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CLINICAL RESEARCH

Omecamtiv Mecarbil in Black Patients With Heart Failure and Reduced Ejection Fraction

Insights From GALACTIC-HF

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ABSTRACT

BACKGROUND Omecamtiv mecarbil improves cardiovascular outcomes in patients with heart failure (HF) with reduced ejection fraction (EF). Consistency of drug benefit across race is a key public health topic.

OBJECTIVES The purpose of this study was to evaluate the effect of omecamtiv mecarbil among self-identified Black patients.

METHODS In GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure) patients with symptomatic HF, elevated natriuretic peptides, and left ventricular ejection fraction (LVEF) ≤35% were randomized to omecamtiv mecarbil or placebo. The primary outcome was a composite of time to first event of HF or cardiovascular death. The authors analyzed treatment effects in Black vs White patients in countries contributing at least 10 Black participants.

RESULTS Black patients accounted for 6.8% (n = 562) of overall enrollment and 29% of U.S. enrollment. Most Black patients enrolled in the United States, South Africa, and Brazil (n = 535, 95%). Compared with White patients enrolled from these countries (n = 1,129), Black patients differed in demographics, comorbid conditions, received higher rates of medical therapy and lower rates of device therapies, and experienced higher overall event rates. The effect of omecamtiv mecarbil was consistent in Black vs White patients, with no difference in the primary endpoint (HR = 0.83 vs 0.88, *P*-interaction = 0.66), similar improvements in heart rate and N-terminal pro-B-type natriuretic peptide, and no significant safety signals. Among endpoints, the only nominally significant treatment-by-race interaction was the placebo-corrected change in blood pressure from baseline in Black vs White patients (+3.4 vs −0.7 mm Hg, *P* for interaction = 0.02).

CONCLUSIONS GALACTIC-HF enrolled more Black patients than other recent HF trials. Black patients treated with omecamtiv mecarbil had similar benefit and safety compared with White counterparts. (J Am Coll Cardiol HF 2023;11:569–579)

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ABBREVIATIONS AND ACRONYMS

EF = ejection fraction

HF = heart failure

LVEF = left ventricular ejection fraction

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

Heart failure (HF) is a well-known global health issue that disproportionately affects Black patients whose risk of developing HF has been estimated as high as 20 times that of White patients,[1] and who bear a disproportionate burden in terms of prevalence, hospitalization rates, and mortality.[2,3] Exacerbating this disparity is the under-representation of Black patients in biomedical research,[4,5] including pivotal drug trials.[6] A recent systematic review indicated that, even as late as 2019, only about half of clinical trials reported race data and that average participation of Black patients remains approximately 5%,[7] with similar estimates of participation rates seen for HF-specific trials.[8] Moreover, this is not just an academic issue; at least 29 medications have been reported to have racial differences in effectiveness,[9] including several relevant to HF treatment.[10-12]

The GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure) trial evaluated the effects of omecamtiv mecarbil, a first-in-class myosin activator, in patients with HF and reduced ejection fraction (EF). Omecamtiv mecarbil augments myosin-actin cross-bridges resulting in increased contractility.[13] This novel approach avoids the increases in intracellular calcium levels and myocardial oxygen demand commonly associated with adverse effects of traditional inotropes (calcitropes), such as myocardial ischemia, ventricular arrhythmias, and death.[14,15] The GALACTIC-HF trial demonstrated an 8% lower relative risk (HR: 0.92 [95% CI: 0.86-0.99]; $P = 0.025$) of a composite primary outcome of time to first event of HF or death from cardiovascular causes without increased risk of myocardial ischemic events, ventricular arrhythmias, or death from cardiovascular causes.[16] The primary results reported the race subgroup analysis of the primary endpoint compared across 4 groups (White, Black, Asian, and other) showing no statistically significant difference in effect estimates for Black vs White patients.[16] The current study performed a more complete and detailed evaluation of the efficacy and safety of omecamtiv mecarbil among self-identified Black patients compared with White patients participating in GALACTIC-HF.

METHODS

PATIENTS AND TRIAL. The design, baseline characteristics, and main findings from the GALACTIC-HF trial have been previously published.[16-18] Briefly, the GALACTIC-HF trial randomized patients between 18-85 years of age with symptomatic HF (New York Heart Association functional class II, III, or IV) and left ventricular ejection fraction (LVEF) ≤35%, elevated natriuretic peptides, and either were currently hospitalized for HF (inpatients) or had either made an urgent visit to the emergency department or been hospitalized for HF within 1 year before screening (outpatients). Key exclusion criteria included hemodynamic or clinically unstable state, mechanical circulatory support, renal failure (estimated glomerular filtration rate of <20 mL/min/1.73 m^2 of body surface area), systolic blood pressure <85 mm Hg, or recent acute coronary syndrome. Patients were randomized 1:1 to receive omecamtiv mecarbil or placebo in addition to standard care using an interactive Web-response or voice-response system and a sequestered, fixed randomized schedule. The omecamtiv mecarbil doses were 25 mg, 37.5 mg, or 50 mg twice daily, adjusted according to plasma levels of the drug in a double-blinded fashion. Postrandomization assessments (clinical and serum) were performed at weeks 2, 4, 6, 8, 12, 24, 36, and 48 and every 16 weeks thereafter. The study protocol was approved by the relevant ethics committees and all participants provided informed consent.

