Cardiac myosin activation: will theory and practice coincide?

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Albert Einstein wrote: "In theory, theory and practice are the same. But in practice, they are not." In *The Lancet*, two papers[1,2] investigate a novel cardiac myosin activator, omecamtiv mecarbil, a compound with inotropic action that is a potential therapeutic alternative to present treatments for patients with heart failure and systolic dysfunction. An insightful review describes several new and appealing inotropic agents;[3] the mechanism of cardiac myosin activation, which directly affects the cross-bridge cycle and does not involve adrenergic pathways or affect myocyte intracellular calcium, is novel and intuitively attractive.

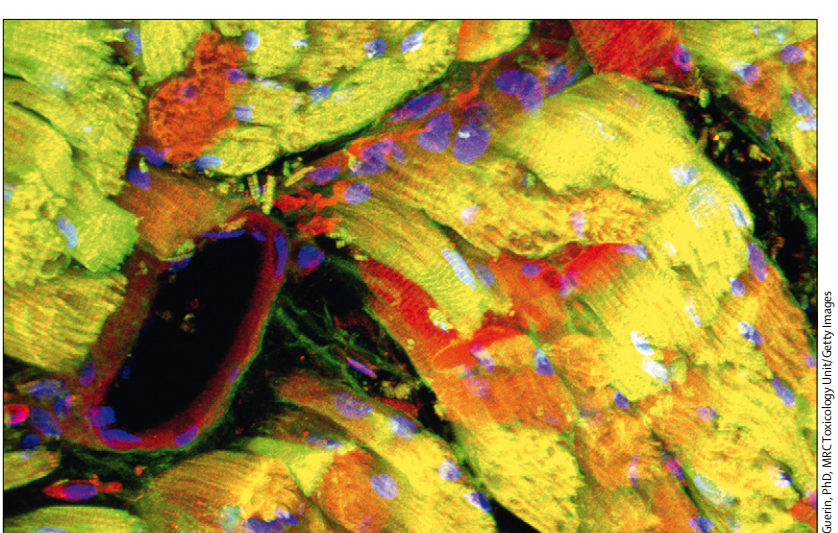
The two papers are complementary. The study by John Teerlink and colleagues[1] is the first-in-man assessment in healthy volunteers, and the subsequent study by John Cleland and colleagues[2] investigates the agent in patients with heart failure. Both reports focus on tolerability and provide dose-ranging information based on robust pharmacokinetic and pharmacodynamic data collection.

Conventional inotropic agents increase the rate at which ventricles develop pressure (dP/dt) but do not prolong the duration of systole. Treatment has not been shown to improve survival in chronic heart failure.[4] Myosin activation involves binding of a small molecule to the myosin catalytic domain to increase the transition rate of myosin into the strongly actin-bound force-generating state and permit more cross-bridges to form during systole.[5] An increase in the number of attachments of myosin heads to actin increases systolic ejection time and stroke volume, thereby increasing the extent of myocardial contraction without increasing the rate of contraction or myocardial oxygen consumption.[6] This increase in contraction should result in an energy efficient inotropic effect and improvement in heart failure symptoms. The mechanism makes sense and Teerlink and colleagues[1] use the captivating metaphor "more hands pulling on the rope".

A dose-ranging study of omecamtiv mecarbil in 34 healthy volunteers is reported by Teerlink and colleagues.[1] The primary efficacy measure was systolic ejection time, a sensitive and reliable measure of dose-related drug effect.[7] This effect is measured by echocardiogram and doppler imaging as the duration of the time-velocity integral signal sampled in the left ventricular outflow tract. The results show a convincing dose-related and plasma concentration-related prolongation of systolic ejection time, an increase in stroke volume and ejection fraction, and improved atrial contractile function.

Omecamtiv mecarbil was found to have a half-life of about 19 h; a steady-state concentration was not achieved during the 6 h infusion. As the authors concede, the goal of determining the maximum tolerated dose for future studies was only partly achieved. The agent was well tolerated across the doses assessed, but with a signal suggesting possible ischaemia at high-dose infusion due to excessive prolongation of systolic ejection time.

