMIC-HF. Additionally, if $C_{predose}$ was between 200 and 300 ng/mL, then participants escalated to a new intermediate dose of 37.5 mg BID. Given this individualized dosing strategy, achieved concentrations of omecamtiv mecarbil (including maximum and overall distributions) across the 3 doses were expected to be similar, and the percentage of participants predicted to exceed 1,000 mg/mL was less than 0.1% overall.

Results from GALACTIC-HF confirmed that the dose titration algorithm used in this study was largely successful at avoiding omecamtiv mecarbil exposure > 1,000 ng/mL. Three (0.07%) participants treated with omecamtiv mecarbil had plasma concentrations > 1,000 ng/mL but all were < 1,200 ng/mL during the trial; none of these participants experienced AEs associated with elevated concentrations.

As described in Section 3.3.5, a substantial proportion of participants remained on 25 mg BID and were not up-titrated because of missing omecamtiv mecarbil plasma concentrations or failure to confirm participant compliance. However, those participants who achieved the therapeutic concentration range of 200 to 750 ng/mL appeared to experience greater treatment benefit with omecamtiv mecarbil compared with placebo based on concentration-response analyses of the primary composite endpoint (Figure 17), reinforcing the importance of appropriate dose adjustments.

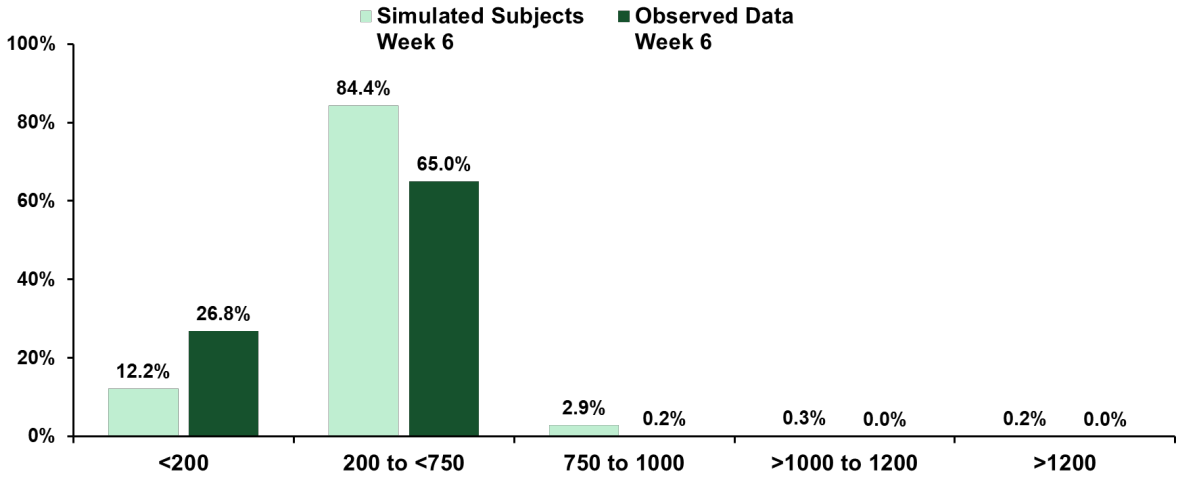
Figure 17: Primary Composite Endpoint by Quintiles of Maximum Plasma Concentration of Omecamtiv Mecarbil Compared with Placebo



5.2. Proposed Commercial Dosing Regimen

In order to simplify dosing and avoid barriers to titration, Cytokinetics originally proposed scheduled dose titration in the NDA for omecamtiv mecarbil based on discussions with FDA. This proposal was supported by the observation that the frequency of excessive C_{min} plasma concentrations was estimated to be very low when simulating forced titration to the maximum dose of 50 mg BID (Figure 18). These modeling results suggested that PK-guided dosing is not essential for the safe and effective use of omecamtiv mecarbil. As such, scheduled dose titration was the original proposed dosing regimen submitted in the NDA for omecamtiv mecarbil.