The primary outcome was a composite of time to first HF event or death from cardiovascular causes. Additional endpoints of interest were components of the primary composite endpoint, stroke, biomarkers of treatment effect, and safety outcomes. The

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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prespecified safety analyses included serious adverse events, adverse events associated with discontinuation of therapy, and adverse events of interest including ventricular arrhythmias, major cardiac ischemic events, and death.

Because enrollment of Black patients varied greatly across nations in this global trial, and included many nations with very low enrollment of Black patients, to avoid confounding by country or region (in terms of variations in care), we restricted our analytic cohort to patients enrolled in countries contributing at least 10 Black participants—Brazil, South Africa, and the United States—which together accounted for 95% of all Black patient enrollment (n = 535). White patients were chosen as the comparison group because they were the largest single race group in the overall trial as well as within the 3 countries included in the current analysis (n = 1,129). Alternative approaches such as using composite race groups (eg, non-Black or non-White) were not pursued as they are inherently less informative (due to conflating distinct race groups) and because there is recent consensus that this approach is not the preferred method of reporting and analyzing race data.[19,20]

STATISTICAL ANALYSIS. Continuous variables were summarized by mean ± SD or median (IQR), as appropriate. Categorical variables were summarized with counts and percentages. Potential differences in treatment effects across race groups were assessed using interaction tests comparing the estimated effects of omecamtiv mecarbil (vs placebo) in Black compared with White patients. Time-to-event outcomes were analyzed using Kaplan-Meier estimates and Cox proportional hazards models. We also performed sensitivity analyses using Fine-Gray competing risk models to incorporate mortality as a competing risk for other outcomes of interest. All analyses were conducted using Stata (StataCorp, 2019, Version 16). Values of $P < 0.05$ were considered statistically significant. No adjustment was made for multiple comparisons.

RESULTS

The GALACTIC-HF trial analyzed a total of 8,232 patients, all of whom had race data available. Among these, 562 (6.8%) self-identified as Black.[16] The mean age of Black patients was 58 years, the mean LVEF was 24%, and 34% were female. Most Black patients were enrolled in the United States (n = 357), Brazil (n = 100), and South Africa (n = 78), accounting for 29%, 21%, and 45% of patients enrolled from within these countries, respectively, with no other country enrolling ≥10 Black patients. These 3 nations accounted for 95% of all Black patients (n = 535) and also contributed 1,129 White patients, which together formed the analytic cohort for the comparative results by race, in which there were 260 primary events (48.6%) among the Black participants and 484 primary events (42.9%) among White participants.

TABLE 1 Baseline Characteristics of Black vs White Patients in GALACTIC-HF (Brazil, South Africa, and the United States)

	Black Patients (n = 535)	White Patients (n = 1,129)	*P* Value
Demographics			
Age, y	58.0 ± 12.4	65.0 ± 11.4	<0.001
Female	181 (33.8)	270 (23.9)	<0.001
Randomization setting: inpatient	97 (18.1)	179 (15.9)	0.24
Clinical characteristics			
Atrial fibrillation or flutter at screening	72 (13.5)	237 (21.0)	<0.001
History of hypertension	443 (82.8)	821 (72.7)	<0.001
Type 2 diabetes mellitus	250 (46.7)	504 (44.6)	0.42
History of stroke	59 (11.0)	107 (9.5)	0.32
Ischemic HF etiology	151 (28.2)	618 (54.7)	<0.001
History of myocardial infarction	116 (21.7)	456 (40.4)	<0.001
History of coronary artery bypass surgery	44 (8.2)	285 (25.2)	<0.001
History of percutaneous coronary revascularization	86 (16.1)	346 (30.6)	<0.001
Ejection fraction, %	23.9 ± 6.6	25.0 ± 6.6	0.001
NYHA functional class			0.79
II	289 (54.0)	592 (52.4)	
III	227 (42.4)	492 (43.6)	
IV	19 (3.6)	45 (4.0)	
KCCQ total symptom score	66.7 (45.8-89.6)	68.8 (46.9-87.5)	0.97
Outpatient	75.0 (51.0-91.7)	71.9 (52.1-89.6)	0.42
Inpatient	41.7 (25.0-58.3)	40.6 (21.9-67.7)	0.82
SBP, mm Hg	117.3 ± 15.7	114.0 ± 16.4	<0.001
Heart rate, beats/min	75.8 ± 13.2	73.2 ± 12.1	<0.001
NT-proBNP, pg/mL	1,849 (852-3,852)	1,930 (903-4,234)	0.32
Cardiac troponin I, ng/L	31 (13-61)	26 (12-48)	0.004
eGFR, mL/min/1.73 m^2	65.3 (51.0-84.1)	56.1 (43.1-70.2)	<0.001
HF therapies			
ACEI, ARB, or ARNI	458 (85.6)	886 (78.5)	<0.001
ARNI	128 (23.9)	289 (25.6)	0.46
Beta-blocker	513 (95.9)	1,047 (92.7)	0.013
Beta-blocker subgroup			0.035
HF indicated	498 (93.1)	1,009 (89.4)	
Other beta-blocker	15 (2.8)	38 (3.4)	
None	22 (4.1)	82 (7.3)	
MRA	382 (71.4)	610 (54.0)	<0.001
Sodium-glucose cotransporter 2 inhibitors	7 (1.3)	29 (2.6)	0.10
Ivabradine	13 (2.4)	40 (3.5)	0.23
Digitalis glycosides	97 (18.1)	199 (17.6)	0.80
Cardiac resynchronization therapy	55 (10.3)	211 (18.7)	<0.001
ICD	200 (37.4)	538 (47.7)	<0.001