In the second study, Cleland and colleagues[2] report on the use of the cardiac myosin activator in a population of patients with mild heart failure. This investigation was a multicentre, double-blind, placebo-controlled, crossover, dose escalation study with 151 infusions of active drug or placebo in 45 patients, in five cohorts enrolled sequentially. Although apparently complex, the trial had two objectives. First, to assess safety and tolerability in patients with symptomatic heart failure and systolic dysfunction; and second, to assess dose effect on systolic ejection time, prolongation of which is believed to be the unique pharmacodynamic signature of myosin activation. Plasma concentrations of omecamtiv mecarbil were sampled frequently and



Confocal light micrograph of heart muscle

CJ Guerin, PhD, MRC Toxicology Unit/Getty Images

related to the safety and tolerability and pharmacodynamic profiles.

After identification of the target plasma concentration resulting in well-tolerated prolongation of systolic ejection time, and in view of the drug's moderate volume of distribution and long half-life, the investigators used an initial higher loading dose followed by a lower maintenance dose. The adverse-effect profile with regard to ischaemic episodes, presumably related to excessive prolongation of systolic ejection time, was closely related to high serum concentrations in both healthy volunteers and patients.

The results show an impressive correlation between plasma concentration and systolic ejection time. As postulated, this dose-related prolongation of ventricular systole resulted in significantly increased stroke volume and cardiac output, reductions in both systolic and diastolic ventricular volumes, and a more modest increase in the duration of atrial systole. Tolerability is reported in detail in both papers. Adverse effects suggestive of ischaemia happened only at the highest doses. Future efficacy studies should further explore the optimum loading dose and strength and duration of infusion.

In view of the mechanism by which omecamtiv mecarbil acts, some important theoretical caveats arise. With no change in heart rate, increased systolic ejection time must occur at the expense of diastole. Although patients with heart failure frequently have shortened systolic ejection time, some important events such as ventricular filling and coronary perfusion occur in diastole. Indeed, in most patients with heart failure, ischaemia is the cause.[8] Improvements in systolic emptying should not compromise diastolic function or coronary flow. In Cleland and colleagues' study,[2] heart rate actually decreased, which serves to attenuate the reduction in total diastolic time. The duration of atrial contraction also increased, suggesting an improvement in atrial myocardial function. The data presented in these two papers support further investigation of omecamtiv mecarbil's potential therapeutic role in appropriate patients. However, very few new agents have survived the most rigorous test, the randomised clinical trial assessing clinical outcomes.[9]

The need for parenteral therapy with omecamtiv mecarbil would define and limit the target population. Cleland and colleagues[2] discuss possible future development of an oral preparation. The authors also mention a new trial of parenteral therapy in patients with acute heart failure (NCT01300013). However, clinical research has not resulted in favourable outcomes for drugs assessed in patients hospitalised for acute decompensation.[10,11]

Acute heart failure often has multifaceted causes, and many patients have haemodynamic instability and acute coronary syndromes needing intervention; the patient's status is a moving target. Drug kinetics can be affected, and concurrent intravenous and oral polypharmacy is unavoidable. Potent parenteral diuretics, vasodilators, inotropes, and devices that result in effective short-term management of patients with acute heart failure are available.[12] Cardiac myosin activation should first be assessed in the large population with chronic systolic dysfunction, signs of heart failure, and New York Heart Association functional class III and IV symptoms. Subsequently, the potential role in patients managed in critical care, especially after cardiovascular surgery, should be explored.

So, in view of the attractive mechanistic theory, omecamtiv mecarbil's safety and tolerability profile, and these encouraging results, what would Einstein have suggested? Probably a controlled, randomised clinical trial assessing the effect on clinical outcomes. Let's find out how this theory performs in practice.

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I have served as an investigator in several clinical trials sponsored by Amgen and will be an investigator in a planned phase 2b trial involving omecamtiv mecarbil (NCT01300013).

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Predictive ability of coronary artery calcium and CRP

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In the general population, less than 10% of healthy adults aged 25–74 years have no modifiable cardiovascular risk factors;[1] therefore, risk of cardiovascular disease can potentially be improved in most people. Statin therapy for lowering cholesterol is an important cornerstone of risk reduction. The absolute benefit of statin treatment increases with increasing patient risk; thus, risk stratification of asymptomatic patients is mandatory in clinical practice. Although accurate identification of future cardiovascular disease risk is difficult when overall risk is low, the Framingham risk score and other global risk scores offer a meaningful approximation.[2] Such algorithms now allow for a practical approach towards risk stratification, translating statistical data into quantification of an individual's global risk. However, many uncertainties remain: because more than 40% of individuals have an intermediate risk of 10–20% in 10 years, treatment options are restricted; the scores are best at predicting long-term risk even though substantial risk factor changes can occur over time; and levels of absolute risk differ across cultural and ethnic groups. Thus, individual risk stratification needs further improvement in asymptomatic adults.

