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CLINICAL RESEARCH

Safety and Tolerability of Omecamtiv Mecarbil During Exercise in Patients With Ischemic Cardiomyopathy and Angina

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ABSTRACT

OBJECTIVES The goal of this study was to assess the safety and tolerability of omecamtiv mecarbil treatment during symptom-limited exercise in patients with ischemic cardiomyopathy and angina. These patients may have increased vulnerability to prolongation of the systolic ejection time.

BACKGROUND Omecamtiv mecarbil is a selective cardiac myosin activator that augments cardiac contractility in patients with systolic heart failure through a dose-dependent increase in systolic ejection time.

METHODS In this double-blind, placebo-controlled study, patients with chronic heart failure were randomized 2:1 to receive omecamtiv mecarbil or placebo in 2 sequential cohorts of escalating doses designed to achieve plasma concentrations previously shown to increase systolic function. Patients underwent 2 symptom-limited exercise treadmill tests (ETTs) at baseline (ETT1 and ETT2) and again before the end of a 20-h infusion of omecamtiv mecarbil (ETT3).

RESULTS The primary pre-defined safety endpoint (i.e., the proportion of patients who stopped ETT3 because of angina at a stage earlier than baseline) was observed in 1 patient receiving placebo and none receiving omecamtiv mecarbil. No dose-dependent differences emerged in the proportion of patients stopping ETT3 for any reason or in the pattern of adverse events.

CONCLUSIONS Doses of omecamtiv mecarbil producing plasma concentrations previously shown to increase systolic function were well tolerated during exercise in these study patients with ischemic cardiomyopathy and angina. There was no indication that treatment increased the likelihood of myocardial ischemia in this high-risk population. (Pharmacokinetics [PK] and Tolerability of Intravenous [IV] and Oral CK-1827452 in Patients With Ischemic Cardiomyopathy and Angina; NCT00682565) (J Am Coll Cardiol HF 2015;3:22–9) © 2015 by the American College of Cardiology Foundation. Open access under CC BY-NC-ND license.

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Omecamtiv mecarbil (formerly CK-1827452 and AMG 423) is a selective, small molecule activator of cardiac myosin that binds to the catalytic domain of myosin and increases the transition rate of myosin into the actin-bound force-generating state without affecting cardiac myocyte intracellular calcium (1). In healthy subjects and in patients with stable heart failure, infusions of omecamtiv mecarbil resulted in statistically significant, dose-related, and concentration-related increases in systolic ejection time associated with increases in indices of left ventricular (LV) systolic function such as stroke volume, fractional shortening, and ejection fraction (2,3). No consistent pattern of adverse events (AEs) was observed in patients who were tolerant of drug infusion. In both healthy subjects and patients with heart failure, the dose-limiting effect of omecamtiv mecarbil was myocardial ischemia. This occurred in some patients at plasma concentrations >1,200 ng/ml and was likely due to excessive prolongation of the systolic ejection time, reducing the time for coronary perfusion during diastole. Because heart rate, coronary blood flow, and myocardial oxygen demand increase while the overall duration of the cardiac cycle shortens, factors that may increase susceptibility to ischemia when systolic ejection time is increased include coronary artery disease or exercise.

Our goal was to understand the effects of exercise on the safety and tolerability of omecamtiv mecarbil in a relevant patient population as a prelude to chronic dosing. The present study was designed to evaluate omecamtiv mecarbil in patients with ischemic cardiomyopathy and angina in a controlled, well-monitored setting by using symptom-limited exercise during intravenous (IV) infusions of omecamtiv mecarbil. The doses of omecamtiv mecarbil were selected to produce plasma drug concentrations associated with increases in systolic ejection time and LV systolic function (2). An additional goal of the study was to obtain the first pharmacokinetic and tolerability data in patients with heart failure after oral dosing to steady state.

METHODS

This double-blind, randomized, placebo-controlled study was conducted between April 2008 and November 2008 at 12 sites in the Republic of Georgia and the Russian Federation. Independent ethics committees at each study site approved the protocol, and all patients provided written informed consent before initiation of study-specific procedures. The study was conducted in compliance with the Declaration of Helsinki.

PATIENTS. Eligible patients were adults (≥18 years of age) with documented ischemic cardiomyopathy and angina. Ischemic heart disease was defined as a history of myocardial infarction documented by elevated creatine phosphokinase (CPK)-MB, troponin I or T, or the presence of electrocardiographic Q waves consistent with myocardial infarction, and/or coronary angiography demonstrating ≥1 major epicardial coronary artery with a stenosis of ≥60% diameter but excluding stenosis of the left main coronary artery unless revascularized by coronary artery bypass grafting. Patients had a history of ≥1 episode of exercise-induced angina within 2 months before screening. Patients were required to have an LV ejection fraction ≤35% and an LV end-diastolic diameter ≥55 mm or LV end-diastolic diameter index ≥32 mm/m^2 (confirmed by the core echocardiography laboratory before randomization); New York Heart Association functional class II or III for ≥3 months before screening; and treatment with stable standard therapy for heart failure ≥4 weeks before screening. Patients had the capacity to complete ≥4 min of a Modified Naughton exercise tolerance test (ETT) (Online Table S1) (4).