Values are mean ± SD, n (%), or median (IQR).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitor; eGFR = estimated glomerular filtration rate; GALACTIC-HF = Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure; HF = heart failure; ICD = implantable cardioverter defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure.

TABLE 2 Primary and Secondary Endpoints in Black vs White Patients Regardless of Treatment Assignment

	Patients, Events/100 Patient-Years		Black vs White Patients, HR (95% CI)	
	Black (n = 535)	White (n = 1,129)	Unadjusted	Adjusted[a]
Primary endpoint	37.8 (48.6)	30.6 (42.9)	1.20 (1.03-1.40)	1.33 (1.13-1.56)
Cardiovascular death	9.5 (7.9)	12.9 (9.0)	0.73 (0.58-0.93)	0.87 (0.67-1.13)
HF hospitalization	29.6 (38.9)	22.8 (32.3)	1.26 (1.06-1.50)	1.38 (1.15-1.65)

Values are n (%) or median (IQR). [a]Adjusted for age, sex, and country.
Abbreviation as in Table 1.

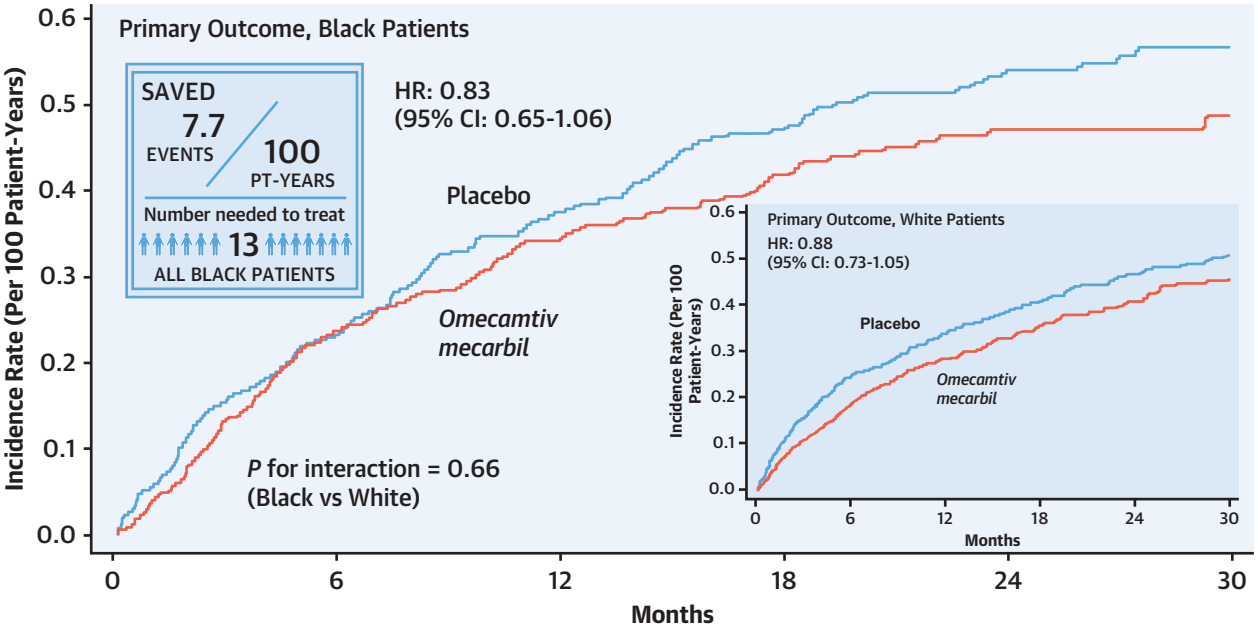
BASELINE CHARACTERISTICS AND OVERALL OUTCOMES OF BLACK AND WHITE PATIENTS IN GALACTIC-HF. The baseline characteristics of Black and White patients from the United States, South Africa, and Brazil are shown in Table 1. Black patients were more often female, younger, had lower LVEF, were more likely to have hypertension, and were less likely to have atrial arrhythmias or ischemic etiology compared with their White counterparts (all $P \leq 0.001$). At baseline, Black patients had higher systolic blood pressure, lower N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, higher cardiac troponin I levels, and higher estimated glomerular filtration rate. Treatments for HF varied substantially across race as well. At the time of enrollment, Black patients were more likely to be prescribed each aspect of guideline-directed medical therapy, including renin-angiotensin-blocking therapies, beta-blockers, and mineralocorticoid receptor antagonists (all $P < 0.05$). However, Black patients were less likely than White patients to have an implanted defibrillator or cardiac resynchronization therapy ($P < 0.001$). Sensitivity analyses based on Fine-Gray competing risk models produced consistent results (Supplemental Table 1).