Figure 18: Comparison of Simulations of Scheduled Titration Versus Observed Data in GALACTIC-HF

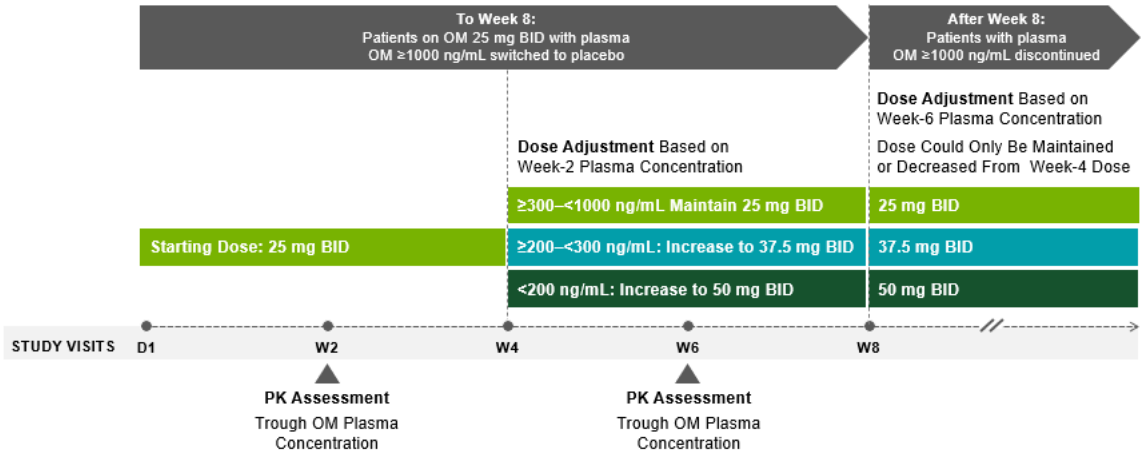


Subsequent discussions with FDA during the review process led Cytokinetics to revise the proposed dosing regimen to align with the PK-guided dose titration strategy used in GALACTIC-HF given the extensive experience with this method of dosing as a means to optimize efficacy and safety. While effectively eliminating the risk of plasma concentrations of omecamtiv mecarbil exceeding 1,200 ng/mL, the use of PK-guided dose titration will also confirm achievement of the therapeutic plasma concentration range (200 to 750 ng/mL).

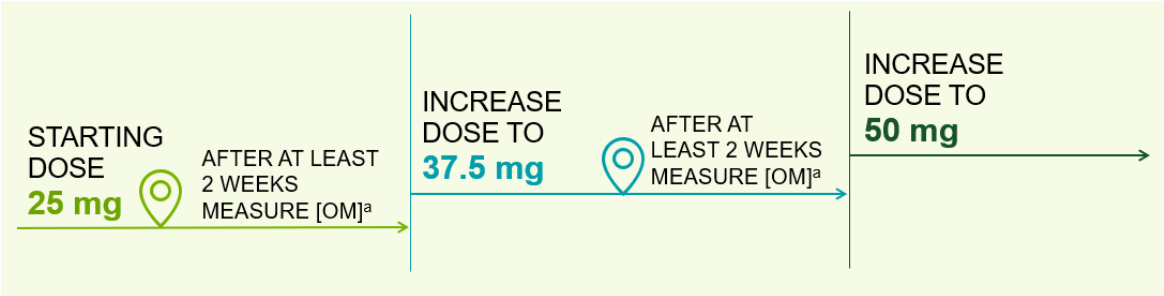
As described in Section 5.1 and illustrated below in Figure 19A, the PK-guided dose selection strategy that was used to achieve therapeutic plasma concentrations of omecamtiv mecarbil in GALACTIC-HF was designed to do so in a single step, using a single PK sample. While there is a potential advantage to this approach, Cytokinetics believes that a simpler, sequential dose titration strategy, targeting the same plasma concentration, will be more reliably implemented and as effective at avoiding excessive concentrations (> 1,200 ng/mL), as illustrated in Figure 19B.

Figure 19: PK-Guided Dose Titration Schemes

A. GALACTIC-HF



B. Post-Marketing Proposal



If plasma concentration is:	Adjust to:
<300 ng/mL	Increase to next higher dose
300 – 750 ng/mL	No change in dose
>750 ng/mL	Decrease to next lower dose

a. [OM] indicates omecamtiv mecarbil plasma concentration

The recommended dosing strategy is to proceed in a stepwise fashion. Omecamtiv mecarbil should be initiated at 25 mg BID and increased to 37.5 mg BID if the plasma concentration of omecamtiv mecarbil is <300 ng/mL after 2 weeks of treatment. After 2 more weeks of treatment, the plasma concentration of omecamtiv mecarbil should be checked again and the dose increased to 50 mg BID if the plasma concentration of omecamtiv mecarbil remains <300 ng/mL. If at any time, the omecamtiv mecarbil concentration is >750 ng/mL, dose adjustment to the next lowest level should be implemented.