Exclusion criteria included acute myocarditis; clinically significant restrictive, constrictive, or hypertrophic obstructive cardiomyopathy; clinically significant congenital heart disease; systolic blood pressure >160 mm Hg documented on ≥3 occasions separated by 10 min; levels of troponin I or T or CPK-MB greater than the upper limit of normal (ULN) within 6 weeks of screening and up to randomization; severe aortic or mitral stenosis; acute coronary syndrome, transient ischemic attack, or revascularization within 6 weeks of screening; significant comorbid conditions that would limit treadmill exercise; renal or hepatic impairment; receipt of an investigational drug or device within 30 days or 5 half-lives before randomization; weight >120 kg; body temperature >38°C; any laboratory abnormality that would preclude participation in the study; or previous treatment with omecamtiv mecarbil.

STUDY DESIGN. Two sequential cohorts of patients were enrolled (**Figure 1**). Before randomization, patients had to complete 2 separate screening ETTs (ETT1 and ETT2) administered at least 24 h apart, achieving ≥4 min of a Modified Naughton Exercise Protocol on both tests (Online Methods). Baseline ETT performance was defined as the shorter of the 2 exercise durations recorded during the screening ETTs. Patients in each cohort were randomly assigned in a 2:1 ratio to receive an IV infusion of omecamtiv

ABBREVIATIONS AND ACRONYMS

AE = adverse event
C_{max} = maximum plasma concentration
CPK = creatine phosphokinase
ECG = electrocardiogram
ETT = exercise treadmill test
IV = intravenous
LV = left ventricular
SAE = serious adverse event
ULN = upper limit of normal

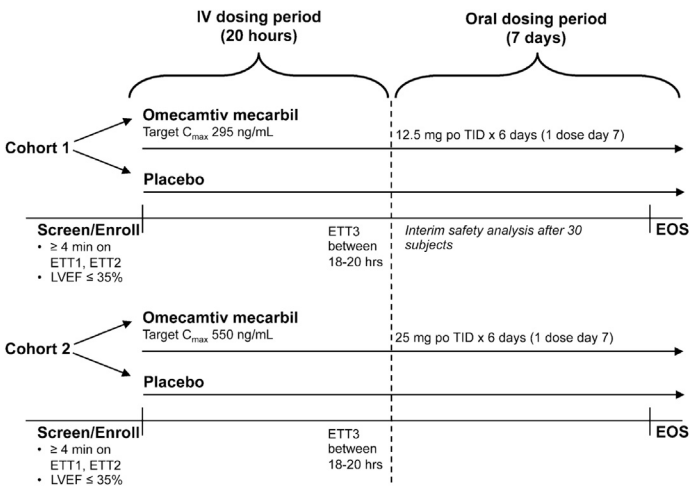

FIGURE 1 Study Schema

C_{max} = maximum plasma concentration; EOS = end of study; ETT = exercise tolerance test; IV = intravenous; LVEF = left ventricular ejection fraction; po = orally; TID = 3 times daily.

mecarbil or placebo over 20 h. A third ETT (ETT3) was performed during the final 2 h of IV dosing. Patients in the omecamtiv mecarbil arms were dosed to target plasma levels of ~295 ng/ml in cohort 1 (24 mg/h for 2 h followed by 6 mg/h for 18 h) and ~550 ng/ml in cohort 2 (48 mg/h for 2 h followed by 11 mg/h for 18 h). Patients who tolerated the IV infusion then self-administered omecamtiv mecarbil orally (immediate release; 12.5 mg and 25 mg for cohorts 1 and 2, respectively) or placebo orally 3 times daily for 7 days. Patients had a follow-up visit 6 to 14 days after the last oral dose. There were no exercise tests during or after oral dosing.

In each cohort, patients were assigned to treatment via central randomization by an independent vendor. An unblinded site pharmacist prepared the study medications and provided them to blinded site staff according to the randomization system assignment.

Core laboratories were used for analysis of echocardiograms (ICON Medical Imaging, Warrington, Pennsylvania) and exercise electrocardiograms (ECGs) (St. Louis University Core ECG Lab, St. Louis, Missouri). Two local core laboratories were used to analyze blood samples for cardiac enzymes (INVITRO Central Laboratory, Moscow, Russia; Medical Center CITO Ltd., Tbilisi, Georgia). The upper reference limit for assays performed by Medical Center CITO was ≥0.11 μg/l and for INVITRO was ≥ 1 μg/l; the limit of detection for Medical Center CITO assays was 0.01 μg/l, and it was not specified for the INVITRO assays.