C-reactive protein (CRP) and coronary artery calcium (CAC) are among the most thoroughly examined measures available for expanded risk stratification. CRP is an acute-phase reactant synthesised mainly in the liver. From an evolutionary perspective, the teleological function of CRP might have been as part of the innate immune system, promoting complement activation and antigen presentation.[3] Within the range of normal values, easily available and highly sensitive assays detect even small amounts of CRP, thus rendering it an attractive and sensitive biomarker of subclinical inflammation. Because atherosclerosis is an inflammatory disease, CRP has been associated with imminent activation of the disease and increased patient vulnerability (ie, the patient is at increased risk of a cardiovascular event). Therefore, a logical option was to investigate the practical applicability of this biomarker. The JUPITER trial[4] examined the effects of statin therapy in patients with no clinical cardiovascular disease, and with LDL in the normal range, but higher than average concentrations of CRP. Reduction of clinical events was of such a magnitude in this group (44% reduction in relative risk) that the trial was ended after only 1·9 years instead of 5 years as first planned. JUPITER did not include a control group of patients with low CRP. Was the beneficial effect of the statin therapy in JUPITER due to optimum patient selection by use of CRP?

In *The Lancet*, the well-designed substudy of the MESA trial by Michael Blaha and colleagues[5] presents data that indicate a different conclusion. MESA recruited 6814 unselected participants free of known cardiovascular disease from six centres throughout the USA. The investigators' main objective was to analyse

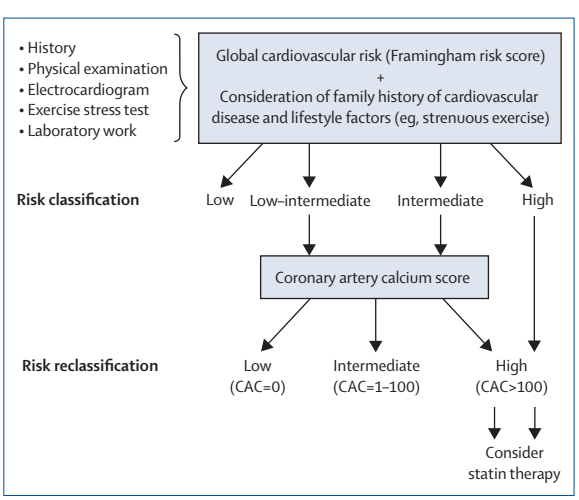

Figure: **The preferred algorithm for risk stratification in our practice**
Percentile values of the coronary artery calcium (CAC) scores are consulted, with scores >75th age-specific and sex-specific percentile signifying an increased risk. For example, in men older than 65 years, a cutoff point of 400 indicates high risk. Other measures of preclinical atherosclerosis are also factored in, if available.

The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure: a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial

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Summary

Background Many patients with heart failure remain symptomatic and have a poor prognosis despite existing treatments. Decreases in myocardial contractility and shortening of ventricular systole are characteristic of systolic heart failure and might be improved by a new therapeutic class, cardiac myosin activators. We report the first study of the cardiac myosin activator, omecamtiv mecarbil, in patients with systolic heart failure.

Methods We undertook a double-blind, placebo-controlled, crossover, dose-ranging, phase 2 trial investigating the effects of omecamtiv mecarbil (formerly CK-1827452), given intravenously for 2, 24, or 72 h to patients with stable heart failure and left ventricular systolic dysfunction receiving guideline-indicated treatment. Clinical assessment (including vital signs, echocardiograms, and electrocardiographs) and testing of plasma drug concentrations took place during and after completion of each infusion. The primary aim was to assess safety and tolerability of omecamtiv mecarbil. This study is registered at ClinicalTrials.gov, NCT00624442.

