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TITLE: The Effect of Omecamtiv Mecarbil in Hospitalized Patients as Compared with Outpatients with HFrEF: an Analysis of GALACTIC-HF

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ABSTRACT

BACKGROUND: In the Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF) trial, omecamtiv mecarbil, compared with placebo, reduced the risk of worsening heart failure (HF) events or cardiovascular death in patients with HF and reduced ejection fraction (HFrEF). The primary aim of this prespecified analysis was to evaluate the safety and efficacy of omecamtiv mecarbil by randomization setting i.e., whether participants were enrolled as outpatients or inpatients.

METHODS AND RESULTS: Patients were randomized either during a HF hospitalization or as an outpatient, within one year of a worsening HF event (hospitalization or emergency department [ED] visit). The primary outcome was a composite of worsening HF event (HF hospitalization or an urgent ED or clinic visit) or cardiovascular death.

Of the 8232 patients analyzed, 2084 (25%) were hospitalized at randomization. Hospitalized patients had higher NT-proBNP concentrations, lower systolic blood pressure, reported more symptoms and were less frequently treated with a renin-angiotensin system blocker or a beta-blocker than outpatients. The rate (per 100 person-years [PY]) of the primary outcome was higher in hospitalized patients (placebo group=38.3/100 PY) than in outpatients (23.1/100 PY); adjusted hazard ratio (HR) 1.21 (95%CI 1.12, 1.31). The effect of omecamtiv mecarbil versus placebo on the primary outcome was similar in hospitalized patients (HR 0.89, 95%CI 0.78, 1.01) and outpatients (HR 0.94, 95%CI 0.86, 1.02) (interaction P=0.51).

CONCLUSION: Hospitalized HFrEF patients had a higher rate of the primary outcome than outpatients. Omecamtiv mecarbil reduced the risk of the primary outcome both when initiated in hospitalized patients and in outpatients.

LAY SUMMARY

- In GALACTIC-HF, hospitalized patients were at a higher risk of cardiovascular death or worsening heart failure compared with outpatients.
- This analysis provides new information on the safety and benefits of starting omecamtiv mecarbil in patients during a heart failure hospitalization and in those who are outpatients with heart failure and reduced ejection fraction.
- This analysis highlights that physicians should take the opportunity to optimize heart failure therapies during hospitalization as these patients are at a high risk of adverse outcomes.

Lay Summary

The GALACTIC-HF trial studied a new drug, omecamtiv mecarbil, which increases the duration of the heart's pumping action. In this trial, patients with heart failure and a reduction in heart pump function were started on this drug or placebo either whilst hospitalized with symptoms of worsening heart or as outpatients in the community. In this analysis, we present data which shows that omecamtiv mecarbil was safe when started in either setting and was equally beneficial in reducing the risk of cardiovascular death or worsening heart failure events.

ABBREVIATIONS

eGFR: estimated glomerular filtration rate

GALACTIC-HF: Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure

HFrEF: heart failure with reduced ejection fraction

KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire Total Symptom Score

LVEF: left ventricular ejection fraction

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

NYHA: New York Heart Association

KEYWORDS: Heart failure, omecamtiv mecarbil, myotrope, clinical trial

INTRODUCTION

Despite advances in the pharmacological and device-based management of heart failure with reduced ejection fraction (HFrEF), patients with HFrEF frequently experience worsening of heart failure requiring hospitalization, a visit to an emergency department, or community-based intensification of treatment. The occurrence of a heart failure hospitalization is an independent predictor of future adverse outcomes and risk remains elevated after discharge, particularly in the first few weeks.¹⁻³ Therefore, hospital admission is an opportune time to initiate new therapies for HFrEF which reduce the risk of subsequent rehospitalization and mortality. Furthermore, inpatient initiation of HFrEF therapies, rather than delayed post-discharge initiation, is associated with a greater likelihood of patients being prescribed these life-saving treatments in the longterm.^{4,5} However, there are limited data on the safety and efficacy of the initiation of many HFrEF therapies in hospitalized patients with evidence for the majority of drugs being extrapolated from trials in patients with ambulatory HFrEF or in small, underpowered trials in hospitalized patients using surrogate endpoints.⁶

In the Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF) trial, omecamtiv mecarbil, compared with placebo, reduced the risk of worsening heart failure events or cardiovascular death in patients with HFrEF.⁷ As a cardiac-specific myosin activator, omecamtiv mecarbil enhances effective myosin cross-bridge formation and duration leading to prolonged myocardial contraction and increased stroke volume. A unique design aspect of GALACTIC-HF was that 25% of patients were enrolled during a heart failure hospitalization, permitting a prespecified within-trial comparison of patients by randomization setting up. In this analysis

of GALACTIC-HF, we examined the efficacy and safety of omecamtiv mecarbil when initiated in hospitalized patients as compared with outpatients.

METHODS

GALACTIC-HF was a prospective randomized, double-blind, placebo-controlled trial in patients with HFrEF comparing the efficacy and safety of omecamtiv mecarbil with matching placebo, in addition to standard care. The design, baseline characteristics and primary results of the trial have been published.⁷⁻⁹ The study protocol was approved by the relevant local ethics committees, and all participants provided informed consent.

