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Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure

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ABSTRACT

BACKGROUND

The selective cardiac myosin activator omecamtiv mecarbil has been shown to improve cardiac function in patients with heart failure with a reduced ejection fraction. Its effect on cardiovascular outcomes is unknown.

METHODS

We randomly assigned 8256 patients (inpatients and outpatients) with symptomatic chronic heart failure and an ejection fraction of 35% or less to receive omecamtiv mecarbil (using pharmacokinetic-guided doses of 25 mg, 37.5 mg, or 50 mg twice daily) or placebo, in addition to standard heart-failure therapy. The primary outcome was a composite of a first heart-failure event (hospitalization or urgent visit for heart failure) or death from cardiovascular causes.

RESULTS

During a median of 21.8 months, a primary-outcome event occurred in 1523 of 4120 patients (37.0%) in the omecamtiv mecarbil group and in 1607 of 4112 patients (39.1%) in the placebo group (hazard ratio, 0.92; 95% confidence interval [CI], 0.86 to 0.99; P=0.03). A total of 808 patients (19.6%) and 798 patients (19.4%), respectively, died from cardiovascular causes (hazard ratio, 1.01; 95% CI, 0.92 to 1.11). There was no significant difference between groups in the change from baseline on the Kansas City Cardiomyopathy Questionnaire total symptom score. At week 24, the change from baseline for the median N-terminal pro–B-type natriuretic peptide level was 10% lower in the omecamtiv mecarbil group than in the placebo group; the median cardiac troponin I level was 4 ng per liter higher. The frequency of cardiac ischemic and ventricular arrhythmia events was similar in the two groups.

CONCLUSIONS

Among patients with heart failure and a reduced ejection, those who received omecamtiv mecarbil had a lower incidence of a composite of a heart-failure event or death from cardiovascular causes than those who received placebo. (Funded by Amgen and others; GALACTIC-HF ClinicalTrials.gov number, NCT02929329; EudraCT number, 2016-002299-28.)

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*A complete list of GALACTIC-HF committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

The defining characteristic of heart failure with a reduced ejection fraction is decreased systolic function leading to reduced cardiac output and increased filling pressures. To date, no medications that directly enhance systolic function have improved outcomes.[1] Cardiac myosin activators are a new class of myotropes[2] that improve myocardial function by directly augmenting cardiac sarcomere function. Omecamtiv mecarbil,[3,4] the first of this class, augments cardiac contractility by selectively binding to cardiac myosin,[5] thus increasing the number of force generators (myosin heads) that can bind to the actin filament and initiate a power stroke at the start of systole. Short-term intravenous administration of omecamtiv mecarbil improved cardiac performance in early clinical studies.[6-8]

In patients with chronic heart failure with a reduced ejection fraction, the administration of omecamtiv mecarbil for 20 weeks increased the left ventricular systolic ejection time and stroke volume, decreased the left ventricular systolic and diastolic volumes (which suggested beneficial reverse cardiac remodeling), and reduced the plasma natriuretic peptide levels and heart rate.[9] On the basis of these findings, we designed and conducted the randomized, placebo-controlled, phase 3 Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure (GALACTIC-HF) trial to assess whether treatment with omecamtiv mecarbil in patients with heart failure who had a reduced ejection fraction would lower the risk of heart-failure events and cardiovascular death.[10,11]

Methods

Trial Design and Oversight

The executive committee designed and oversaw the conduct and analysis of the trial in collaboration with the sponsors, Amgen, Cytokinetics, and Servier.[10] The trial was conducted and reported in accordance with the protocol and the statistical analysis plan, which are available in the same document with the full text of this article at NEJM.org. The trial was approved by the regulatory agencies in the participating countries and by the institutional review board or ethics committee at each trial center. An independent data monitoring committee evaluated patient safety.

The executive committee and sponsors participated in the trial design and in the selection of participating centers and interpretation of the data; Amgen was responsible for site monitoring and for the collection, storage, and initial analyses of the data, evaluations that were replicated by an independent academic statistician (Table S1 in the Supplementary Appendix, available at NEJM.org). The first author had unrestricted access to the data and drafted the initial version of the manuscript, which was reviewed and edited by all the authors, who made the decision to submit the manuscript for publication. The executive committee vouches for the accuracy and completeness of the analyses and for the fidelity of the trial to the protocol.