STUDY ENDPOINTS. The primary endpoint of this safety study was the proportion of patients who stopped ETT3 because of angina and at a stage earlier than baseline. Secondary safety endpoints included the proportion of patients who stopped ETT3 for any reason at a stage earlier than baseline; duration of exercise during ETT3; proportion of patients with angina during ETT3; time to angina during ETT3; proportion of patients with 1-mm ST-segment depression on their ECG during ETT3; time to 1-mm ST-segment depression during ETT3; and AEs and serious adverse events (SAEs).

Secondary objectives were the assessment of tolerability and steady-state omecamtiv mecarbil plasma concentrations at trough and 1 h after dosing 3 times daily for 7 days with an immediate-release, blend-in-capsule oral formulation.

STATISTICAL ANALYSIS. Sample size was empirically determined to provide an adequate assessment of tolerability. Patients who received placebo in both cohorts were pooled for this analysis. For change in duration of exercise between baseline and ETT3, the comparison between patients who received omecamtiv mecarbil and patients who received placebo was performed by using an analysis of covariance model, with treatment group as the main effect and baseline ETT exercise duration as a covariate. For categorical variables, treatment differences in proportion with 95% confidence intervals between omecamtiv mecarbil and placebo were constructed by using the Meittinen-Nurminen approach. For the time to angina and time to 1-mm ST-segment depression during ETT3, survival analysis techniques were used. The log-rank test was used to test the equality of time to onset of 1-mm ST-segment depression and time to onset of angina between omecamtiv mecarbil and placebo. Pharmacokinetic analyses according to standard noncompartmental methods were performed by using WinNonlin Professional (Pharsight, St. Louis, Missouri). Treatment-emergent AEs and SAEs occurring from the first dose through 30 days after the last dose were summarized and coded by using the Medical Dictionary for Regulatory Activities version 10.1. Statistical analyses were performed by using SAS version 9.1.3 (SAS Institute, Inc., Cary, North Carolina).

The safety population represented all patients who were randomized to a treatment group and received any study drug. The safety ETT population comprised all patients in the safety population who received any study drug and performed ETT3. The pharmacokinetics population included patients in the safety population who had ≥1 measurable plasma sample for pharmacokinetics testing and no protocol violations

that could have affected the pharmacokinetics of omecamtiv mecarbil.

RESULTS

PATIENTS. A total of 95 patients were randomized to treatment, and 1 patient withdrew from the study because of influenza just before dosing. Of the 94 patients who received the study drug, 46 were allocated to cohort 1 (31 omecamtiv mecarbil; 15 placebo) and 48 were allocated to cohort 2 (34 omecamtiv mecarbil; 14 placebo) (Online Figure S1). All patients in cohort 1 completed IV dosing, and only 1 patient did not complete oral dosing (omecamtiv mecarbil arm). The patient who discontinued omecamtiv mecarbil in cohort 1 had an asymptomatic elevated CPK-MB level (36 U/l; ULN 24 U/l); troponin I was undetectable at the coincident time point and all other time points. All patients in cohort 2 completed IV dosing, and 3 patients did not complete oral dosing (omecamtiv mecarbil arm). Of these, 1 patient had an SAE (described in the following discussion); 1 patient had troponin levels of 1.1 ng/ml (ULN 1.0 ng/ml) after ETT3 in the absence of other specific clinical signs or symptoms of cardiac ischemia; and 1 patient had asymptomatic elevated CPK-MB (6.4 ng/ml; ULN 5.8 ng/ml; troponin I was undetectable at the coincident time point and all other time points).

Baseline demographic and clinical characteristics were similar among patients receiving placebo or omecamtiv mecarbil (**Table 1**, Online Table S2). All patients were white, and most (80%) were men; their mean age was 63.4 years. Eleven patients (11.7%) stopped one of the baseline exercise tests conducted before study drug infusion (ETT1 or ETT2) because of angina (none in cohort 1; 4 on placebo; 7 on omecamtiv mecarbil in cohort 2).

PRIMARY AND SECONDARY SAFETY ENDPOINTS. In the placebo arm, 1 patient (3.4%) stopped ETT3 (during infusion) at a stage earlier than baseline because of angina while none did so in the omecamtiv mecarbil arm at either dose (**Table 2**, Online Table S3).