Regardless of randomization assignment, Black patients had higher rates of the primary outcome than White patients (Table 2). The primary event rate in Black patients was 38 per 100 patient-years compared with 31 per 100 patient-years in White patients ($P = 0.017$). When adjusted for age, sex, and country, the HR for the primary event in Black vs White patients was 1.33 (95% CI: 1.13-1.56). Similarly, there was greater risk of HF hospitalization among Black patients, with an adjusted HR of 1.38 (95% CI: 1.15-1.65). On the other hand, there was no significant difference detected in terms of the risk of cardiovascular mortality in the adjusted model (HR: 0.87, 95% CI: 0.67-1.13). We also performed sensitivity analyses stratified by U.S. (n = 1,177, 357 Black patients and 820 White patients) or non-U.S. enrollment (n = 487, 178 Black patients and 309 White patients), summarized in Supplemental Table 2. Black patients from U.S. sites had higher rates of the primary outcome compared with White U.S. patients (adjusted HR: 1.37, 95% CI: 1.14-1.64), whereas Black patients outside the United States (ie, Brazil and South Africa, n = 178) showed a directionally similar but statistically nonsignificant trend toward higher primary event rates when compared with their White counterparts (adjusted HR: 1.18, 95% CI: 0.83-1.67).

EFFECT OF OMECAMTIV MECARBIL IN BLACK PATIENTS COMPARED WITH WHITE PATIENTS. The overall results of treatment with omecamtiv mecarbil were broadly consistent between Black and White patients (Central Illustration). The primary, secondary, and biomarker outcomes in Black patients compared with White patients are summarized in Table 3. In testing the effect of omecamtiv mecarbil on the primary endpoint (time to cardiovascular death or first HF event) across race, we found no statistically significant difference between Black and White patients (Figure 1). The estimated treatment effect on the primary endpoint in Black patients (HR: 0.83, 95% CI: 0.65-1.06) was similar to that of White patients from the same countries (HR: 0.88, 95% CI: 0.73-1.05). In terms of absolute event rates, among Black patients the estimated effect of omecamtiv mecarbil was a reduction in the primary event rate of 7.7 events per 100 patient-years (95% CI: −17.9 to +2.4), compared with saving 6.0 events per 100 patient-years in White patients (95% CI: −11.9 to 0.0). Similarly, the secondary endpoints of time to first HF hospitalization and time to cardiovascular death did not show any statistically significant interaction by race comparing Black and White patients (Figure 2). The estimated treatment effect on absolute event rates for HF hospitalization was saving 6.0 events per 100 patient-years in Black patients (95% CI: −14.9 to +2.8) compared with saving 3.8 events per 100 patient-years in White patients (95% CI: −8.9 to +1.2). Sensitivity analyses based on Fine-Gray competing risk models produced consistent results (Supplemental Table 3).

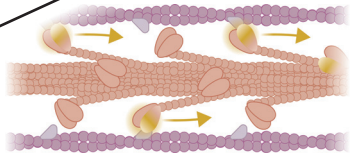
Examination of the effect of omecamtiv mecarbil on vital signs and biomarkers (measured as a change from baseline to 24 weeks and comparing omecamtiv mecarbil with placebo) revealed similar treatment effects in Black compared with White patients (Table 3). Changes in heart rate, troponin, and NT-proBNP appeared consistent across race with omecamtiv mecarbil treatment causing a decrease in heart rate and NT-proBNP levels, and a small increase in troponin I levels in both groups. Similarly, both race groups showed no association of omecamtiv mecarbil with changes in creatinine, potassium, or adverse

CENTRAL ILLUSTRATION **Effects of Omecamtiv Mecarbil in Black Compared With White Patients**



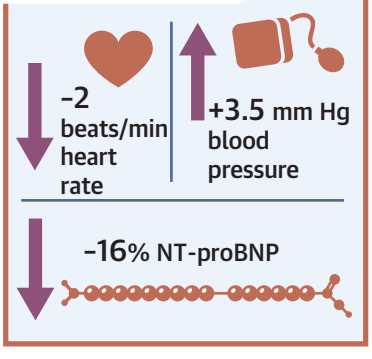
Omecamtiv mecarbil

- Cardiac myosin activator
- Increases actin–myosin force-producing interaction



Trial	Total Black Patients (%)	U.S. Black Patients (%)
GALACTIC-HF[18]	562 (6.8)	357 (29)
PARADIGM-HF[35,36]	428 (5.1)	111 (26)
EMPEROR-Reduced[40,41]	257 (6.9)	100 (23.5)[a]
VICTORIA[38]	249 (4.9)	–
DAPA-HF[26,39]	226 (4.8)	121 (17.9)[a]
PARAGON-HF[42]	102 (2.2)	–

BIOMARKER EFFECTS OF *OMECAMTIV MECARBIL* in Black Patients



Lanfear DE, et al. J Am Coll Cardiol HF. 2023;11(5):569-579.