Findings 45 patients received 151 infusions of active drug or placebo. Placebo-corrected, concentration-dependent increases in left ventricular ejection time (up to an 80 ms increase from baseline) and stroke volume (up to 9·7 mL) were recorded, associated with a small reduction in heart rate (up to 2·7 beats per min; $p<0·0001$ for all three measures). Higher plasma concentrations were also associated with reductions in end-systolic (decrease of 15 mL at >500 ng/mL, $p=0·0026$) and end-diastolic volumes (16 mL, $p=0·0096$) that might have been more pronounced with increased duration of infusion. Cardiac ischaemia emerged at high plasma concentrations (two patients, plasma concentrations roughly 1750 ng/mL and 1350 ng/mL). For patients tolerant of all study drug infusions, no consistent pattern of adverse events with either dose or duration emerged.

Interpretation Omecamtiv mecarbil improved cardiac function in patients with heart failure caused by left ventricular dysfunction and could be the first in class of a new therapeutic agent.

Funding Cytokinetics Inc.

Introduction

For many patients, treatment of heart failure remains unsatisfactory. Available treatments that are aimed at diverse targets including sodium retention, arterial and venous constriction, neuroendocrine activation, increased heart rate, cardiac dyssynchrony, and arrhythmias often fail to control symptoms or restore quality of life.[1] Moreover, morbidity and mortality remains high in this population. Another target for treatment of heart failure due to reduced left ventricular systolic function is to improve myocardial contractility, although realisation of this goal remains elusive. Inotropic agents increase the velocity and force of contraction but do not increase, and in fact usually shorten, the duration of systole.[2] Cardiac myosin activators are a new mechanistic class designed specifically to increase myocardial contractility; by contrast with existing inotropic drugs, they instead increase the duration of systole (systolic ejection time) without changing the rate of left ventricular pressure development, thereby increasing stroke volume and cardiac output.[3,4]

In systolic heart failure, the reasons for reduced myocardial contractility are complex and include the loss of cardiac myocytes, changes in the extracellular matrix, reduced availability of high energy substrates such as ATP and creatinine phosphate,[5] impaired calcium recycling,[6] and myofilament abnormalities.[7] Within the myofilament, cardiac myosin is central to myocardial contractility. During myocardial contraction, myosin forms cross-bridges with actin. Initially weakly bound to the actin filament, transition to a strongly bound cross-bridge state is needed for myosin to undergo a force-generating power stroke. As described in the companion paper,[8] cardiac myosin activators increase the transition rate from the weakly bound to the strongly bound force-generating state,[3] increasing myocardial contraction. In preclinical studies, cardiac myosin activators increased myocardial

contraction and stroke volume without increasing oxygen consumption, thereby increasing myocardial efficiency.[4]

The cardiac myosin activator omecamtiv mecarbil has been studied in healthy volunteers in whom it produced dose-dependent and concentration-dependent increases in systolic ejection time, fractional shortening, and ejection fraction.[8] We report the first study of omecamtiv mecarbil given intravenously to patients with systolic heart failure. We aimed to assess the drug's safety and tolerability and define a range of pharmacodynamically active, well tolerated target plasma concentrations for later trials.

Methods

Study design

We undertook a double-blind, placebo-controlled, cross-over, dose-escalation study of the cardiac myosin activator omecamtiv mecarbil (formerly CK-1827452; Cytokinetics Inc, South San Francisco, CA, USA) in patients with stable chronic systolic heart failure. The study enrolled patients in the UK, Russia, the USA, and Georgia. The study was approved by the relevant regulatory bodies and by ethics committees at each participating site that also set and approved appropriate patient remuneration according to local standards. All patients gave written informed consent. The coordinating centre was ICON Development Solutions (Manchester, UK), which also acted as the central laboratory and pharmacokinetic core laboratory. Site surveillance and source data verification were undertaken by Campbell Charles Associates (Cobham, UK) in the UK, by World Wide Clinical Trials (St Petersburg, Russia; Tbilisi, Georgia) in Russia and Georgia, and by Cytokinetics in the USA.

Patients

Patients aged 18 years or older with a clinical diagnosis of heart failure who had a left ventricular ejection fraction on echocardiogram of 40% or less (or ≤30% in cohort 4) and who were willing and able to give written informed consent could be enrolled. Patients had to be in sinus rhythm, on stable therapy for heart failure including angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers and β blockers if tolerated, and have good quality echocardiogram images. Ejection fraction was confirmed in the core echocardiogram laboratory (ICON Medical Imaging, Philadelphia, PA, USA) for cohorts 3 and beyond before the patient could be recruited. Patients were excluded if their Modification of Diet in Renal Disease estimate of glomerular filtration rate was 35 mL/min per 1·73 m² or less, if they had been admitted to hospital for cardiovascular problems in the previous 6 weeks, or if they had Canadian Class III or IV angina.