Seven patients (1 taking placebo; 4 taking omecamtiv mecarbil in cohort 1; 2 taking omecamtiv mecarbil in cohort 2) stopped ETT3 for any reason at a stage earlier than baseline (**Table 2**). The differences in the proportions of patients who stopped ETT3 for any reason at a stage earlier than baseline between patients receiving omecamtiv mecarbil and those receiving placebo (treatment difference in proportion [95% confidence intervals] for cohort 1: 9.5% [-6.2 to 26.2]; cohort 2: 2.4% [-12.2 to 16.4]) were not statistically significant. The most common reason for stopping ETT3 at a stage earlier than baseline was limiting fatigue.

There were 9 patients who also stopped at least one of the baseline ETTs (ETT1 and/or ETT2) because of angina; 7 of these 9 patients stopped both baseline ETTs because of angina. During ETT3, the same 9

TABLE 1 Patient Demographic and Clinical Characteristics at Baseline (Safety Population)

	Placebo (n = 29)	Omecamtiv Mecarbil Cohort 1* (n = 31)	Omecamtiv Mecarbil Cohort 2† (n = 34)	All Patients (N = 94)
Age, yrs				
Mean ± SD	62.3 ± 9.8	65.2 ± 10.0	62.6 ± 8.1	63.4 ± 9.3
Range	42-80	40-79	46-76	40-80
Male	23 (79.3)	23 (74.2)	29 (85.3)	75 (79.8)
Weight, kg	80.0 ± 11.9	78.7 ± 10.8	78.5 ± 14.1	79.0 ± 12.3
BMI, kg/m^2	26.5 ± 3.4	26.3 ± 3.4	26.8 ± 4.1	26.5 ± 3.6
White race	29 (100)	31 (100)	34 (100)	94 (100)
Primary ischemic etiology	29 (100)	31 (100)	34 (100)	94 (100)
Previous MI	21 (72.4)	21 (67.7)	30 (88.2)	72 (76.6)
Smoking history				
Current	6 (20.7)	5 (16.1)	9 (26.5)	20 (21.3)
Never	11 (37.9)	14 (45.2)	13 (38.2)	38 (40.4)
Quit <6 months	1 (3.4)	1 (3.2)	1 (2.9)	3 (3.2)
Quit ≥6 months	11 (37.9)	11 (35.5)	11 (32.4)	33 (35.1)
SBP, mm Hg	120 ± 10	120 ± 11	122 ± 13	121 ± 11
Heart rate, beats/min	74.3 ± 12.7	73.5 ± 16.1	69.4 ± 12.5	72.3 ± 13.9
Rales present	9 (31.0)	13 (41.9)	12 (35.2)	34 (36.2)
Peripheral edema				
0	15 (51.7)	15 (48.4)	21 (61.8)	51 (54.3)
1+	3 (10.3)	2 (6.5)	6 (17.6)	11 (11.7)
2+	8 (27.6)	11 (35.5)	5 (14.7)	24 (25.5)
3+	3 (10.3)	3 (9.7)	2 (5.9)	8 (8.5)
LVDD, cm				
Mean ± SD	7.2 ± 0.7	7.1 ± 1.1	7.2 ± 0.9	7.1 ± 0.9
Range	5.1-8.7	5.2-10.3	5.5-9.2	5.1-10.3
LVEF, %	23 (6)	22 (7)	21 (7)	22 (7)
Medical therapy				
ACEI/ARB	29 (100)	31 (100)	34 (100)	94 (100)
Beta-blocker	29 (100)	31 (100)	34 (100)	94 (100)
Spironolactone	26 (89.7)	28 (90.3)	26 (76.5)	80 (85.1)
Digoxin	5 (17.2)	9 (29.0)	7 (20.6)	21 (22.3)
Baseline ETT‡ exercise duration, s				
Mean ± SD	380 ± 121	377 ± 124	369 ± 112	375 ± 118
Range	300-720	300-900	300-720	300-900
Stopped ETT-1 or ETT-2 for angina	4 (13.8)	0	7 (20.6)	11 (11.7)
ECG assessable for 1-mm ST-segment depression	10 (34.5)	8 (25.8)	12 (35.4)	30 (31.9)
Patients with 1-mm ST-segment depression during ETT-1	2 (20.0)	0 (0.0)	1 (8.3)	3 (10.0)

Values are mean ± SD, range, or n (%). *Cohort 1: Omecamtiv mecarbil infused at 24 mg/h for 2 h followed by 6 mg/h for 18 h. Patients who tolerated the infusion then received omecamtiv mecarbil 12.5 mg orally 3 times daily for 7 days. †Cohort 2: Omecamtiv mecarbil infused at 48 mg/h for 2 h followed by 11 mg/h for 18 h. Patients who tolerated the infusion then received omecamtiv mecarbil 25 mg orally 3 times daily for 7 days. ‡Baseline ETT was the shorter of the screening ETTs (ETT1 or ETT2).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; ETT = exercise tolerance test; LVDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SBP = systolic blood pressure.