From GALACTIC-HF (United States, South Africa, and Brazil only, n = 535). [a]North America (not United States only). DAPA-HF = Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; EMPEROR-Reduced = EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction; GALACTIC-HF = Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PARADIGM-HF = Prospective comparison of Angiotensin Receptor-neprilysin inhibitor (ARNI) with Angiotensin converting enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and morbidity in Heart Failure; PARAGON-HF = Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction; PT = patient; VICTORIA = VerICiguaT GlObal Study in Subjects With Heart Failure With Reduced EjectIon FrAction.

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TABLE 3 Outcomes of Omecamtiv Mecarbil Treatment (vs Placebo) in Black vs White Patients[a]

	Black Patients (n = 535) Difference (95% CI)	*P* Value	White Patients (n = 1,129) Difference (95% CI)	*P* Value	Interaction *P* Value
Primary endpoint (HR)	0.83 (0.65-1.06)	0.13	0.88 (0.73-1.05)	0.16	0.66
Cardiovascular death (HR)	1.07 (0.70-1.63)	0.74	0.98 (0.76-1.25)	0.85	0.76
HF hospitalization (HR)	0.81 (0.62-1.07)	0.14	0.90 (0.73-1.11)	0.32	0.57
SBP (mm Hg)	+3.4 (0.2-6.7)	0.039	−0.7 (−2.6 to 1.3)	0.49	0.02
Heart rate (beats/min)[b]	−2.3 (−4.4 to −0.2)	0.032	−2.2 (−3.6 to −0.9)	0.001	0.95
Potassium (mmol/L)[b]	−0.03 (−0.12 to 0.06)	0.51	0.05 (−0.02 to 0.11)	0.14	0.16
Creatinine (mg/dL)[b]	−0.00 (−0.06 to 0.06)	0.92	−0.00 (−0.05 to 0.05)	0.89	0.87
NT-proBNP (pg/mL) (ratio)[b]	0.84 (0.68-1.03)	0.09	0.81 (0.72-0.91)	<0.001	0.76
Troponin I (ng/L) (ratio)[b]	1.14 (1.00-1.29)	0.06	1.24 (1.13-1.36)	<0.001	0.25

[a]Patients were from Brazil, South Africa, and the United States. [b]Measured baseline to 24 wk.
Abbreviations as in Table 1.

events (Table 4). Among the numerous endpoints examined, the only nominally significant interaction of treatment with race was for blood pressure. Among Black patients, treatment with omecamtiv mecarbil was associated with a 3.4 mm Hg increase in systolic blood pressure (95% CI: 0.2-6.7), whereas among White patients there was no significant change in systolic blood pressure (−0.7 mm Hg, 95% CI: 2.6-1.3), with an unadjusted interaction *P* value of 0.02.

We performed sensitivity analyses of treatment effect stratified by U.S. (n = 1,177, 357 Black patients and 820 White patients) or non-U.S. enrollment (n = 487, 178 Black patients and 309 White patients). There were no statistically significant differences by race in the effect of omecamtiv mecarbil on the primary outcome regardless of whether examining U.S. patients (interaction $P = 0.48$) or non-U.S. patients (interaction $P = 0.66$). Full results are summarized in Supplemental Table 4.