Patients

Eligibility requirements included an age between 18 and 85 years, along with New York Heart Association functional class II, III, or IV symptoms and a left ventricular ejection fraction of 35% or less. The patients were currently hospitalized for heart failure (inpatients) or had either made an urgent visit to the emergency department or been hospitalized for heart failure within 1 year before screening (outpatients). All the patients had an N-terminal pro–B-type natriuretic peptide (NT-proBNP) level of 400 pg per milliliter or more or a BNP level of 125 pg per milliliter or more; among the patients with atrial fibrillation or flutter, the cutoff NT-proBNP level was 1200 pg per milliliter or more and the cutoff BNP level was 375 pg per milliliter or more. Patients were required to receive pharmacologic and device therapy for heart failure in accordance with regional clinical practice guidelines and with doses optimized according to the investigator's judgment.

Key exclusion criteria were current hemodynamic or clinical instability leading to the use of mechanical support or intravenous medication, a systolic blood pressure of less than 85 mm Hg, an estimated glomerular filtration rate (GFR) of less than 20 ml per minute per 1.73 m^2 of body-surface area, a recent acute coronary syndrome event or cardiovascular procedure (including a planned procedure), and other conditions that would adversely affect participation in the trial. A full description of the eligibility criteria has been published previously[10] and is available in the Supplementary Appendix. All the patients provided written informed consent.

Trial Procedures

We randomly assigned patients in a 1:1 ratio to receive either oral omecamtiv mecarbil or placebo

using an interactive Web-response or voice-response system and a sequestered, fixed randomization schedule, with balanced blocks within strata defined according to the randomization setting (inpatient or outpatient) and geographic region. The patients were assigned to receive omecamtiv mecarbil at a dose of 25 mg, 37.5 mg, or 50 mg twice daily on the basis of plasma levels of the drug, as described in the Supplementary Appendix. All the patients and investigators were unaware of the plasma levels and the dispensed dose. Postrandomization assessments were performed at weeks 2, 4, 6, 8, 12, 24, 36, and 48 and every 16 weeks thereafter (Fig. S1 and Table S2). The administration of omecamtiv mecarbil or placebo was temporarily suspended if the patient had clinical signs or symptoms consistent with acute myocardial infarction or ischemia.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was a composite of a heart-failure event or cardiovascular death, whichever occurred first, in a time-to-event analysis. A heart-failure event was defined as an urgent clinic visit, emergency department visit, or hospitalization for subjectively and objectively worsening heart failure leading to treatment intensification beyond a change in oral diuretic therapy.[12] Secondary outcomes were cardiovascular death, the change in the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) from baseline to week 24 (on a scale of 0 to 100, with higher scores indicating a lower frequency and severity of symptoms), the first heart-failure hospitalization, and death from any cause. All deaths, heart-failure events, major cardiac ischemic events (myocardial infarction, hospitalization for unstable angina, and coronary revascularization), and strokes were adjudicated by an external clinical-events committee at the Duke Clinical Research Institute, whose members were unaware of trial group assignments and used standardized definitions. (Details are provided in the Supplementary Appendix.[12])

STATISTICAL ANALYSIS

We determined that the enrollment of approximately 8000 patients would provide a power of 90% to detect a hazard ratio of 0.80 for cardiovascular death in the group receiving omecamtiv mecarbil (Fig. S2). The trial was event driven with a target of approximately 1590 cardiovascular deaths. The overall type I error was 0.05 for two-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, the alpha error would be divided unequally between cardiovascular death (96% of the overall alpha error, or 0.048) and the change from baseline to week 24 in the KCCQ total symptom score (4% of the overall alpha error, or 0.002).[13] On the basis of a one-sided alpha level of 0.0005, a single interim efficacy analysis was conducted after approximately two thirds of the targeted number of cardiovascular deaths had occurred. Given the negligible effect of this interim analysis on the final alpha level, the full alpha error of 0.05 was used in the final analysis, consistent with the Haybittle–Peto approach.[14,15]

We performed the efficacy analysis in the full analysis set of the intention-to-treat population, which included all the patients who had undergone randomization except for 24 patients from a single site who were excluded on the basis of Good Clinical Practice violations. We evaluated time-to-event data using Kaplan–Meier estimates and Cox proportional-hazards models with baseline hazards stratified according to the randomization setting (inpatient or outpatient) and geographic region and with the trial group and the baseline estimated GFR as covariates. The mean differences in the change in the KCCQ total symptom score 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 estimated GFR, 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 one subset of trial patients (inpatients or outpatients) was used to test the treatment effect for the KCCQ total symptom score.