TABLE 2 Safety Endpoints Summary (Safety ETT Population)

	Placebo (n = 29)	Omecamtiv Mecarbil	
		Cohort 1* (n = 31)	Cohort 2† (n = 34)
Primary endpoint			
Patients who stopped ETT3 for angina at stage earlier than baseline	1 (3.4)	0 (0.0)	0 (0.0)
Secondary endpoints			
Patients who stopped ETT3 for any reason at stage earlier than baseline	1 (3.4)	4 (12.9)	2 (5.9)
Patients who stopped ETT3 for angina	2 (6.9)	0 (0.0)	7 (20.6)
Time to angina during ETT3, s	325.5 ± 123.7	NA	345.9 ± 69.4
Change from baseline ETT in exercise duration during ETT3, s	60.1 ± 71.2	41.5 ± 113.1	40.5 ± 70.6
Patients with 1-mm ST-segment depression during ETT3, n/N assessable‡ (%)	2/7 (28.6)	0/10 (0.0)	1/12 (8.3)
Time to 1-mm ST-segment depression, s	300, 620§	NA	235‖

Values are n (%) or mean ± SD. *Cohort 1: Omecamtiv mecarbil infused at 24 mg/h for 2 h followed by 6 mg/h for 18 h. Patients who tolerated the infusion then received omecamtiv mecarbil 12.5 mg orally 3 times daily for 7 days. †Cohort 2: Omecamtiv mecarbil infused at 48 mg/h for 2 h followed by 11 mg/h for 18 h. Patients who tolerated the infusion then received omecamtiv mecarbil 25 mg orally 3 times daily for 7 days. ‡Patients were not considered to have electrocardiographs interpretable for ST-segment analysis if they had baseline ST-segment depression ≥1 mm, left bundle branch block or right bundle branch block, or ventricular pacing or if they were receiving digoxin. §Values for 2 patients with 1-mm ST-segment depression during ETT-3. ‖Value for 1 patient with 1-mm ST-segment depression during ETT-3.

NA = not applicable; other abbreviation as in Table 1.

patients (2 in the placebo group; 7 in the omecamtiv mecarbil group in cohort 2) stopped again because of angina (Table 2). In 3 of these 9 patients, the duration of ETT3 was shorter than the baseline ETT (1 patient in the placebo group; 2 in the omecamtiv mecarbil group in cohort 2). The exercise stage at which each of these 9 patients stopped ETT3 was the same stage at which their baseline ETT was stopped, and hence they did not contribute to the primary endpoint.

Exercise time during ETT3 compared with baseline increased in all treatment groups (Table 2). Although the overall increase in exercise time was greater with placebo than with omecamtiv mecarbil in each of cohorts 1 and 2, the difference was not statistically significant, and the increase in exercise time was similar for both dose levels of omecamtiv mecarbil. A greater proportion of patients exercised to stage 4 or above during ETT3 compared with ETT1 or ETT2 across all treatment groups (Figure 2).

Patients with heart failure due to ischemic cardiomyopathy frequently had reasons that precluded interpretation of exercise-induced ischemia on their ECG (e.g., resting ST-segment depression, left bundle branch block, treatment with digoxin) (5). Of the 94 patients, 29 had ECGs interpretable for ST-segment analysis; exclusions included those who were receiving digoxin and those who had baseline ST-segment depression ≥1 mm, left bundle branch block or right bundle branch block, or ventricular pacing. Of these 29 patients, only 2 patients receiving placebo and 1 patient receiving omecamtiv mecarbil in cohort 2 had ≥1-mm ST-segment depression during ETT3. In the 1 patient taking omecamtiv mecarbil, time to the onset of 1-mm ST-segment depression during ETT3 (235 s) was somewhat shorter than ETT2 (311 s), which was new compared with ETT1 when the patient did not have ST-segment depression.

TREATMENT-EMERGENT AEs. Nineteen patients (20.2%) experienced 29 distinct treatment-emergent AEs (Table 3), including 17.2% on placebo, a 6.5% on omecamtiv mecarbil in cohort 1, and 35.3% on omecamtiv mecarbil in cohort 2. Of the 29 distinct AEs, 23 events were reported as mild in severity, 4 as moderate, and 2 as serious/severe (both occurring in the same patient [as discussed in the following section]). The investigators assessed 14 of the 29 AEs as not related to treatment, 8 of the 29 as possibly related to treatment, and 7 of the 29 as probably related to treatment. The majority of the AEs occurred during the infusion phase; in the oral dosing phase, only 4 AEs were reported (2 in patients on placebo and 2 in patients on omecamtiv mecarbil). Although AEs were more frequent in cohort 2 for patients on omecamtiv mecarbil, in all but 2 patients they were mild in severity (1 patient with moderate photopsia and 1 patient described in the following section in more detail) and there was no consistent pattern in the types of AEs reported (Table 3, Online Table S4). All AEs had resolved by the end of the study.