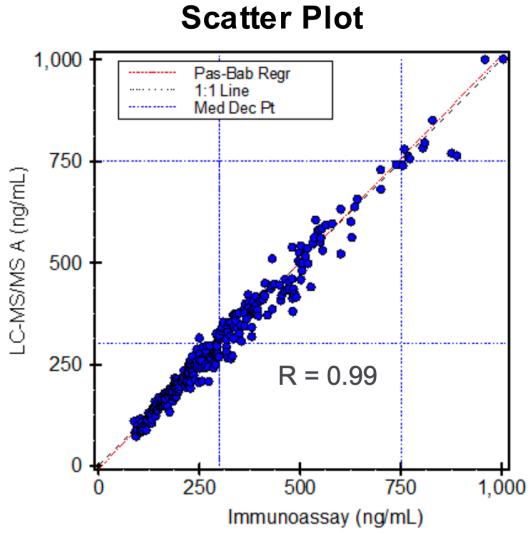
Stepwise dose titration to a target range based on periodic testing will be familiar to cardiologists and other healthcare providers who commonly adjust medications based on blood tests (eg, warfarin, cholesterol lowering medications, renin angiotensin-aldosterone system [RAAS] blockers, digoxin) or physiological parameters (eg, blood pressure with antihypertensive

medications, heart rate with beta blockers), and should not represent a significant barrier to achieving the appropriate dose.

5.3. Proposed Commercial LC/MS/MS Assay

Cytokinetics proposes measurement of plasma concentrations of omecamtiv mecarbil at a central laboratory using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) assay instead of the immunoassay employed in GALACTIC-HF. Prior to the use of the immunoassay, an LC/MS/MS method was used to characterize PK properties and to guide dosing of omecamtiv mecarbil throughout its development program, including in the Phase 2 trial COSMIC-HF. In collaboration with a large commercial national reference laboratory, Cytokinetics has redeveloped and validated an LC/MS/MS assay to be run in a single central laboratory to support dose titration of omecamtiv mecarbil in patients in clinical practice post-approval. This validated LC/MS/MS method provides excellent accuracy and precision as illustrated by the close correlation of measurements with the immunoassay used in GALACTIC-HF (Figure 20). The validation of the LC/MS/MS assay is compliant with the latest guidance documents for analysis of therapeutic drugs as outlined in CLSI C62, FDA Bioanalytical GLP guidance and the commercial laboratory's validation guidance criteria for quantitative methods (incorporating multiple CLSI guidance documents). As requested by FDA, we have submitted the full validation report, which provides clear evidence that the assay is fit for purpose. The validation studies elaborated in the report fully address assessments of analytical performance (eg, accuracy, sensitivity, specificity, repeatability, reproducibility, shelf life, stability), sample collection and preparation, clinical performance, and clinical significance in patients representative of the full intended use population.

Figure 20: Correlation Between the Immunoassay and the LC/MS/MS Assay



Statistical Summary

275 samples

Test	Reference 1	2	3
1	150	5	--
2	5	104	1
3	--	--	10

Legend

	Reference	Test
1	Sub (<=299.99)	Sub (<=299.99)
2	Therap (300 to 750)	Therap (300 to 750)
3	Supra (>750)	Supra (>750)

Data from the immunoassay were obtained at the time of conduct of GALACTIC-HF. Data from the LC/MS/MS assay were generated during assay validation.

6. BENEFIT-RISK AND CONCLUSIONS

There remains a high unmet medical need for patients with HFrEF, particularly those with features of higher risk and persistent or worsening chronic HF where additional treatments with mechanisms complementary to the existing guideline-directed medical therapy (GDMT) could be beneficial. Additionally, optimal doses of GDMTs are often not well-tolerated secondary to side effects such as bradycardia, hypotension, hyperkalemia, and renal insufficiency, which can lead to their underuse and underdosing. It is imperative, therefore, that the addition of new HF agents must be well tolerated and not exacerbate the side effects of existing GDMT.

Although each of the approved treatments evaluated in recent, large, randomized, placebo-controlled CV outcomes trials led to statistically significant reductions in their primary composite endpoints, the event rates, even in the active treatment arms, still ranged from 10.5 to 33.6 events per 100 patient-years of treatment. This demonstrates that these patients continue to experience substantial residual risk of HF hospitalization and CV death. Declining LVEF is an important and powerful predictor of CV outcomes, including all-cause mortality, CV mortality, sudden death, HF-related death, fatal or nonfatal MI, and HF hospitalization (Solomon 2005). A recent analysis from PARADIGM-HF found the relationship between LVEF and outcomes that appeared relatively linear between 15% and 40%, with each 5% drop in EF being associated with approximately a 10% increased risk in cardiovascular death or HF hospitalization after adjusting for baseline covariates (Solomon 2016).