The prespecified safety analyses included serious adverse events, adverse events associated with the discontinuation of omecamtiv mecarbil or placebo, and adverse events of interest (i.e., ventricular arrhythmias leading to treatment and positively adjudicated major cardiac ischemic events that included myocardial infarction, hospitalization for unstable angina, and coronary revascularization). The safety analyses were per-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Omecamtiv Mecarbil (N = 4120)	Placebo (N = 4112)
Age — yr	64.5±11.3	64.5±11.4
Female sex — no. (%)	875 (21.2)	874 (21.3)
Race or ethnic group — no. (%)†		
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 — no. (%)		
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 — no. (%)	1044 (25.3)	1040 (25.3)
Clinical features		
Atrial fibrillation or flutter — no. (%)	1146 (27.8)	1099 (26.7)
Type 2 diabetes mellitus — no. (%)	1652 (40.1)	1657 (40.3)
Ischemic heart failure — no. (%)	2193 (53.2)	2222 (54.0)
Left ventricular ejection fraction — %	26.6±6.3	26.5±6.3
NYHA classification — no. (%)		
II	2195 (53.3)	2173 (52.8)
III	1801 (43.7)	1815 (44.1)
IV	124 (3.0)	124 (3.0)
Median total symptom score on KCCQ (IQR)‡	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 — mm Hg	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/liter	27 (12–52)	27 (13–52)
Median eGFR (IQR) — ml/min/1.73m^2	58.8 (44.3–74.3)	58.7 (43.8–73.7)
Heart-failure therapy — no. (%)		
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)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Additional baseline characteristics are provided in Tables S3 and S4 in the Supplementary Appendix. ACE denotes 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, and SGLT2 sodium–glucose cotransporter 2.

† Race or ethnic group was reported by the patients. The category of Other includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or multiple patient-identified races or ethnic groups.

‡ Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100, with higher scores indicating a lower frequency and severity of symptoms.