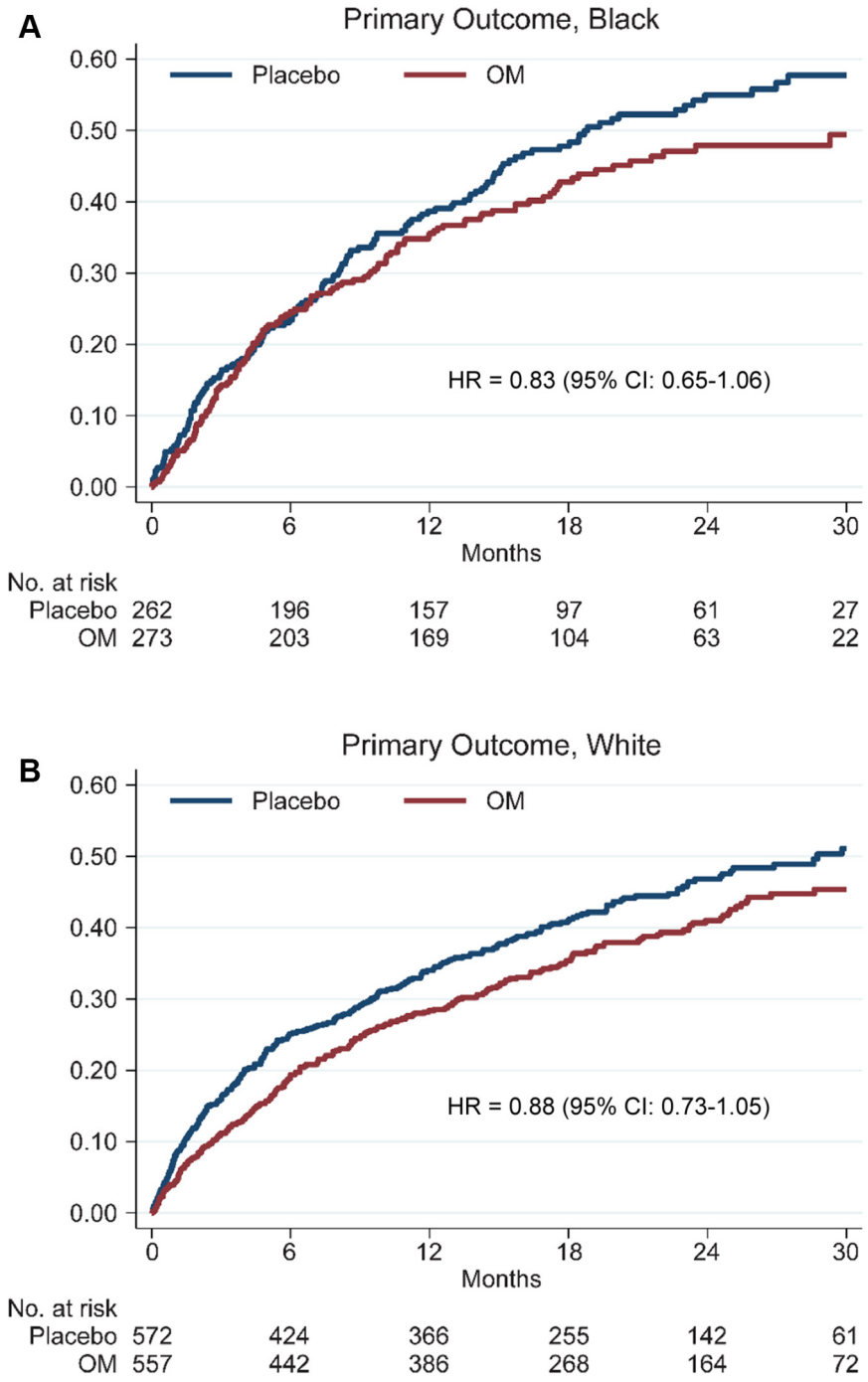
DISCUSSION

Race should never be assumed to modify the treatment effect of medical therapies because this could contribute to discrimination or reduced access,[21-24] but, conversely, quantifying the treatment effects of medications in diverse racial groups is of high public health importance. Moreover, achieving equitable enrollment in clinical trials continues to be a challenge.[8] The current data indicate that the GALACTIC-HF trial was successful in enrolling Black patients, and that Black patients who received omecamtiv mecarbil had a trend toward benefit in clinical outcomes that was not statistically different from that in White patients or the overall trial result. These data should provide reassurance for patients, providers, and policy-makers that Black patients should be treated similarly with respect to this novel medication.

The overall effect of omecamtiv mecarbil appeared consistent across the 2 race groups, including similar event and biomarker indicators of both efficacy and safety. Indeed, the primary endpoint effect estimates in this current analysis are numerically closer than those in the original race subgroup analysis included in the primary results.[16] This subtle difference could theoretically be explained by geographic/regional differences confounding the effect of race, but this is statistically difficult to explore with so few Black patients in many participating countries/regions. Although there was 1 statistically significant interaction by race (ie, change in systolic blood pressure), it is important to view this finding in the context of examining a wide variety of endpoints without adjustment for multiple comparisons. Blood pressure effects of omecamtiv mecarbil in Black patients may deserve further investigation, but additional evidence would be required before this could be accepted as a true difference. Reassuringly, for both Black and White patients, omecamtiv mecarbil was associated with statistically significant reductions in heart rate and NT-proBNP, and no significant adverse events.

Omecamtiv mecarbil had a consistent effect across the 2 race groups studied despite substantial differences in baseline patient characteristics and overall event rates between Black and White patients. The baseline characteristics of Black patients in this study were similar to those seen in previous studies, with Black patients with HF more likely to have comorbid hypertension, younger age, lower LVEF, and less likely to have atrial fibrillation or ischemic etiology.[3,25,26] Notable among these differences are 2 key characteristics that are associated with differences in omecamtiv mecarbil benefit: atrial fibrillation and LVEF.[27] For both characteristics, the differences by race (less atrial fibrillation and lower LVEF in Black patients) would be expected to associate with greater