The key benefits and risks of omecamtiv mecarbil in higher-risk patients with persistent or worsening chronic HFrEF have been characterized primarily from participants in the pivotal Phase 3 trial GALACTIC-HF who received omecamtiv mecarbil in addition to standard of care treatment for HFrEF (mean study duration of 21.5 months) with supporting data from Phase 2 clinical studies in similar populations of participants with HFrEF.

In GALACTIC-HF, there was a statistically significant and clinically meaningful reduction in the risk of the composite endpoint of CV death and HF events. This favorable positive effect on clinical outcomes with omecamtiv mecarbil is bolstered by confirmatory evidence that provides strong mechanistic support of effectiveness as observed in the Phase 2 COSMIC-HF trial, which demonstrated improvements in cardiac structure and function including SET, SV, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, NT-proBNP, and heart rate. These findings are consistent with the mechanism of action of omecamtiv mecarbil to increase myocardial contractility and improve cardiac function.

Importantly, prespecified subgroup analyses indicate that LVEF was the most significant treatment effect modifier and that higher-risk patients with lower LVEF experienced greater risk reduction for the primary composite endpoint. More specifically, participants with baseline LVEF ≤28% (median), which represented a majority (54%) of the overall participant population, experienced 16% relative risk reduction and 5.1% absolute risk reduction with omecamtiv mecarbil for the primary composite endpoint ($p < 0.001$). This finding is also consistent with the mechanism of action of omecamtiv mecarbil to increase cardiac contractility, particularly in patients with lower LVEF and worsening HF whose compensatory mechanisms are compromised. In addition, omecamtiv mecarbil substantially reduced the risk of adjudicated stroke, which is a common cause of morbidity and mortality in the HFrEF population; again, this

observation is consistent with the mechanism of action of increasing cardiac contractility and subsequently decreasing intracardiac stasis and risk of thromboembolism.

Omecamtiv mecarbil was well-tolerated and was not associated with side effects commonly observed with neurohormonal therapies. In GALACTIC-HF, discontinuations due to AEs and SAEs were similar between omecamtiv mecarbil and placebo; and there were no clinically meaningful changes in blood pressure, renal function, heart rate, or serum potassium. Therefore, the addition of omecamtiv mecarbil to current GDMT is not expected to exacerbate some of the side effects associated with these HF therapies, such as hypotension, renal impairment, bradycardia, and hyperkalemia. Omecamtiv mecarbil may also be an important treatment option in patients with worsening heart failure and declining systolic function who are unable to tolerate or maximally titrate GDMT.

Acute myocardial ischemia and MI are identified risks that have been observed in some participants with excessive plasma concentrations of omecamtiv mecarbil (>1,200 ng/mL). The expected frequency of excessive plasma concentrations of omecamtiv mecarbil is expected to be negligible with the proposed stepwise, PK-guided dose titration scheme. Incidences of acute myocardial ischemia and MI were similar between the omecamtiv mecarbil and placebo treatment groups in GALACTIC-HF which employed a PK-guided dosing strategy in 8,256 participants. Measurement of plasma concentrations will guide dose titration and maximize achievement of the therapeutic plasma concentration range of 200 to 750 ng/mL, as demonstrated in GALACTIC-HF and as proposed in Section 5.1.

In GALACTIC-HF, prespecified subgroup analyses indicated a significant treatment-covariate interaction between omecamtiv mecarbil and atrial fibrillation. While treatment benefit was not observed in participants with atrial fibrillation in the overall study population, participants with lower LVEF and atrial fibrillation did experience treatment benefit. Further analyses suggested that the interaction was potentially associated with increased risk of adverse HF outcomes in the small subgroup of participants with atrial fibrillation receiving concomitant digoxin at baseline.

In conclusion, the results of this extensive development program support an overall favorable benefit-risk profile for omecamtiv mecarbil as an add-on therapy to GDMT for treatment of HFrEF. Based on its safety and efficacy profile, omecamtiv mecarbil, when added to standard of care, has the potential to fulfill an unmet need in HFrEF by providing a novel and effective treatment strategy that improves clinical outcomes, particularly in higher-risk patients with worsening HF and those intolerant of or with contraindications to one or more standard of care therapies. Based on these data, Cytokinetics believes that omecamtiv mecarbil should be indicated for the patient population that derived the most benefit, those patients with lower LVEF, and so proposes the following indication statement:

> *Omecamtiv mecarbil is a cardiac myosin activator indicated to reduce the risk of cardiovascular death and heart failure events in patients with symptomatic chronic heart failure with reduced ejection fraction. Benefits are increasingly evident the lower the left ventricular ejection fraction (LVEF).*

Cytokinetics has been in discussions with FDA and supports the use of labeling language that focuses on the patients who experience the greatest treatment effect.

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