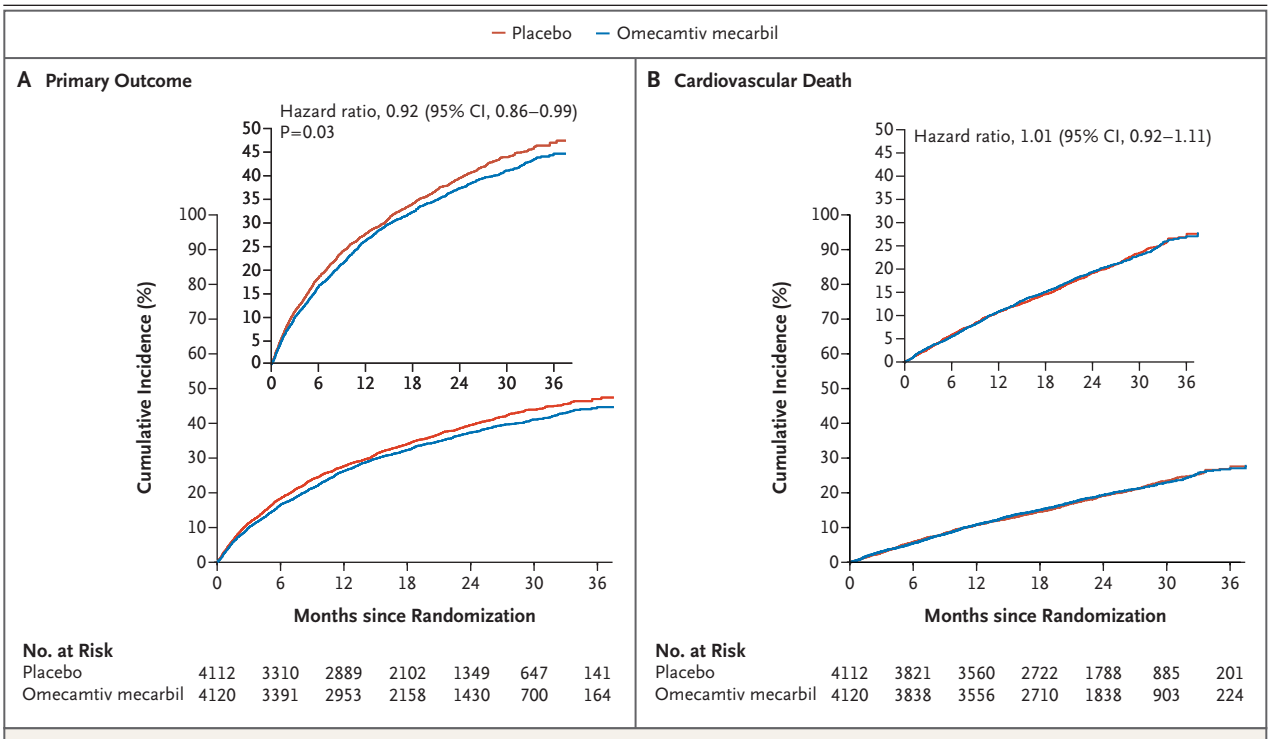

Figure 1. Primary Composite Outcome.

The primary outcome was a composite of a heart-failure event or cardiovascular death, whichever occurred first. The cumulative incidence of the primary composite outcome (Panel A) and death from cardiovascular causes (Panel B) was estimated with the use of the Kaplan–Meier method. Hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models stratified according to randomization location and geographic region, with the trial group as an explanatory variable. Analyses were performed in the intention-to-treat population in the full analysis set. The inset in each panel shows the same data on an enlarged y axis.

formed in patients who had undergone randomization and received at least one dose of omecamtiv mecarbil or placebo, with the exclusion of the same 24 patients who had been excluded from the full analysis set. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From January 6, 2017, to July 9, 2019, a total of 11,121 patients underwent screening at 945 sites in 35 countries. Of these patients, 8256 underwent randomization. After 24 patients were excluded because of Good Clinical Practice violations, 4120 patients were assigned to receive omecamtiv mecarbil and 4112 to receive placebo (Fig. S3). The characteristics of the patients at baseline were well balanced in the two trial groups (Table 1 and Tables S3 and S4).[11] At week 12, among the patients who were assigned to receive omecamtiv mecarbil twice daily, 1192 patients (28.9%) were receiving the 25-mg dose, 559 (13.6%) the 37.5-mg dose, and 1961 (47.6%) the 50-mg dose; the remaining 408 patients (9.9%) were not included in this analysis owing to discontinuation, missing study-visit data, or other reasons.

The overall median duration of follow-up was 21.8 months (interquartile range, 15.4 to 28.6). A total of 41 patients in the omecamtiv mecarbil group and 50 patients in the placebo group discontinued participation before the end of the trial on August 7, 2020. At that time, 16 patients had unknown vital status.

OUTCOMES

The primary outcome of a first heart-failure event or death from cardiovascular causes occurred in 1523 of 4120 patients (37.0%) in the omecamtiv mecarbil group and in 1607 of 4112 patients (39.1%) in the placebo group (hazard ratio, 0.92; 95% confidence interval [CI], 0.86 to 0.99; P=0.03) (Fig. 1A and Table 2). The effect

Table 2. Primary and Secondary Cardiovascular Outcomes.*

Variable	Omecamtiv Mecarbil (N=4120)		Placebo (N=4112)		Hazard Ratio or Difference (95% CI)†	P Value
	Value	Events	Value	Events		
		no./100 patient-yr		*no./100 patient-yr*		
Primary composite outcome — no. (%)‡	1523 (37.0)	24.2	1607 (39.1)	26.3	0.92 (0.86 to 0.99)	0.03
Cardiovascular death as first event	346 (8.4)		371 (9.0)			
Hospitalization for heart failure as first event	1107 (26.9)		1133 (27.6)			
Urgent outpatient visit for heart failure as first event	70 (1.7)		103 (2.5)			
Secondary outcomes						
Cardiovascular death — no. (%)	808 (19.6)	10.9	798 (19.4)	10.8	1.01 (0.92 to 1.11)	0.86§
Change in KCCQ total symptom score at wk 24						0.03§
Inpatients	23.7±0.7	NA	21.2±0.7	NA	2.5 (0.5 to 4.5)	
Outpatients	5.8±0.3	NA	6.3±0.3	NA	−0.5 (−1.4 to 0.5)	
First hospitalization for heart failure — no. (%)	1142 (27.7)	18.0	1179 (28.7)	19.1	0.95 (0.87 to 1.03)	NA
Death from any cause — no. (%)	1067 (25.9)	14.4	1065 (25.9)	14.4	1.00 (0.92 to 1.09)	NA
Exploratory outcome						
Heart-failure event — no. (%)	1177 (28.6)	18.7	1236 (30.1)	20.3	0.93 (0.86 to 1.00)	NA