Procedures

Five cohorts each consisting of eight to ten patients were enrolled sequentially. The first two cohorts had dose escalation through the range of plasma concentrations that were well tolerated by healthy volunteers.[8] First, infusions were limited to 2 h since drug concentrations would fall rapidly after discontinuation of the infusion should symptoms of intolerance emerge. After the tolerability of this range of plasma concentrations was established, the duration of the infusion was extended first to 24 h and then to 72 h, by adjustment of the dose rate of the maintenance infusion to target the same range of plasma concentrations that were tolerated during shorter duration infusions. Omecamtiv mecarbil has a moderate volume of distribution and a half-life of roughly 19 h, and was therefore infused at a higher initial rate (loading dose) followed by a lower maintenance rate, modelled to achieve target plasma concentrations. In cohorts 1–4, patients each received four double-blind treatments: three escalating doses of omecamtiv mecarbil and one placebo treatment, which was interpolated into

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	Period 1	Period 2	Period 3	Period 4
A	X	Y	Z	Placebo
B	X	Y	Placebo	Z
C	X	Placebo	Y	Z
D	Placebo	X	Y	Z

Patients in cohorts 1–4 were randomly assigned to one treatment sequence (A, B, C, or D) consisting of four periods; at least two patients were assigned to each sequence. In cohort 5, there were only two periods during which active or placebo were administered in random order. X, Y, and Z denote ascending doses of omecamtiv mecarbil.

Table 1: **Randomisation scheme for cohorts 1–4**

	Loading dose (mg/kg per h)	Maintenance dose (mg/kg per h)	C_{max} (ng/mL)	
			Mean (SD)	Range
Cohort 1 (1 h+1 h; n=8)				
X	0·125	0·0625	96 (28)	52–151
Y	0·25	0·125	195 (69)	96–318
Z	0·5	0·25	366 (123)	209–561
Cohort 2 (1 h+1h; n=9)				
X	0·5	0·25	328 (97)	233–488
Y	0·75	0·375	558 (157)	370–829
Z	1·0	0·5	636 (158)	419–847
Cohort 3 (1 h+23 h; n=10)				
X	0·25	0·025	165 (51)	100–271
Y	0·5	0·05	280 (55)	212–382
Z	1·0	0·1	633 (161)	412–883
Cohort 4 (1 h/1 h+22 h; n=8)				
X	0·25/0·125	0·025	178 (103)	86–415
Y	0·5/0·25	0·05	403 (226)	167–835
Z	1·0/0·5	0·1	681 (159)	459–866
Cohort 5 (1 h/1 h+70 h; n=10)*				
..	1·0/0·5	0·1	885 (316)	501–1373
..	0·75/0·375	0·075	727 (62·4)	683–771

C_{max}=maximum measured plasma concentration of omecamtiv mecarbil. X, Y, and Z=ascending doses of omecamtiv mecarbil. *In cohort 5, patients received one of the two treatment schedules shown.

Table 2: **Dosing table for cohorts 1–5**

the dosing sequence to maintain masking (table 1). There were at least 7 days between the start of each treatment period. In cohort 5, patients received two treatments, omecamtiv mecarbil and placebo, in a double-blind, crossover fashion. The second treatment started at least 7 days after completion of the first study treatment.

To begin, the same single-blind 1-h placebo infusion was given to all patients during baseline assessments, followed by administration of double-blind study drug (either active or placebo). Table 2 shows the doses, durations, and maximum plasma concentrations attained. In cohorts 1 and 2, patients received a 1-h loading dose of study drug followed by a 1-h maintenance infusion at half the initial dose rate (2 h total). In cohort 3, patients received a 1-h loading dose of study drug followed by a constant maintenance infusion at one-tenth the initial dose rate for 23 h (24 h total). In cohort 4, patients received a 2-h loading dose of study drug (the second hour delivered at half the initial dose rate) followed by a constant maintenance infusion at one-tenth the initial dose rate for 22 h (24 h total). Finally, in cohort 5, patients received a 2-h loading dose of study drug (the second hour delivered at half the initial dose rate) followed by a constant maintenance infusion at one-tenth the initial dose rate for 70 h (72 h total).