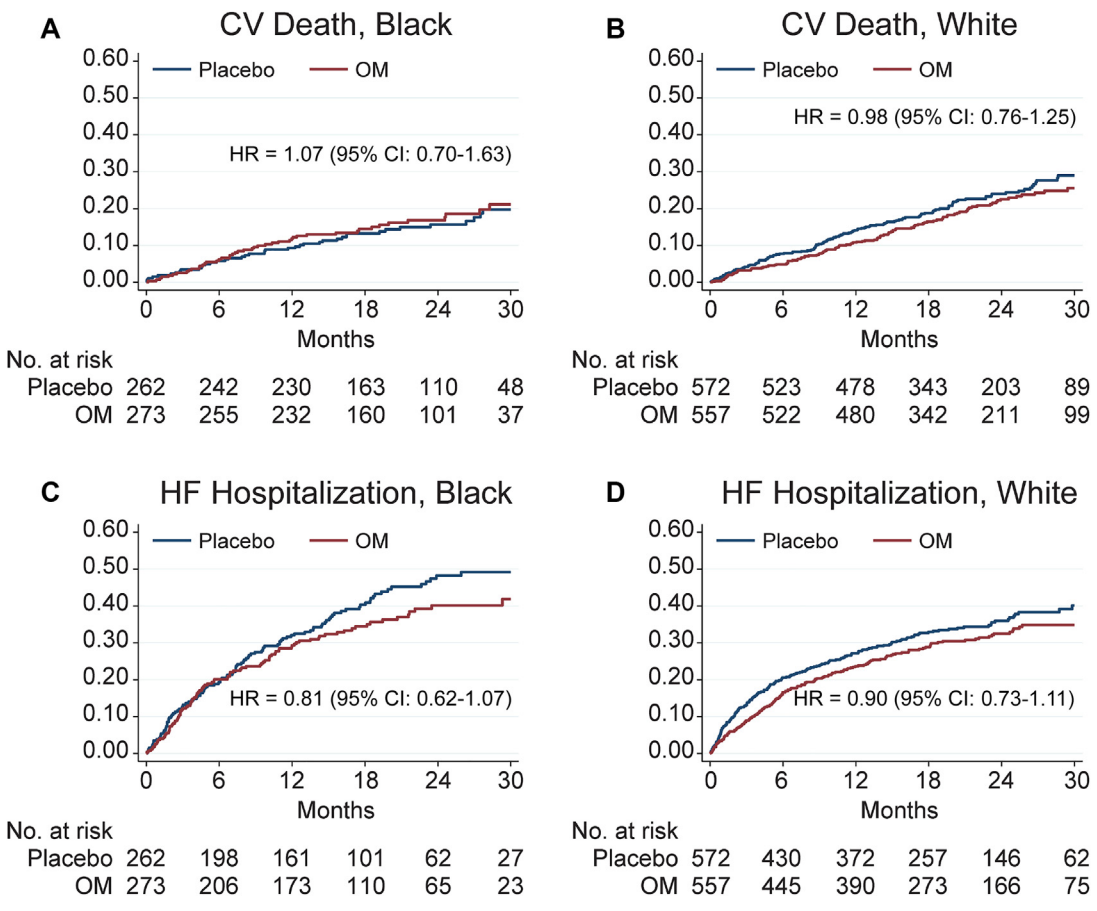
FIGURE 1 **Effect of OM on the Primary Outcome**



Study in Black compared with White patients. OM = omecamtiv mecarbil.

benefit of omecamtiv mecarbil.[27] These factors may help explain the favorable effect estimate among Black patients. Interestingly, Black patients were significantly more likely to receive guideline-directed medical therapy compared with White patients. Although this might seem counterintuitive in the context of previous published reports reflecting broad racial disparities in medicine and health,[28-30] similar

FIGURE 2 Effect of OM on Time to CVD and HF



Study in Black compared with White patients. CV = cardiovascular; HF = heart failure; other abbreviation as in Figure 1.

findings were recently reported in both HF clinical trials and population studies.[26,31] In the specific setting of GALACTIC-HF, the higher rate of medication use in Black patients could theoretically also reflect the higher prevalence of hypertension and higher baseline blood pressure among Black patients when compared with White patients. In contrast to medical therapy, there were disparities in the use of

TABLE 4 Safety Outcomes of Omecamtiv Mecarbil Treatment (vs Placebo) in Black vs White Patients

	Black Patients (n = 535)	*P* Value	White Patients (n = 1,129)	*P* Value	Interaction *P* Value
Any treatment-emergent SAE	0.93 (0.82-1.04)	0.21	0.99 (0.95-1.03)	0.57	0.47
Ventricular tachyarrhythmia	0.92 (0.49-1.75)	0.81	1.01 (0.85-1.21)	0.89	0.83
Torsade/QT interval	0.85 (0.41-1.74)	0.65	0.93 (0.74-1.16)	0.53	0.95
SAE ventricular arrhythmia leading to treatment	1.29 (0.55-3.02)	0.55	1.00 (0.76-1.32)	0.99	0.36
First major cardiac ischemic event	1.04 (0.51-2.11)	0.92	1.05 (0.85-1.31)	0.64	0.69
First stroke	0.87 (0.36-2.11)	0.76	0.75 (0.53-1.06)	0.11	0.30

Values are HR (95% CI) unless otherwise indicated. Patients were from Brazil, South Africa, and the United States.
SAE = serious adverse event.

implanted defibrillators and cardiac resynchronization therapies (both less frequent in Black patients), which have been described in previous registry and public data.[32,33] These data also demonstrate higher overall event rates among Black patients with HF driven mostly by hospitalization.