* Plus–minus values are least-squares means ±SE. P values for efficacy outcomes are reported only for outcomes that were included in the hierarchical-testing strategy. NA denotes not applicable.

† All listed values are hazard ratios except for the between-group differences in the changes in the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ).

‡ The primary outcome was a composite of heart-failure events (hospitalization or unscheduled urgent clinic, office, or emergency department visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes.

§ The between-group difference in this category was not determined to be significant. After the determination of significance for the primary outcome, cardiovascular death was tested against an alpha of 0.048, and the change from baseline in the KCCQ total symptom score was tested against an alpha of 0.002 with a joint test for an effect among inpatients and outpatients. (Additional details about the statistical analysis are provided in the Supplementary Appendix.)

of omecamtiv mecarbil was generally consistent across most prespecified subgroups, with the exception of a possible interaction between trial group and ejection fraction at baseline (Fig. 2).

The secondary outcome of death from cardiovascular causes occurred in 808 patients (19.6%) in the omecamtiv mecarbil group and in 798 patients (19.4%) in the placebo group (hazard ratio, 1.01; 95% CI, 0.92 to 1.11; P=0.86) (Fig. 1B and Table 2). In the prespecified analysis of the change from baseline to week 24 in the KCCQ total symptom score according to randomization setting, the mean between-group difference in the change (omecamtiv mecarbil minus placebo) was 2.5 points (95% CI, 0.5 to 4.5) among inpatients and −0.5 (−1.4 to 0.5) among outpatients

Figure 2 (facing page). Primary Composite Outcome, According to Prespecified Subgroup.

Shown is the primary outcome of the trial, a composite of a heart-failure event or cardiovascular death, according to baseline values in subgroups that were prespecified in the protocol. Patients with atrial fibrillation or flutter at screening were not included in the analysis of NT-proBNP at baseline. Race or ethnic group were reported by the patients. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, ARN angiotensin receptor–neprilysin, BP blood pressure, CRT cardiac-resynchronization therapy, eGFR estimated glomerular filtration rate, ICD implantable cardioverter–defibrillator, LVEF left ventricular ejection fraction, MRA mineralocorticoid-receptor antagonist, NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.

(P=0.03 by joint omnibus F-testing). The combined P value for these comparisons did not meet the significance threshold of 0.002, according to the testing procedure for multiplicity control.

A first hospitalization for heart failure occurred in 1142 patients (27.7%) in the omecamtiv mecarbil group and in 1179 (28.7%) in the placebo group (hazard ratio, 0.95; 95% CI, 0.87 to 1.03); death from any cause occurred in 1067 patients (25.9%) and 1065 patients (25.9%), respectively (hazard ratio, 1.00; 95% CI, 0.92 to 1.09) (Table 2 and Figs. S4 and S5). The exploratory outcome of a first heart-failure event occurred in 1177 patients (28.6%) in the omecamtiv mecarbil group and in 1236 (30.1%) in the placebo group (hazard ratio, 0.93; 95% CI, 0.86 to 1.00) (Table 2 and Fig. S6). Sensitivity analyses for competing risks, potentially informative data censoring, and missing data regarding the KCCQ total symptom score because of death produced similar results to those of the primary analyses (Tables S5 through S8).

Other outcomes of interest included the effects of omecamtiv mecarbil on vital signs and selected laboratory values (Table 3). There was no difference in the change in systolic blood pressure between baseline and 24 or 48 weeks between the omecamtiv mecarbil group and the placebo group; the heart rate was slightly lower in the omecamtiv mecarbil group than in the placebo group at the two time points. The change from baseline in the NT-proBNP level at week 24 was 10% lower (95% CI, 6 to 14) in the omecamtiv mecarbil group than in the placebo group.