Two SAEs were reported in 1 patient receiving omecamtiv mecarbil in cohort 2. After tolerating 18 h of omecamtiv mecarbil infusion without issue, in the last 2 h of the infusion, the patient underwent his third exercise test. He terminated ETT3 because of intolerable angina and ST-segment depression, which he also experienced during ETT2. The patient received nitroglycerin during the recovery period of ETT3, during which his symptoms resolved; he subsequently underwent coronary stent implantation for a severe proximal lesion in the left anterior descending artery. After stent implantation, the patient had a peak troponin I level of 2.45 ng/ml. The maximum plasma concentration of omecamtiv mecarbil for this patient was 651 ng/ml. The investigator reported SAEs of acute coronary syndrome and non-Q-wave myocardial infarction associated with percutaneous transluminal coronary angioplasty. The patient was discontinued from the study.

No clinically meaningful changes in vital signs (systolic blood pressure/diastolic blood pressure,

heart rate, respiratory rate, and oxygen saturation) or cardiac enzymes (troponin I, CPK-MB, and total creatine kinase) for any of the treatment groups were observed. Systolic blood pressure and heart rate data throughout the study are shown in Online Tables S5 and S6. Overall, few patients had detectable or elevated levels of troponin I (Online Table S7) or CPK-MB above the ULN (Online Table S8) at any time during the study. Before study drug infusion, 1 patient in the placebo group and 1 patient in cohort 1 had detectable or elevated troponin I levels at screening, and 1 patient in the placebo group had detectable or elevated troponin I levels before and after ETT1. Two patients taking omecamtiv mecarbil had troponin I results that were just above the ULN after study drug infusion following ETT3: peak troponin I levels were 0.13 μg/l (ULN <0.11 μg/l) for a patient in cohort 1 and 1.1 μg/l (ULN <1.0 μg/l) for a patient in cohort 2. There were no other clinical signs or symptoms of ischemia in these 2 patients.

PHARMACOKINETICS. Mean plasma concentrations of omecamtiv mecarbil at 20 h after IV dosing were 283 ng/ml for cohort 1 and 575 ng/ml for cohort 2, consistent with the predicted values (295 ng/ml and 550 ng/ml for cohorts 1 and 2, respectively) derived by using pharmacokinetic parameters from healthy volunteers (3). Increases in mean maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from time 0 to the time of last quantifiable plasma concentration values from cohort 1 to cohort 2 were modestly higher than predicted from a strictly dose-proportional increase; C_{max} levels were 344 ± 265 ng/ml and 708 ± 268 ng/ml in cohorts 1 and 2, respectively. Time to C_{max} was similar between doses (**Table 4**). Mean plasma concentrations 1 h after the last oral dose were 74 ng/ml for cohort 1 and 208 ng/ml for cohort 2.

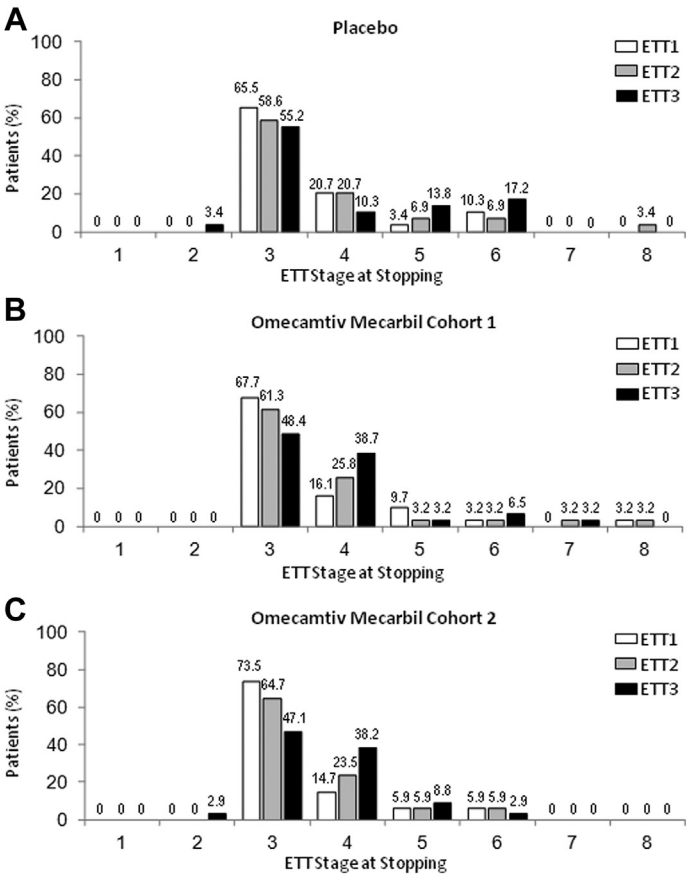

FIGURE 2 Percentage of Patients Achieving Each Stage of the Modified Naughton ETT at Baseline and on Blinded Study Drug Treatment During ETT3

The highest stage achieved for 2 symptom-limited exercise treadmill tests (ETTs) at baseline (ETT1 and ETT2) and ETT3 after treatment for patients receiving **(A)** placebo, **(B)** omecamtiv mecarbil in cohort 1, and **(C)** omecamtiv mecarbil in cohort 2 are shown.