Trial Patients

Men and women aged ≥ 18 to ≤ 85 years were eligible if they had symptomatic HFrEF with at least 30 days history of treatment for heart failure, were in New York Heart Association (NYHA) functional class II to IV, had a left ventricular ejection fraction (LVEF) $\leq 35\%$, had elevated natriuretic peptide levels (N-terminal pro-B-type natriuretic peptide [NT-proBNP] level ≥ 400 pg/ml [1200 pg/ml for patients in atrial fibrillation] or B-type natriuretic peptide [BNP] ≥ 125 pg/ml [375 pg/ml for patients in atrial fibrillation]) and were optimally treated with pharmacological and device HFrEF therapy according to local guidelines. Patients were eligible for randomization during a hospitalization if the primary reason for admission was worsening heart failure or as an outpatient if they had been hospitalized for worsening heart failure or had an urgent emergency department visit for heart failure within one year before screening. Key exclusion criteria included systolic blood pressure < 85 mmHg, estimated glomerular filtration rate (eGFR) < 20 ml/min/1.73m² and, in hospitalized patients,

the use of inotropes or vasopressors within 72 hours and use of IV vasodilators or diuretics within 12 hours of screening. Full details of the inclusion and exclusion criteria have been published.^{7,8}

Trial Procedures

Following the provision of informed consent, eligible patients were randomized 1:1 to omecamtiv mecarbil or matching placebo. Randomization was stratified according to randomization setting (inpatient or outpatient) and geographic region. The initial dose of omecamtiv mecarbil was 25mg twice daily and a guided dose-titration strategy was employed based on plasma concentrations of omecamtiv mecarbil (available doses were 25mg, 37.5mg, and 50mg twice daily), as detailed previously.⁸ Post randomization follow-up visits were performed at weeks 2, 4, 6, 8, 12, 24, 36, and 48 and every 16 weeks thereafter.

Trial Outcomes

The primary outcome of the trial was a composite of time-to a first episode of worsening heart failure (defined as an urgent clinic visit, emergency department visit, or hospitalization for worsening heart failure requiring treatment intensification beyond a change in oral diuretic therapy) or cardiovascular death. Pre-specified secondary outcomes included the time to cardiovascular death; change in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) from baseline to week 24; time to a first heart failure hospitalization; and time to all-cause death. Time to first worsening heart failure event was an exploratory outcome. Results relating to the effect of omecamtiv mecarbil on KCCQ-TSS by randomization setting (outpatient or inpatient) have previously been published and are

not included in the present manuscript.⁷ All endpoints were independently adjudicated by a Clinical Events Committee (Duke Clinical Research Institute) using standardized definitions.⁸

Statistical Analysis

The comparison between randomization setting was a prespecified subgroup analysis for the primary composite outcome according to the statistical analysis plan.⁷ The additional post hoc analyses presented in this manuscript are exploratory. Baseline characteristics were summarized as counts and percentages for categorical variables and means and standard deviations (SD) or medians and interquartile ranges (IQR) for normally or non-normally distributed continuous variables, respectively.

The relationship between randomization setting and subsequent risk of the primary outcome was examined by means of event rates per 100-person years (PY) and a Cox proportional hazards model with adjustment for randomized treatment (omecamtiv mecarbil or placebo), atrial fibrillation, HF etiology, ejection fraction, NYHA class, systolic blood pressure, heart rate, log-transformed NT-proBNP and eGFR. All patients, irrespective of treatment allocation, were included in this analysis. Models with the same adjustment variables were used to examine the relationship between time from most recent worsening heart failure event before randomization and outcomes in the outpatient strata. A further model was performed including variables for treatment at baseline with an ACE-inhibitor, ARB, or ARNI (yes/no), beta-blocker (yes/no), MRA (yes/no), CRT (yes/no) and ICD (yes/no).

The effect of omeccamtiv mecarbil compared with placebo was examined individually in each randomization setting (inpatient or outpatient) using a Cox proportional hazards model adjusted for eGFR and stratified by region as in the primary GALACTIC-HF analysis.⁷ The treatment effect of omeccamtiv mecarbil compared with placebo relative to time from

qualifying heart failure hospitalization or emergency department visit in the outpatient randomization strata was examined using a Poisson regression model to estimate incidence rates, rate differences, and rate ratios. This model was adjusted for the same factors as above and utilized restricted cubic splines with 4 knots to allow for a non-linear relationship between time from qualifying event and treatment effect. In the restricted cubic spline figure, the 4 knots were placed at the 5th, 35th, 65th, and 95th percentiles of the distribution of the exposure variable. The qualifying event in the outpatient strata was defined as that which occurred most recently before screening and if both events occurred on the same day, the qualifying event was defined as a heart failure hospitalization. Modification of treatment effect was examined by including a randomization setting-by-treatment interaction term in these models. Sensitivity analyses accounting for the competing risk of non-cardiovascular death for the endpoint of cardiovascular death, and all-cause death for non-fatal worsening heart failure endpoints were not significantly different to the results generated by the Cox models described above. All analyses were conducted using STATA version 16 (StataCorp, College Station, Texas). All p values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics

Of the 8232 patients enrolled in GALACTIC-HF, 2084 (25.3%) were hospitalized at the time of randomization. Among the 6148 (74.7%) enrolled as outpatients, the most recent manifestation of worsening heart failure before screening was a heart failure hospitalization in 5669 (92.2%), an emergency department visit in 458 (7.4%) and unspecified in 21 (0.3%).