SAFETY

In the safety-analysis set, omecamtiv mecarbil was discontinued in 847 of 4110 patients (20.6%) and placebo in 897 of 4101 patients (21.9%). An adverse event was the reason for discontinuation in 371 patients (9.0%) in the omecamtiv mecarbil group and 382 (9.3%) in the placebo group. The trial agent was withheld because of concern of active myocardial infarction or ischemia in 103 patients in the omecamtiv mecarbil group and in 101 patients in the placebo group.

Patients in the two groups had no change in potassium or creatinine levels during the course of the trial. The median change from baseline in the level of cardiac troponin I at week 24 was 4 ng per liter higher in the omecamtiv mecarbil group than that in the placebo group, according to results on the Siemens ADVIA Centaur Ultra Troponin I assay (lower limit of detection, 6 ng per liter; upper reference limit, 40 ng per liter).

Adjudicated major cardiac ischemic events occurred in 200 patients (4.9%) in the omecamtiv mecarbil group and in 188 (4.6%) in the placebo group; among these patients, myocardial infarction accounted for 122 events (3.0%) and 118 events (2.9%), respectively (Fig. S7). Ventricular arrhythmic events occurred at a similar rate in the two groups. Additional adverse-event data are provided in Tables S9 and S10.

DISCUSSION

In this randomized, placebo-controlled trial involving patients with heart failure and a reduced ejection fraction receiving guideline-based pharmacologic and device therapy, those in the omecamtiv mecarbil group had an 8% lower relative risk (absolute difference, 2.1 percentage points) of the composite primary outcome of a heart-failure event or death from cardiovascular causes than those in the placebo group. This effect was observed without evidence of an increase in the risk of myocardial ischemic events, ventricular arrhythmias, or death from cardiovascular causes or any cause.

The modest but significant lowering of the incidence of the primary outcome was observed across a broad range of both inpatients and outpatients,[11] including those with moderate or severe heart-failure symptoms and a reduced ejection fraction, systolic blood pressure, and renal function. The benefit was consistent across most subgroups, but a possible heterogeneity of effect was suggested by a potentially greater treatment effect in patients with an ejection fraction of 28% or less than in those with an ejection fraction of more than 28%. Although subgroup analyses have inherent limitations, potential differences in benefit according to ejection fraction are biologically plausible, since omecamtiv mecarbil specifically increases cardiac performance.[9,16] These findings support the hypothesis that improving cardiac function by selectively targeting the cardiac sarcomere with omecamtiv mecarbil can improve clinical outcomes.

This trial did not show that omecamtiv mecarbil improved any of the secondary outcomes.

Table 3. Laboratory Measures and Safety Outcomes.*

Variable	Omecamtiv Mecarbil (N=4110)	Placebo (N=4101)	Relative Risk or Difference (95% CI)†
Change from baseline in vital signs and laboratory measures			
Systolic blood pressure — mm Hg			
At wk 24	1.4±15.3	1.5±15.6	−0.1 (−0.9 to 0.6)
At wk 48	2.0±16.1	1.9±16.0	0.2 (−0.6 to 1.0)
Heart rate — beats/min			
At wk 24	−2.1±12.6	−0.5±12.8	−1.6 (−2.2 to −1.0)
At wk 48	−2.0±13.1	−0.2±13.2	−1.8 (−2.4 to −1.1)
Potassium – mmol/liter			
At wk 24	−0.01±0.57	−0.01±0.57	0.00 (−0.03 to 0.03)
At wk 48	−0.03±0.59	−0.02±0.58	−0.01 (−0.04 to 0.02)
Creatinine — mg/dl			
At wk 24	0.03±0.33	0.02±0.32	0.01 (−0.01 to 0.02)
At wk 48	0.06±0.39	0.05±0.38	0.01 (−0.01 to 0.03)
Median NT-proBNP (IQR) — pg/ml‡			
At wk 24	−251 (−1180 to 295)	−180 (−915 to 441)	0.90 (0.86 to 0.94)
Median cardiac troponin I (IQR) — ng/liter			
At wk 24	4 (−2 to 21)	0 (−9 to 8)	4 (3 to 5)
At wk 48	2 (−4 to 18)	0 (−9 to 8)	2 (1 to 3)
Safety outcomes — no. (%)§			
Discontinuation because of adverse event	371 (9.0)	382 (9.3)	0.97 (0.85 to 1.11)
Serious adverse event	2373 (57.7)	2435 (59.4)	0.97 (0.94 to 1.01)
Adverse event of interest			
Ventricular tachyarrhythmia	290 (7.1)	304 (7.4)	0.95 (0.82 to 1.11)
Torsades de pointes or QT prolongation	176 (4.3)	195 (4.8)	0.90 (0.74 to 1.10)
Serious adverse ventricular arrhythmia leading to treatment	119 (2.9)	127 (3.1)	0.93 (0.73 to 1.20)
Adjudicated major cardiac ischemic event	200 (4.9)	188 (4.6)	1.06 (0.87 to 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 to 0.91)