	Patients (n=45)
Sex	
Male	39 (87%)
Female	6 (13%)
Cause of heart failure	
Ischaemic	29 (64%)
Non-ischaemic	16 (36%)
Medical history	
Angina	23 (51%)
CABG	12 (27%)
PCI	18 (40%)
Hypertension	22 (49%)
Diabetes mellitus	10 (22%)
Heart failure treatment	
ACE inhibitor or ARB	44 (98%)
β blocker	44 (98%)
Aldosterone antagonist	23 (51%)
Digoxin	8 (18%)
Loop diuretic	33 (73%)
Age (years)	58 (51–69)
Weight (kg)	78 (69–86)
BMI (kg/m^2)	27 (23–29)
Heart rate (beats per min)	69 (61–75)
Systolic blood pressure (mm Hg)	121 (107–131)
Diastolic blood pressure (mm Hg)	75 (68–83)
Ejection fraction (%)	33% (27–38)
Haemoglobin (g/L)	130 (120–140)
Serum creatinine (μmol/L)	104 (83–112)

Data are n (%) or mean (IQR). CABG=coronary artery bypass graft. PCI=percutaneous coronary intervention. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. BMI=body-mass index.

Table 3: **Demographic characteristics**

Omecamtiv mecarbil is formulated as a clear, colourless, aseptic solution at 1 mg/mL with 50 mmol/L citrate in sterile water, adjusted to pH 5·0 with NaOH in 100 mL vials. Individual doses were prepared aseptically for infusion by an independent research trial-accredited pharmacy (UK) or site-specific pharmacies (other jurisdictions) using 50 mmol/L citrate (pH 5·0) in sterile water as a diluent. Doses were administered to patients who were under observation in hospital or clinical research facility throughout. Placebo was prepared from the diluent in an identical fashion to maintain masking. Randomisation was done via an internet-based system (WebEZ, Almac) and implemented by pharmacy personnel who were the only people aware of study drug assignment and were not involved in any study assessments.

In healthy volunteers, plasma concentrations greater than 1200 ng/mL had caused side-effects, including chest pain, electrocardiograph (ECG) changes, and in one case an increase in troponin, suggesting that excessive prolongation of systole might provoke myocardial ischaemia. As a component of safety monitoring, plasma concentrations of drug were checked in a core facility after each treatment period before the patient received the next, higher, dose. If the predicted peak plasma concentration would be greater than 900 ng/mL with the next dose, the patient repeated the last dose rather than escalate to the higher one. Troponin was measured with either the Immulite 2000 Troponin I (Siemens Healthcare Diagnostics, Deerfield, IL, USA) or Elecsys Troponin T (Roche Diagnostics, Burgess Hill, UK) assay platforms.

Patients were assessed clinically (including vital signs and ECGs) and had blood taken for safety monitoring and testing of drug concentrations during and after completion of the study drug infusion. Echocardiograms were recorded with standard protocols at baseline, 1·5, and 24 h (all cohorts) and additionally at 48 h (cohort 4) or 72 h and 96 h (cohort 5) after the start of the infusion. At the start of study, measurements of heart rate and blood pressure were made only in the supine position, but shortly thereafter the protocol was amended so that they were measured supine and standing.

There were four echocardiogram measures of cardiac function of special interest for pharmacodynamic assessment: left ventricular systolic ejection time as measured from the duration of the left ventricular outflow tract doppler echocardiogram signal, because that was previously defined in healthy volunteers as the most sensitive measure of drug effect; left ventricular stroke volume derived from the left ventricular outflow tract doppler echocardiogram; left ventricular fractional shortening; and left ventricular ejection fraction. Ejection fraction was calculated as left ventricular stroke volume divided by left ventricular end-diastolic volume estimated by Simpson's method of discs. The transmitral early