Baseline characteristics by randomization setting are presented in Table 1 and by randomized treatment in Supplementary Table 1. Patients enrolled during hospitalization, as compared with outpatients, were older, more frequently male, were in a higher (worse) NYHA functional class, and had lower (worse) KCCQ-TSS, mean systolic blood pressure and median eGFR. Hospitalized patients, in comparison with outpatients, were more frequently in atrial fibrillation at screening and had a higher heart rate and concentrations of NT-proBNP and cardiac troponin I. Treatment with a renin-angiotensin system blocker alone, or in combination with a neprilysin inhibitor, and a beta-blocker was less common in hospitalized patients, as compared with outpatients. Conversely, inpatients were more frequently taking a mineralocorticoid receptor antagonist than outpatients.

Cardiovascular outcomes according to randomization setting

Patients enrolled during hospitalization had a higher rate of the primary composite outcome (placebo group rate per 100 patient years [PY] = 38.3) than outpatients (23.1/100 PY); adjusted hazard ratio (HR) 1.21, 95% confidence interval (CI) 1.12, 1.31. After further adjustment for baseline differences in HF treatments the HR was 1.24 (95% CI 1.14, 1.34). The rates of the individual components of the primary composite outcome and other secondary outcomes were similarly greater in hospitalized patients as compared with outpatients - Figure 1 and Supplementary Figure 1. Among patients randomised as inpatients, the event rate was highest in the 3 months following randomization (placebo group = 71.9/100 PY) and fell to 30.4/100 PY at 9 to 12 months following randomization. Among the patients randomized as outpatients, there was a stepwise gradient in risk with those randomized within 3 months of a worsening heart failure event at the highest risk of the primary outcome (placebo group = 26.6/100 PY) as compared with those 9 to 12 months

after an event (19.0/100 PY); adjusted HR 1.20 (95%CI 1.01, 1.42), p for trend = 0.008 -

Figure 2 and Supplement Table 2.

Efficacy of omecamtiv mecarbil by randomization setting

The effect of omecamtiv mecarbil, compared with placebo, on cardiovascular outcomes is summarized by randomization setting in Figure 1 and presented as Kaplan-Meier estimates in Supplementary Figure 1. In the overall population, omecamtiv mecarbil reduced the risk of the primary composite endpoint of time-to-first worsening heart failure event or cardiovascular death by 8% (HR 0.92; 95% CI 0.86 to 0.99). There was no significant modification of treatment effect on the primary outcome whether patients were randomized while hospitalized (HR 0.89; 95% CI 0.78 to 1.01) or as an outpatient (HR 0.94; 95% CI 0.86 to 1.02) - interaction p = 0.51. Due to their higher baseline risk of subsequent events, the absolute benefit in hospitalized patients was greater (absolute risk reduction of 4.2 events per 100 PY; number needed to treat (NNT) over 3 years = 33) than in outpatients (absolute risk reduction of 1.6 events per 100 PY; NNT = 38).

In those randomized as outpatients, the effect of omecamtiv mecarbil on the primary outcome was consistent across the range of time from the most recent worsening heart failure event (either time from admission for most recent hospitalization or time from most recent emergency department visit, whichever occurred most recently before screening) when examined as a categorical variable (interaction p = 0.29 – Figure 3) or as a continuous variable (interaction p = 0.78 - Supplementary Figure 2).

The effects of omecamtiv mecarbil compared with placebo on the individual components of the primary composite outcome and other outcomes are summarized in Figure 1 and

Supplementary Figure 1. There was no modification of treatment effect by randomization setting on time to a first episode of worsening heart failure event (interaction $p = 0.64$) or heart failure hospitalization (interaction $p = 0.66$). However, there was a greater effect in reducing the risk of cardiovascular mortality (interaction $p = 0.055$) or death from any cause (interaction $p = 0.02$) in patients randomized during hospitalization as compared with outpatients.

Safety of omecamtiv mecarbil by randomization setting

Adverse events by randomization setting and randomized treatment are summarized in Supplementary Table 3. Treatment-emergent serious adverse events occurred more frequently in patients randomized as inpatients, as compared with outpatients, but did not differ significantly between the treatment groups.

Supplementary Table 4 summarizes the changes in laboratory measurements and vital signs in those randomized as inpatients and outpatients, and by randomized treatment. The placebo-corrected change in systolic blood pressure from baseline to week 2 was similar in hospitalized patients (0.1 mmHg [95%CI -1.1, 1.3]) and outpatients (-0.7 mmHg [95%CI -1.3, -0.1]). The placebo-corrected change in creatinine at week 12 in hospitalized patients was 0.01 mg/dL (95%CI -0.03, 0.05) and 0.01 mg/dL (95%CI -0.01, 0.03) in outpatients.

DISCUSSION

In this analysis of GALACTIC-HF, the beneficial effect of omecamtiv mecarbil in reducing the risk of worsening HF events or cardiovascular death was consistent regardless of whether patients were randomized during hospitalization for HF or as an outpatient within a year of a worsening HF event. A unique design aspect of GALACTIC-HF was that the proportion of

patients randomized during hospitalization for worsening heart failure was prespecified to account for 25% of the total trial population.⁸ This resulted in the largest cohort of hospitalized patients recruited along with outpatients in a randomized controlled trial in HFrEF to date, facilitating a within-trial comparison of patient characteristics and outcomes by randomization setting.