* Plus–minus values are means ±SD. To convert the values for potassium to milligrams per deciliter, divide by 0.2558. To convert the values for creatinine to micromoles per liter, multiply by 88.4.
† The data are reported as relative risk for all safety outcomes.
‡ For the NT-proBNP value, the between-group difference is the geometric mean ratio as determined by the exponentiation of the change from baseline in log-transformed values from a mixed model containing the log baseline value, geographic region, baseline eGFR, scheduled visit, trial group, and interaction of trial group with the scheduled visit.
§ The safety population included all patients who had undergone randomization and received at least one dose of omecamtiv mecarbil or placebo.

The lack of effect on death from either cardiovascular causes or any cause is surprising, given the prior evidence with omecamtiv mecarbil of improvements in left ventricular volumes and function, as well as decreases in heart rate and NT-proBNP in the Chronic Oral Study of Myosin

Activation to Increase Contractility in Heart Failure (COSMIC-HF)[9] and the reduced heart rate and NT-proBNP level observed in GALACTIC-HF. A prior meta-analysis suggested that treatments that reduce ventricular volumes and increase the ejection fraction are likely to reduce mortality.[17] Two meta-analyses of heart-failure trials showed no significant correlation between therapy-induced changes in the NT-proBNP level and mortality,[18,19] but in one of these meta-analyses, a relationship between a decrease in the NT-proBNP level and a reduction in heart-failure hospitalizations was observed.[19] In our trial, the inpatients at the time of enrollment had a higher burden of symptoms than those enrolled as outpatients, as suggested by their worse KCCQ total symptom score at baseline. However, according to the prespecified testing procedure, there was no significant difference between the omecamtiv mecarbil group and the placebo group among either inpatients or outpatients.[20]

The identification of medicines that increase cardiac performance has been a goal of heart-failure therapeutics for more than a century, yet the drugs that have been developed have consistently increased the incidence of myocardial ischemia, ventricular arrhythmias, or death[1,10] because of their mechanisms of increasing the magnitude of intracellular calcium transients in cardiomyocytes. As a selective cardiac myosin activator, omecamtiv mecarbil has no effect on these calcium transients,[3] and in GALACTIC-HF, the incidences of myocardial ischemia, ventricular arrhythmias, and death were similar in the two trial groups with almost 7500 patient-years of follow-up. These findings suggest that despite the small increase in plasma levels of troponin that have been noted in some trials[8,9] and in the current trial, treatment with omecamtiv mecarbil did not increase the risk of these clinical adverse effects. In addition, no detrimental effects of omecamtiv mecarbil were detected with respect to blood pressure, heart rate, and creatinine or potassium levels.

Our trial has some limitations. It excluded patients over the age of 85 years and those with a clinically unstable condition. The underrepresentation of racial groups and women in clinical trials is a continuing concern.[21] Only 7% of the patients reported their race as Black, although the number of Black patients was larger than those in many previous heart-failure trials. Only approximately 21% of the patients were women, a percentage that is consistent with findings in other trials involving patients with heart failure and a reduced ejection fraction. Although the background therapy was generally excellent and more than 19% of the patients were receiving sacubitril–valsartan at baseline, the compelling results from recent trials of sodium–glucose cotransporter 2 inhibitors[22,23] were not available until after GALACTIC-HF had completed enrollment, which limited the use of these drugs to only 2.6% of the patients.

Our trial showed that among patients with heart failure and a reduced ejection fraction, those who received omecamtiv mecarbil had a lower risk of a composite of heart-failure events and cardiovascular death than those who received placebo.

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APPENDIX

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