	Baseline*	Omecamtiv mecarbil (ng/mL)†						p value for correlation‡
		>0–100	>100–200	>200–300	>300–400	>400–500	>500	
Left ventricular outflow tract doppler								
SET (ms)	316 (41, n=43)	0·6 (4, n=84), p=0·88	18 (4, n=62), p<0·0001	47 (5, n=42), p<0·0001	58 (6, n=24), p<0·0001	59 (6, n=20), p<0·0001	80 (5, n=46), p<0·0001	<0·0001
SV (mL)	69 (23, n=43)	−0·3 (2, n=84), p=0·85	0·7 (2, n=62), p=0·70	5·4 (2, n=41), p=0·010	11 (3, n=24), p<0·0001	9·0 (3, n=20), p=0·0013	9·7 (2, n=46), p<0·0001	<0·0001
CO (mL/min)	4423 (1623, n=43)	−32 (116, n=84), p=0·78	52 (123, n=62), p=0·67	180 (141, n=41), p=0·20	408 (173, n=24), p=0·019	400 (189, n=20), p=0·034	330 (142, n=46), p=0·020	0·0005
Two-dimensional/M-mode echo								
FS (%)	18 (7, n=41)	0·6 (1, n=81), p=0·037	1·5 (1, n=56), p=0·036	2·9 (1, n=37), p=0·0004	2·6 (1, n=23), p=0·0086	2·4 (1, n=17), p=0·032	4·6 (1, n=44), p<0·0001	<0·0001
EF (%)	32 (16, n=43)	0·2 (1, n=84), p=0·83	1·2 (1, n=62), p=0·35	2·7 (2, n=41), p=0·074	7·9 (2, n=24), p<0·0001	6·8 (2, n=20), p=0·0009	10 (1, n=46), p<0·0001	<0·0001
LVESV (mL)	168 (72, n=44)	0·8 (4, n=84), p=0·84	3·4 (4, n=64), p=0·43	−5·0 (5, n=45), p=0·30	−11 (6, n=25), p=0·077	−13 (7, n=21), p=0·056	−15 (5, n=47), p=0·0026	<0·0001
LVEDV (mL)	243 (85, n=44)	0·8 (5, n=84), p=0·87	5·3 (5, n=64), p=0·33	−1·7 (6, n=45), p=0·79	−14 (8, n=25), p=0·066	−15 (8, n=21), p=0·068	−16 (6, n=47), p=0·0096	0·0005
Mitral inflow doppler								
E peak (cm/s)	79 (29, n=42)	−1·6 (2, n=79), p=0·33	−2·5 (2, n=61), p=0·15	−3·2 (2, n=42), p=0·093	−4·7 (2, n=23), p=0·057	−4·4 (3, n=19), p=0·094	−7·8 (2, n=45), p<0·0001	0·04
A peak (cm/s)	68 (25, n=41)	2·0 (1, n=80), p=0·17	5·3 (2, n=59), p=0·0006	10 (2, n=41), p<0·0001	12 (2, n=22), p<0·0001	11 (3, n=16), p<0·0001	8·9 (2, n=41), p<0·0001	<0·0001
E/A ratio	1·3 (0·8, n=40)	−0·1 (0·1, n=77), p=0·22	−0·2 (0·1, n=58), p=0·0012	−0·3 (0·1, n=41), p<0·0001	−0·4 (0·1, n=22), p<0·0001	−0·4 (0·1, n=16), p=0·0001	−0·4 (0·1, n=41), p<0·0001	<0·0001
A duration (ms)	189 (39, n=40)	9·1 (5, n=79), p=0·096	5·6 (6, n=59), p=0·33	14 (6, n=41), p=0·037	12 (8, n=22), p=0·16	14 (10, n=16), p=0·14	32 (7, n=41), p<0·0001	<0·0001
Tissue doppler								
E′ (cm/s)	8·3 (4, n=34)	−0·2 (0·3, n=73), p=0·55	−0·4 (0·3, n=51), p=0·16	−0·5 (0·3, n=38), p=0·14	−0·5 (0·4, n=17), p=0·25	−1·3 (0·5, n=13), p=0·0071	−0·8 (0·3, n=37), p=0·0096	0·0006
S′ (cm/s)	6·0 (2·4, n=34)	−0·1 (0·2, n=74), p=0·73	0·0 (0·2, n=48), p=0·100	0·0 (0·2, n=39), p=0·82	−0·2 (0·3, n=18), p=0·49	−0·1 (0·3, n=14), p=0·80	−0·1 (0·2, n=38), p=0·79	0·52
E/E′ ratio	12 (7, n=33)	−0·9 (0·6, n=68), p=0·12	0·2 (0·6, n=49), p=0·72	0·0 (0·7, n=38), p=0·94	−0·7 (0·9, n=16), p=0·44	1·7 (1, n=12), p=0·12	0·6 (0·7, n=36), p=0·37	0·068