DISCUSSION

Increasing cardiac contractility would seem to be a rational approach to treating patients with systolic heart failure. However, inotropic drugs increase the risk of ischemia, arrhythmias, and death, and this risk has limited their utility in treating acute and chronic heart failure (6-10). Currently available inotropic drugs increase cardiac contractility indirectly by increasing cardiac myocyte intracellular calcium concentration (11). Another approach to increasing cardiac contractility by directly activating the sarcomere with a cardiac myosin activator may overcome the limitations of the currently available inotropic drugs (12).

Omecamtiv mecarbil is a novel, direct cardiac myosin activator that increases cardiac contractility and may become an important therapy for heart failure patients with systolic dysfunction. The echocardiographic hallmark for the pharmacodynamic activity of omecamtiv mecarbil is an increase in the systolic ejection time that is highly correlated with omecamtiv mecarbil plasma concentration (2,3). Because the majority of coronary blood flow occurs during diastole, this effect of omecamtiv mecarbil could reduce the time for myocardial perfusion. Thus, it was critical to evaluate omecamtiv mecarbil in patients with ischemic cardiomyopathy and angina during exercise in a well-controlled and monitored setting.

The present study was designed to provide an indication of the safety and tolerability of omecamtiv mecarbil in ambulatory patients with chronic heart

TABLE 3 Treatment-Emergent AEs (Safety Population)

	Placebo (n = 29)	Omecamtiv Mecarbil Cohort 1* (n = 31)	Omecamtiv Mecarbil Cohort 2† (n = 34)	All Patients (N = 94)
Patients with ≥1 AE	5 (17.2)	2 (6.5)	12 (35.3)	19 (20.2)
Mild	3 (10.3)	2 (6.5)	11 (32.4)	16 (17.0)
Moderate	2 (6.9)	1 (3.2)	1 (2.9)	4 (4.3)
Severe	0	0	1 (2.9)	1 (1.1)
AEs				
Acute coronary syndrome	0	0	1 (2.9)	1 (1.1)
Increased blood CPK-MB	0	0	1 (2.9)	1 (1.1)
Increased cardiac enzyme	0	0	1 (2.9)	1 (1.1)
Dizziness	0	0	1 (2.9)	1 (1.1)
Dyspnea	1 (3.4)	0	3 (8.8)	4 (4.3)
Gout	0	0	1 (2.9)	1 (1.1)
Headache	1 (3.4)	0	0	1 (1.1)
Hypertension	0	0	1 (2.9)	1 (1.1)
Hypotension	0	1 (3.2)	1 (2.9)	2 (2.1)
Infusion site erythema	0	1 (3.2)	0	1 (1.1)
Infusion site pain	1 (3.4)	1 (3.2)	0	2 (2.1)
Photopsia	1 (3.4)	0	1 (2.9)	2 (2.1)
Post-procedural myocardial infarction	0	0	1 (2.9)	1 (1.1)
Pyrexia	1 (3.4)	0	0	1 (1.1)
Rhinitis	0	0	1 (2.9)	1 (1.1)
Sinus bradycardia	0	0	1 (2.9)	1 (1.1)
Supraventricular tachycardia	0	0	1 (2.9)	1 (1.1)
Increased troponin I	0	0	1 (2.9)	1 (1.1)
Upper abdominal pain	0	1 (3.2)	0	1 (1.1)
Ventricular extrasystoles	0	0	2 (5.9)	2 (2.1)

Values are n (%). *Cohort 1: Omecamtiv mecarbil infused at 24 mg/h for 2 h followed by 6 mg/h for 18 h. Patients who tolerated the infusion then received omecamtiv mecarbil 12.5 mg orally 3 times daily for 7 days. †Cohort 2: Omecamtiv mecarbil infused at 48 mg/h for 2 h followed by 11 mg/h for 18 h. Patients who tolerated the infusion then received omecamtiv mecarbil 25 mg orally 3 times daily for 7 days.

AE = adverse event; CPK = creatine phosphokinase.