Several key differences in baseline characteristics by randomization setting (inpatient vs. outpatient) are worth highlighting, including higher median NT-proBNP (2510 pg/mL vs. 1884 pg/mL) and troponin I (37 ng/L vs. 24 ng/L) concentrations, lower mean systolic blood pressure (114 mmHg vs. 117 mmHg) and a lower median eGFR (54 mL/min/1.73m² vs. 60 mL/min/1.73m²). Collectively, these indicated that inpatients were, unsurprisingly, sicker than outpatients. Consequently, and consistent with other trials, the rate of the primary composite outcome of time-to-first cardiovascular death or an episode of worsening HF was higher among inpatients (placebo group event rate 38 per 100 PY) as compared with those randomized as outpatients (23 per 100 PY) and this elevated risk persisted after adjustment for established prognostic variables including NT-proBNP. When compared to other contemporary heart failure trials which recruited hospitalized patients, event rates in hospitalized patients were lower in GALACTIC-HF than in AFFIRM-AHF (A Randomised, Double-blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalisations and Mortality in Iron Deficient Subjects Admitted for Acute Heart Failure) and VICTORIA (The Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction); in those trials, the placebo-group rates of time to first cardiovascular death or HF hospitalization, among inpatients, were 47 and 52 per 100

PY, respectively.^{3,10} These differences likely reflect a lower natriuretic peptide concentration eligibility threshold in GALACTIC-HF than in AFFIRM-AHF and VICTORIA. Indeed, the median NT-proBNP concentration in inpatients in GALACTIC-HF was 2510 pg/mL, as compared with approximately 4700 pg/mL in AFFIRM-AHF and 3100 pg/mL in the VICTORIA subgroup which included inpatients and outpatients randomized within 3 months of a hospitalization.^{3,10} The greater risk of subsequent events among inpatients, as compared with outpatients (all of whom had experienced a worsening HF event in the preceding year), along with the observation of a declining gradient in risk in outpatients from the time from the most recent worsening HF event, highlights that clinicians should view the occurrence of a HF hospitalization as a marker of immediate and serious danger and seize the opportunity to implement disease-modifying therapies to reduce the risk of future adverse outcomes, particularly early after discharge. It is important to highlight that patients with a first presentation of HF, i.e. de novo HF, were not studied in GALACTIC-HF. Prior analyses have reported that these patients have a lower rate of rehospitalization or mortality as compared with patients with worsening chronic HF.¹¹ Nevertheless, these patients are an important sub-group in whom further research is required to evaluate the safety and efficacy of omecamtiv mecarbil.

The beneficial effect of omecamtiv mecarbil in reducing the risk of worsening heart failure events or cardiovascular death was consistent regardless of whether patients were randomized as inpatients or as outpatients. There was similarly no heterogeneity in the effect of treatment on either the time-to a first episode of worsening heart failure or heart failure hospitalization. There was the suggestion of a greater effect on both cardiovascular

and all-cause mortality in inpatients as compared with outpatients, however, these subgroup results must be considered in the context of a non-significant effect on mortality endpoints in the overall GALACTIC-HF population.⁷ In light of their greater baseline risk, the absolute benefit was greater in hospitalized patients as compared with outpatients (NNT of 33 vs. 38 to prevent one primary outcome event over 3 years). Among outpatients, there was no suggestion of heterogeneity of treatment effect depending on the time from the most recent worsening heart failure event to randomization. A similar consistent benefit irrespective of time from recent hospitalization was seen with sacubitril/valsartan and dapagliflozin in the PARADIGM-HF (Prospective Comparison of ARNI with to Determine Impact on Global Mortality and Morbidity in Heart Failure) and DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trials, respectively.^{10,11} This is in contrast to a recent report from the VICTORIA trial where there was an apparent attenuation of the benefit of the soluble guanylate cyclase stimulator vericiguat the closer in time to a heart failure hospitalization a patient was randomized.³

Factors which limit the initiation and continuation of HFrEF therapies in hospitalized patients include pre-existing kidney dysfunction and hypotension, or a clinician's (often misplaced) fear of inducing these. In GALACTIC-HF, the effect of omecamtiv mecarbil on serum creatinine and systolic blood pressure, measured at the earliest available time point following randomization, was minimal and did not differ between the randomization setting. Furthermore, omecamtiv mecarbil represents a viable treatment option when the degree of hypotension and renal impairment precludes the initiation of other therapies for HFrEF; the lower eligibility thresholds for these in GALACTIC-HF (i.e., a systolic blood pressure of ≥ 85

mmHg and an eGFR ≥ 20 mL/min/1.73m²) were less than for the initiation of most HFrEF therapies. In addition, it has previously been shown in both inpatients requiring intravenous diuretics and in outpatients, treatment with omecamtiv mecarbil increased systolic ejection time and stroke volume and resulted in reductions in left ventricular volumes.^{13,14} In preclinical models, these favorable hemodynamic effects of omecamtiv mecarbil occurred without an increase in myocardial oxygen demand or intracellular calcium and the attendant risk of arrhythmia which is associated with traditional inotropes.¹⁵ It is conceivable that in hospitalized patients (as well as in outpatients), these positive hemodynamic effects may facilitate the continuation of existing or initiation of new neurohumoral modulating treatments, however, we were unable to examine this hypothesis in this study. These data, along with the long-term efficacy and safety demonstrated in GALACTIC-HF, support the use of omecamtiv mecarbil when initiated in hospitalized patients as well as in outpatients.

Limitations of the present study include that qualifying worsening heart failure events prior to randomization were not adjudicated. However, the inclusion of qualifying events that were not really due to heart failure or not severe enough to warrant hospitalization would have biased the results towards the null and attenuated any observed association between events and subsequent risk. Patients with de novo presentations of HFrEF were not included in GALACTIC-HF as all patients were required to have received at least 30 days of treatment for HF. There was an under-representation of some subgroups including women and non-White race groups which may limit the generalizability of these data to these patients. Some of the analyses presented in this manuscript were post hoc and are therefore subject to the limitations inherent of these types of exploratory analyses.