Although the overall proportion of Black patients in GALACTIC-HF of 6.8% seems modest, this represents relatively robust enrollment in countries that have substantial Black populations. For example, in the United States, 29% of patients self-identified as Black, more than double the population average in the country. Similarly, in Brazil, 21% of patients were Black, again more than double the national average of 7.9% in the Brazilian population.[34] Moreover, the total number of Black patients (n = 562) was greater than reported in many contemporary HF pivotal trials (Table 5), including PARADIGM-HF (n = 428, 5.1%),[35,36] PIONEER-HF (comParIson Of sacubitril/valsartaN versus Enalapril on Effect on nt-pRo-bnp in patients stabilized from an acute Heart Failure episode) (n = 316, 36%),[37] VICTORIA (VerICiguaT GlObal Study in Subjects With Heart Failure With Reduced EjectIon FrAction) (n = 249, 4.9%),[38] DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) (n = 226, 4.8%),[26,39] EMPEROR-Reduced (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction) (n = 257, 6.9%),[40,41] and PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) (n = 102, 2.2%).[42] The GALACTIC-HF study team prioritized inclusion of sites that served underrepresented groups during site selection and continued to encourage diverse patient enrollment throughout the trial at investigator meetings and via other site contacts. These are simple strategies and likely contributed to the successful enrollment of Black patients. It is critical that sponsors and investigators continue to prioritize diverse racial participation in clinical trials.[43] Differences in underlying pathophysiology and comorbid conditions raise questions regarding racial differences in drug response[23,44] and lead to lingering questions for many key HF therapies, including angiotensin-converting enzyme inhibitors[10] and beta-blockers.[11,45] Lack of clarity is initially enabled by the inadequate enrollment of Black patients in pivotal clinical trials, and later clarification can take years and significant additional investigation.[46-48] Paying attention to this goal during trial execution can make a great deal of difference in the ultimate scientific value and knowledge gain of a study.

TABLE 5 Black Patient Enrollment in Recent HF Clinical Trials

	Total Black Patients	U.S. Black Enrollment
GALACTIC-HF[18]	562 (6.8)	357 (29)
PARADIGM-HF[35,36]	428 (5.1)	111 (26)
PIONEER-HF[37]	316 (36)	316 (26)
EMPEROR-Reduced[40,41]	257 (6.9)	100 (23.5)[a]
VICTORIA[38]	249 (4.9)	
DAPA-HF[26,39]	226 (4.8)	121 (17.9)[a]
PARAGON-HF[42]	102 (2.2)	

Values are n (%). [a]North America (not United States only).

DAPA-HF = Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; EMPEROR-Reduced = EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction; PARADIGM-HF = Prospective comparison of Angiotensin Receptor-neprilysin inhibitor (ARNI) with Angiotensin converting enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and morbidity in Heart Failure; PARAGON-HF = Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction; PIONEER-HF = comParIson Of sacubitril/valsartaN versus Enalapril on Effect on nt-pRo-bnp in patients stabilized from an acute Heart Failure episode; VICTORIA = VerICiguaT GlObal Study in Subjects With Heart Failure With Reduced EjectIon FrAction; other abbreviation as in Table 1.

STUDY LIMITATIONS. Our work has a few limitations to note. Although the recruitment of Black patients into the study was substantial and compared favorably with contemporary studies, the trial was still not designed to be adequately powered for race-based stratified analyses of the primary and secondary endpoints. Additionally, we did not have data on socioeconomic status or other social determinants of health that may contribute to varying outcomes among participants, so these data cannot shed more light on specific questions related to these factors. Similarly, although subgroup analysis of race was prespecified, the full analytic detail for this work was determined after trial completion and this work still suffers all the inherent limitations in such analyses, including increased type I error risk. Despite these limitations, the favorable direction of the effect estimates and overall consistency of the results are reassuring. Furthermore, the strong enrollment of Black patients and inclusion of 260 primary events should be able to provide reasonable estimates of the treatment effect of omecamtiv mecarbil in this important patient population. Finally, to maintain sharp focus we did not consider ethnicity (Hispanic compared with non-Hispanic) or other race groups in the trial (eg, Asian patients).

CONCLUSIONS

GALACTIC-HF enrolled more Black patients than any contemporary HF trial. The effect of omecamtiv mecarbil in Black patients was similar to White counterparts from the same countries of enrollment. Black patients treated with omecamtiv mecarbil

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experienced significant reductions in natriuretic peptide levels and heart rate, and showed beneficial effect estimates on the primary outcome (cardiovascular death or HF events), consistent with the treatment effect seen in White patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: These data support a similar beneficial treatment effect of omecamtiv mecarbil, in terms of reducing the risk of cardiovascular death or a HF event, in Black patients compared with White patients with HF and reduced LVEF.

COMPETENCY IN SYSTEMS-BASED PRACTICE: These data underscore the importance of diverse patient enrollment in clinical trials, specifically including groups that are traditionally under-represented such as Black patients, so patients and providers can have confidence that overall study findings can be safely applied to these subgroups.

TRANSLATIONAL OUTLOOK: Although the overall effect was similar across race groups, there was a possible differential effect on blood pressure. Future research should explore if this is a chance finding or not, and whether it may be mediated by differences in baseline characteristics such as hypertension or lower LVEF.

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APPENDIX For supplemental tables, please see the online version of this paper.