TABLE 4 Pharmacokinetic Parameters After IV Dosing (PK Population)

	Omecamtiv Mecarbil Cohort 1* (n = 26)	Omecamtiv Mecarbil Cohort 2† (n = 30)
C_{max}, ng/ml	344 ± 265	708 ± 268
T_{max}, h	13.6 ± 8.6	15.7 ± 6.4
AUC_{last}, h × ng/ml	7,800 ± 3,400	18,400 ± 6,700

Values are mean ± SD. *Cohort 1: Omecamtiv mecarbil infused at 24 mg/h for 2 h followed by 6 mg/h for 18 h. †Cohort 2: Omecamtiv mecarbil infused at 48 mg/h for 2 h followed by 11 mg/h for 18 h.

AUC_{last} = area under the plasma concentration–time curve from time 0 to the time of last quantifiable plasma concentration; C_{max} = maximum plasma concentration; IV = intravenous; T_{max} = time to maximum plasma concentration.

failure before embarking on larger and longer studies that would more definitively assess the risk/benefit profile of this agent. The results of this study showed that in patients who theoretically would be most vulnerable to prolongation of the systolic ejection time (i.e., those with ischemic cardiomyopathy and a history of angina), treatment with omecamtiv mecarbil had no substantial deleterious effects on a broad range of safety assessments in the setting of symptom-limited exercise. Potential measures of cardiac ischemia such as the primary endpoint of this study (i.e., the proportion of patients who stopped ETT3 because of angina and at a stage earlier than baseline) and the time to or appearance of ST-segment depression (which were assessable on ECG) were not adversely affected. Exercise time was also not adversely affected. This study was neither specifically designed nor powered to detect a potentially clinically significant improvement in exercise performance. Given the average baseline exercise time and variability in this study, it would have required >3 times the number of patients per treatment arm than were actually enrolled to detect a 15% improvement in exercise time (80% power with a 2-sided alpha at 0.05). Finally, there were no consistent dose-related changes in the AE profile, and the majority of AEs were mild in severity.

Troponin I levels were abnormal in 2 patients after exercise; in each case, the levels were just above the upper laboratory reference limit and occurred in the absence of other clinical signs or symptoms of cardiac ischemia. The background rate of detectable troponin after exercise testing in this patient population is not well established, but was approximately 10% in 2 small studies (13,14). Given the number of patients studied, our findings do not rule out the possibility that increases in troponin I might occur in some heart failure patients with coronary disease during exercise while receiving omecamtiv mecarbil treatment, but they do indicate that the occurrence of this event is likely to be low. The use of a high-sensitivity troponin assay in this study might have provided additional insights into the development of ischemia in this population during exercise.

STUDY LIMITATIONS. Although the present study provides the first evaluation of omecamtiv mecarbil in heart failure patients under nonsedentary conditions, it has some important limitations. No hypothesis was formally tested, and the sample size was therefore empirically determined to be sufficient to provide an adequate assessment of the tolerability of the 2 target omecamtiv mecarbil plasma levels during symptom-limited exercise tolerance in patients with ischemic cardiomyopathy and angina. In addition, the sample size was too small to assess the effect on exercise time, and thus either a positive or negative effect on exercise duration could

not be established. The study did not formally assess the effect of omecamtiv mecarbil on inducible ischemia or chest pain, and the angina burden of the study population was not thoroughly characterized. The majority of ECGs in the enrolled population were noninterpretable for ischemia, which is common in patients with heart failure, and only a minority had angina while performing exercise in this study. Confining enrollment to heart failure patients with evidence of reproducible exercise-induced ischemia on ECG and/or exercise-limiting angina while at the same time increasing the sample size to assess the question of exercise capacity would have made execution of the study unfeasible, however (15). A limitation of the present study is that the troponin assays used at the time of this study did not meet current standards for troponin assays as required for the diagnosis of myocardial infarction.

The present study supports the conclusion that omecamtiv mecarbil did not increase the likelihood of myocardial ischemia in patients with ischemic cardiomyopathy and angina and serves as a prelude to the chronic dosing of omecamtiv mecarbil in ambulatory patients with chronic heart failure. Nonetheless, vigilance is warranted as the drug is tested in larger populations of patients that include those with underlying coronary disease. Results of this study, together with previous studies evaluating the pharmacodynamic effects of omecamtiv mecarbil in healthy volunteers and patients with stable heart failure (2,3), support further clinical assessment of omecamtiv mecarbil in patients with acute and chronic heart failure. A Phase II trial of ~600 patients with acute heart failure and LV dysfunction who received omecamtiv mecarbil IV was recently completed (NCT01300013). Oral formulations of omecamtiv mecarbil are currently under evaluation to enable the assessment of the potential benefits of omecamtiv mecarbil related to symptoms, quality of life, exercise capacity, morbidity, and mortality in larger and longer clinical trials.

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APPENDIX For a supplemental Methods section including tables and a figure, please see the online version of this article.