CONCLUSIONS

In GALACTIC-HF, hospitalized HFrEF patients had a higher rate of morbidity and mortality than outpatients. Omecamtiv mecarbil reduced the risk of cardiovascular death or a worsening HF event when initiated in both hospitalized patients and outpatients. The initiation of omecamtiv mecarbil was safe and well-tolerated in both settings. These results support the use of omecamtiv mecarbil in both inpatients stabilized after a hospitalization for worsening HF and outpatients to reduce the risk of cardiovascular death and worsening HF events.

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TABLE 1: Baseline characteristics according to randomization setting

	Inpatients (n=2084)	Outpatients (n=6148)	P-value
<u>Demographics</u>			
Age - yr	65.0 ± 11.3	64.4 ± 11.4	p=0.020
Sex, Female	411 (19.7%)	1338 (21.8%)	p=0.049
<u>Race</u>			
Asian	184 (8.8 %)	526 (8.6 %)	p<0.001
Black	105 (5.0 %)	457 (7.4 %)	
Other	89 (4.3 %)	474 (7.7 %)	
White	1706 (81.9%)	4691 (76.3%)	
<u>Geographic Region</u>			
Asia	177 (8.5 %)	493 (8.0 %)	p<0.001
Eastern Europe/Russia	915 (43.9%)	1766 (28.7%)	
Latin America	326 (15.6%)	1248 (20.3%)	
US And Canada	180 (8.6 %)	1206 (19.6%)	
Western Europe/South Africa/Australasia	486 (23.3%)	1435 (23.3%)	
<u>Clinical Characteristics</u>			
Atrial fibrillation or flutter at screening	723 (34.7%)	1522 (24.8%)	p<0.001
Hypertension	1495 (71.7%)	4289 (69.8%)	p=0.09
Type 2 diabetes mellitus	870 (41.7%)	2439 (39.7%)	p=0.09
History of stroke	198 (9.5 %)	556 (9.0 %)	p=0.53
Ischemic heart failure etiology	1145 (54.9%)	3270 (53.2%)	p=0.17
History of myocardial infarction	893 (42.9%)	2542 (41.3%)	p=0.23
History of coronary artery bypass surgery	320 (15.4%)	997 (16.2%)	p=0.35
History of percutaneous coronary revascularization	599 (28.7%)	1839 (29.9%)	p=0.31
LVEF - %	26.5 ± 6.4	26.6 ± 6.2	p=0.55
<u>NYHA Classification</u>			
Class II	768 (36.9%)	3600 (58.6%)	p<0.001
Class III	1190 (57.1%)	2426 (39.5%)	
Class IV	126 (6.0 %)	122 (2.0 %)	
Median KCCQ Total Symptom Score	53.1 [33.3, 70.8]	75.0 [55.2, 91.7]	p<0.001
Systolic blood pressure — mmHg	113.9 ± 14.3	117.3 ± 15.6	p<0.001
Heart rate — beats/min	73.2 ± 11.6	72.1 ± 12.3	p<0.001
Median NT-proBNP — pg/mL	2510 [1240, 5133]	1884 [924, 3773]	p<0.001
Sinus rhythm — pg/mL	2065 [1021, 4512]	1580 [775, 3374]	p<0.001
Atrial fibrillation/flutter — pg/mL	3198 [1787, 6076]	2707 [1656, 4845]	p<0.001
Median cardiac troponin I — ng/L	37 [19, 68]	24 [12, 46]	p<0.001
Median eGFR — mL/min/1.73m ²	54.4 [41.3, 70.2]	60.0 [45.2, 75.0]	p<0.001
Baseline BMI (kg/m ²)	28.0 ± 6.1	28.6 ± 6.2	p<0.001
Baseline weight (kg)	81.7 ± 20.3	82.8 ± 20.7	p=0.026
<u>Heart Failure Therapies</u>			
ACEi, ARB or ARNi	1743 (83.6%)	5416 (88.1%)	p<0.001
ARNi	331 (15.9%)	1270 (20.7%)	p<0.001
Beta-blocker	1940 (93.1%)	5823 (94.7%)	p=0.006
MRA	1709 (82.0%)	4688 (76.3%)	p<0.001
SGLT2 inhibitor	55 (2.6 %)	163 (2.7 %)	p=0.98
Ivabradine	156 (7.5 %)	377 (6.1 %)	p=0.030
Digitalis glycosides	357 (17.1%)	1028 (16.7%)	p=0.67
Cardiac resynchronization therapy	267 (12.8%)	891 (14.5%)	p=0.06
Implantable Cardioverter Defibrillator	598 (28.7%)	2016 (32.8%)	p<0.001

Data are presented as n (%) or mean ± standard deviation, unless otherwise specified.

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared);

eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter 2.

FIGURE LEGENDS



In GALACTIC-HF, omecamtiv mecarbil reduced the risk of cardiovascular death or worsening HF when initiated in hospitalized patients and in outpatients



Outpatients

42%
25%
117 mmHg
1884 µg/mL
60 mL/min/1.73m²

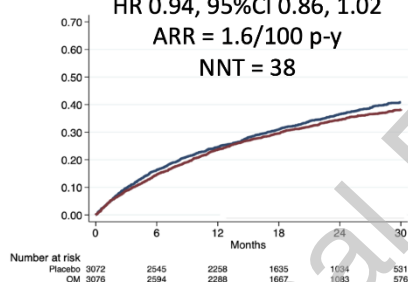
NYHA class III/IV
Atrial fibrillation
Systolic BP
NT-proBNP
eGFR

Hospitalized patients

63%
35%
114 mmHg
2510 µg/mL
54 mL/min/1.73m²

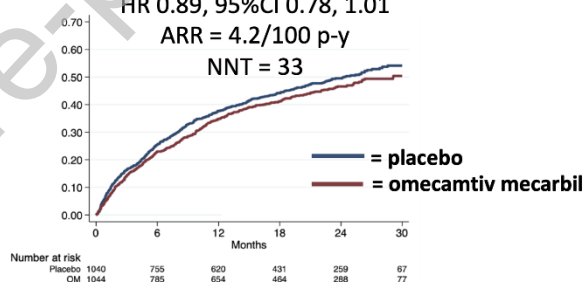
Outpatients

HR 0.94, 95%CI 0.86, 1.02
ARR = 1.6/100 p-y
NNT = 38



Hospitalized patients

HR 0.89, 95%CI 0.78, 1.01
ARR = 4.2/100 p-y
NNT = 33



Interaction p value = 0.51

CENTRAL ILLUSTRATION: The effect of omecamtiv mecarbil compared with placebo according to randomization setting in GALACTIC-HF

Abbreviations: BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NNT, number needed to treat (over 3 years); NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; P-Y, person years.

FIGURE 1: Effect of omecamtiv mecarbil compared with placebo on cardiovascular outcomes according to randomization setting

Event rates are displayed as per 100 person-years.

Hazard ratios derived from Cox proportional hazards model adjusted for eGFR and stratified by region.

Figure 2: Primary composite outcome event rate by randomization setting, time from most recent heart failure event and randomized treatment

Primary outcome was the composite of time-to a first episode of worsening heart failure (defined as an urgent clinic visit, emergency department visit, or hospitalization for worsening heart failure requiring treatment intensification beyond a change in oral diuretic therapy) or cardiovascular death.

Abbreviations: ED, emergency department; HF, heart failure.

FIGURE 3: Effect of omecamtiv mecarbil compared with placebo in outpatients on primary outcome according to time from most recent worsening heart failure event

Hazard ratios derived from Cox proportional hazards model adjusted for adjusted for eGFR and stratified by region.

FIGURE 1:

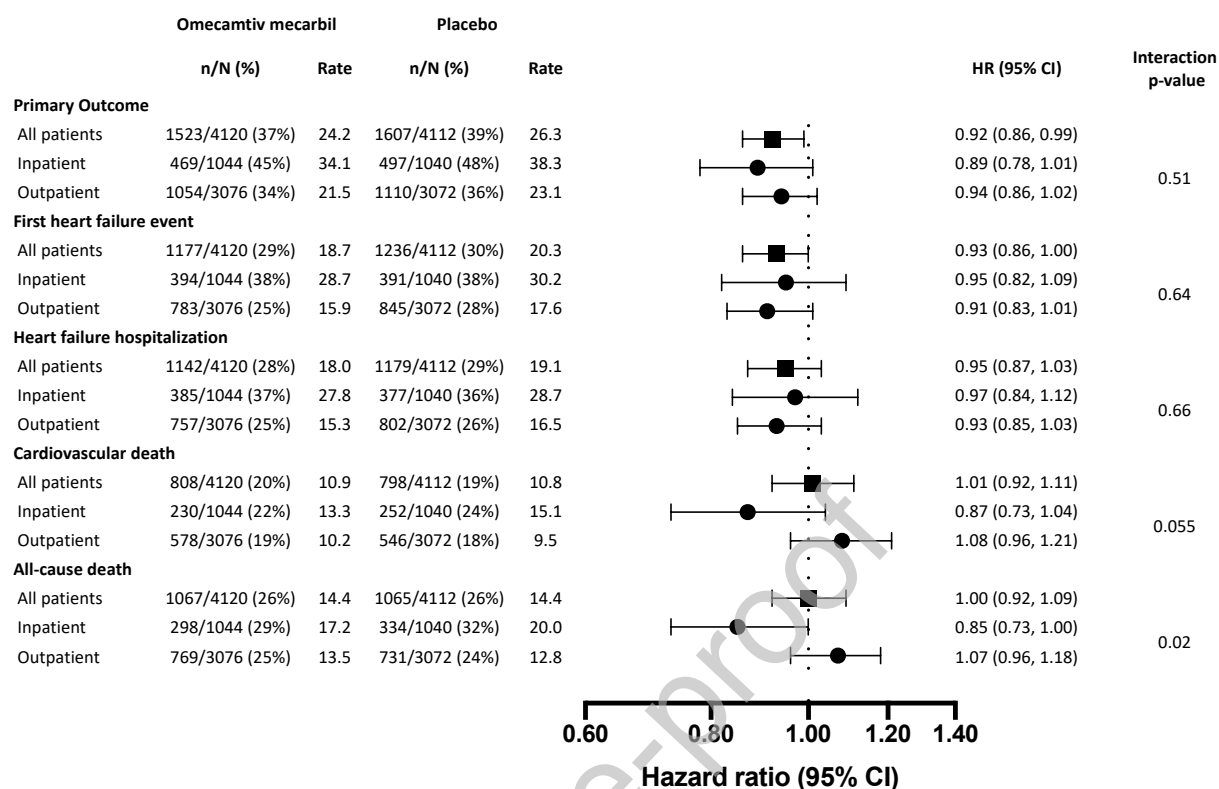


Figure 2:

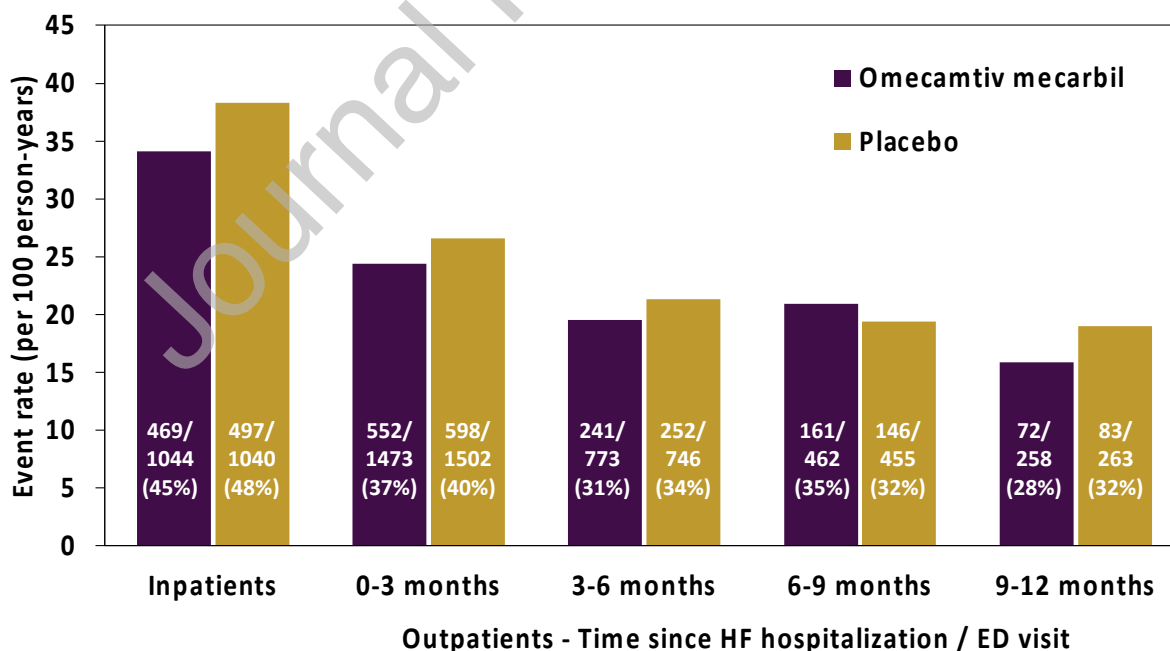
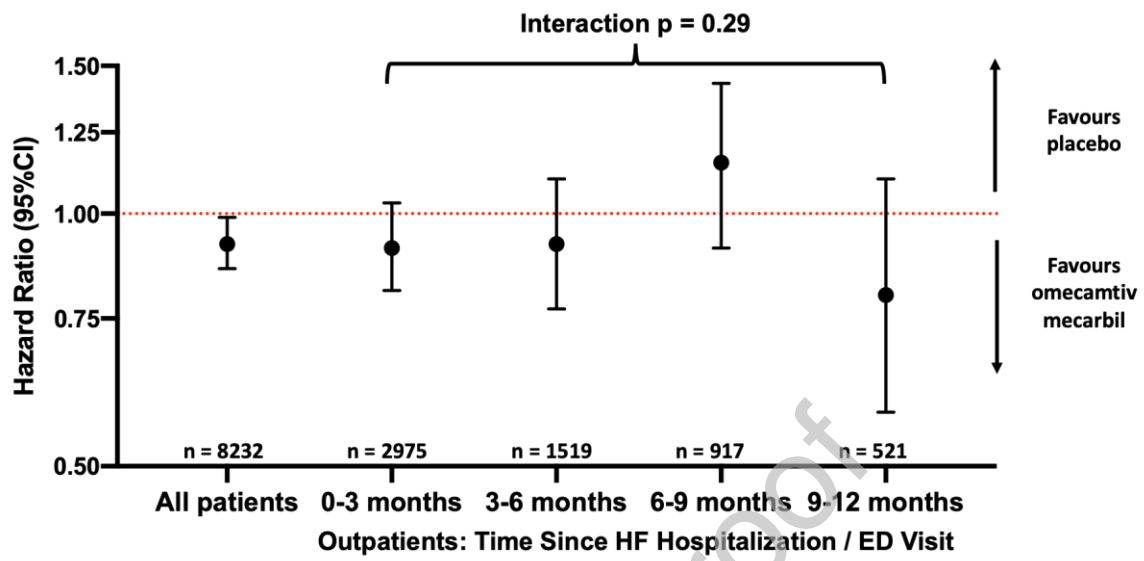


FIGURE 3:



DECLARATIONS OF INTEREST

K.F.D. has received financial support to attend educational meetings from Cytokinetics during the conduct of the study, personal fees from AstraZeneca, consulting fees from Us2.ai and research grants to his institution from AstraZeneca and Boehringer Ingelheim outside the submitted work. J.J.V.M. has received funding to his institution from Amgen and Cytokinetics for his participation in the Steering Committee for the ATOMIC-HF, COSMIC-HF, and GALACTIC-HF trials and meetings and other activities related to these trials; has received payments through Glasgow University from work on clinical trials, consulting and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardurion, Dal-Cor, GlaxoSmithKline, Ionis, KBP Biosciences, Novartis, Pfizer, and Theracos; has received personal lecture fees from the Corpus, Abbott, Hikma, Sun Pharmaceuticals, Medscape/Heart.Org, Radcliffe Cardiology, Servier Director, and Global Clinical Trial Partners (GCTP). R.D. has received research grants and other payment or honoraria from Amgen. G.M.F. has received grant funding to his institution from American Heart Association, Amgen, Bayer, Bristol Myers Squibb, CSL-Behring, Cytokinetics, Merck, Myokardia, and National Institutes of Health; has received consulting fees from Abbott, American Regent, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cardionomic, Cytokinetics, Medtronic, Myovant, Novartis, Reprieve, Sequana, Windtree Therapeutics, and WhiteSwell; and has participated on Data Safety Monitoring boards or advisory boards for EBR Systems, LivaNova, Medtronic, Siemens, Rocket Pharma, and V-Wave. M.M. has received funding to his institution from Amgen and Cytokinetics as participant to the Executive Committee during the trial and for patients' enrolment; has received consulting fees for participation to advisory boards from AstraZeneca, Bayer, and Boehringer Ingelheim; has received personal fees as member of Executive or Data Monitoring Committees of sponsored clinical trials from LivaNova and Vifor Pharma; has received speaker fees from Abbott Vascular and Edwards Therapeutics for speeches at sponsored meetings; and has participated on Data Safety Monitoring boards for Actelion. S.D.S. has received grant funding to his institution from Actelion, Alnylam, Amgen, AstraZeneca, Bayer, Bellerophon, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis Pharmaceuticals, Lilly, Mesoblast, MyoKardia, National Institutes of Health/National Heart, Lung, and Blood Institute, Neurotronik, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI; and has received consulting fees from Abbott, Action, Akros, Alnylam, American Regent, Amgen, Anacardio, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiac Dimensions, Cardior, Cardurion, CellProthera, Corvia, Cytokinetics, Daiichi Sankyo, Dinaqor, GlaxoSmithKline, Janssen, Lexicon, Lilly, Merck, Moderna, Myokardia, Novartis, Puretech Health, Quantum Genomics, Roche, Sanofi Pasteur, Sarepta, Tenaya, Theracos, and Tremeau. K.F.A. has received research grants from Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim Pharmaceuticals Inc., Eli Lilly USA, LivaNova USA, Merck, Novartis, and Otsuka; acted as a consultant to Amgen, Cytokinetics, Inc., Novartis, Roche Diagnostics, Relypsa, and Windtree Therapeutics. M.B. has received funds from the Deutsche Forschungsgemeinschaft (German Research Foundation; TTR 219, project No. 322900939) and personal fees from Abbott, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Cytokinetics, Medtronic, Novartis, ReCor, Servier, Vifor Pharma, and Boehringer Ingelheim.

A.R.G. reports consulting fees for clinical trials from Amgen, Novartis, KOWA, and Bayer outside the submitted work; personal payments or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Boehringer Ingelheim, AstraZeneca, and Novo Nordisk outside the submitted work; support for attending meetings and/or travel from Pfizer, AstraZeneca, and Boehringer Ingelheim; leadership or fiduciary role as President, Bulgarian Society of Cardiology 2020-22. J.G.H. has received grants and consulting fees from Amgen, AstraZeneca, Boehringer Ingelheim, Novartis, Novo Nordisk, and Pfizer; has received personal fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis, Novo Nordisk, and Pfizer; and is Co-Chair of the Heart Failure Pathway Group of the Province of Alberta, Heart Failure lead at University of Calgary, and in the Canadian Cardiovascular Society Guidelines and Development Committees. M.L. has received grant funding and personal fees from Amgen; has received honoraria from Novartis; and has served as the New Zealand Chairperson for Cardiac Society Australia and New Zealand. P.P. has received research grants to his institution from Amgen and Vifor Pharma; and has received consulting fees or honoraria from Abbott Vascular, AstraZeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Bristol Myers Squibb, Cibiem, Coridea, Impulse Dynamics, Novartis, Pfizer, Renal Guard Solutions, Servier, and Vifor Pharma. M.B.Y. reports funding to his institution from Amgen, Bayer, Novartis, and Dalcour Pharmaceuticals outside the submitted work. F.Z. reports consulting fees from Cardior, Cereno pharmaceutical, Cellprothera, Owkin, Novo Nordisk, Vifor, and Fresenius; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Boehringer and Bayer; payment for expert testimony from Cardioentis; stock or stock options in Cereno pharmaceutical; and steering committee personal fees from Applied Therapeutics, Amgen, Bayer, Boehringer, CVRx, Novartis, and Merck. B.L.C. has received consulting fees from Amgen, Cardurion, Corvia, Myokardia, and Novartis. Z.M.M. has no conflicts of interest to disclose. S.A.A. is an employee and shareholder of Amgen. P.H.D., S.B.H., S.K., and F.I.M. are employees and shareholders of Cytokinetics. J.R.T. has received personal fees as Chairperson of the GALACTIC-HF Executive Committee from Amgen and Cytokinetics; has received personal fees for research contracts and/or consulting fees from 3ive Labs, Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardurion, Medtronic, Merck, Novartis, Verily, ViCardia, and Windtree Therapeutics; has served as Secretary and Treasurer of Heart Failure Society of America; and is currently President-Elect of the Heart Failure Society of America. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.



Author photo

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