SET=systolic ejection time. SV=left ventricular outflow tract doppler-derived stroke volume. CO=cardiac output. FS=fractional shortening. EF=ejection fraction. LVESV=left ventricular end-systolic volume. LVEDV=left ventricular end-diastolic volume. E peak=peak E wave velocity from mitral inflow Doppler. A peak=peak A wave velocity from mitral inflow Doppler. A duration=duration of A wave. NS=non-significant. PK/PD=pharmacokinetic/pharmacodynamic. *Data are mean (SD, n). †Data are placebo-corrected least square mean differences from baseline (SEM, n), meaning the least square mean difference from baseline on placebo has been subtracted from each bin. ‡The p value for correlation tests the hypothesis that the slope of the regression line for the PK/PD relationship is non-zero—ie, that a PK/PD correlation is present.

Table 4: **Effect of omecamtiv mecarbil on echocardiogram measures**

filling (E) wave velocity and peak filling velocity associated with atrial contraction (A) were obtained from the mitral inflow signal and E/A ratio calculated. The mitral annular velocity during systole (S′) and diastole (E′) were calculated with pulsed tissue doppler of the lateral mitral annulus. All echocardiogram measurements were made in a core laboratory (ICON Medical Imaging, Philadelphia, PA, USA) by staff with final values established by an expert independent reader (JHG). All were masked to assigned treatment and timepoint.

The primary aim of the study was to assess the safety and tolerability of omecamtiv mecarbil and secondarily the relation between plasma concentration and echocardiogram effect to define a range of pharmacodynamically active, well tolerated target plasma concentrations for subsequent clinical trials of both intravenous and oral preparations. Important additional aims were to assess the pharmacokinetic characteristics of omecamtiv mecarbil, the effect in patients with severely depressed ejection fraction (<30%), and treatment durations up to 72 h.

Statistical analysis

SAS (version 8.02) was used for all analyses. The statistical analysis of change from baseline for variables of interest was done between active treatments and placebo at each available timepoint with an ANCOVA procedure. Patients were included in the model as a random effect, treatments as a fixed effect, and baseline values as a covariate.

A concentration bin analysis was done with ANCOVA, with treatment replaced with concentration bin group. In this analysis, echocardiogram data were paired with the plasma concentration of omecamtiv mecarbil measured at the time of the echocardiogram. The data were then binned by omecamtiv mecarbil concentration in

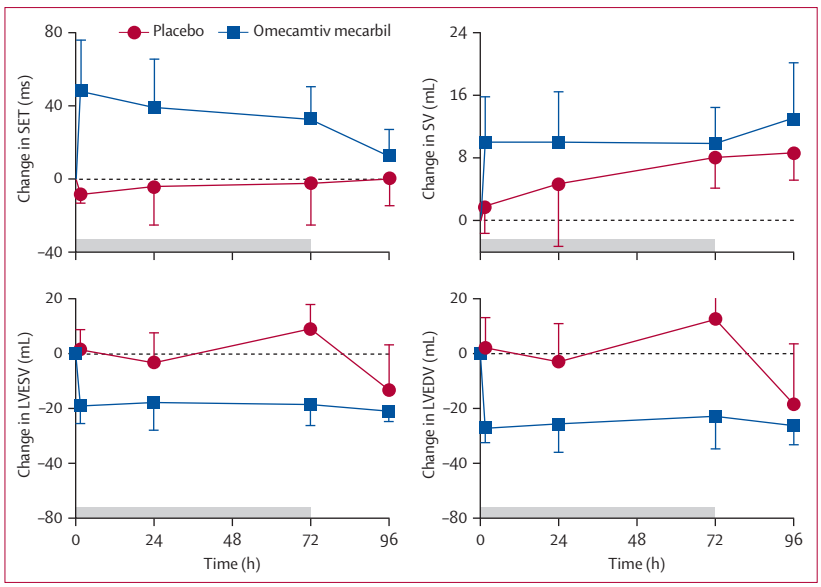

Figure 1: **Time-dependent changes from baseline in key echocardiogram measures for eight patients treated in cohort 5 with 72-h infusions of omecamtiv mecarbil or placebo**
Data are mean; error bars show SEM. Patients received 1·0 mg/kg per h for 1 h, followed by 0·5 mg/kg per h for 1 h, and then 0·1 mg/kg per h for 70 h. SET=systolic ejection time. SV=stroke volume. LVESV=left ventricular end-systolic volume. LVEDV=left ventricular end-diastolic volume.

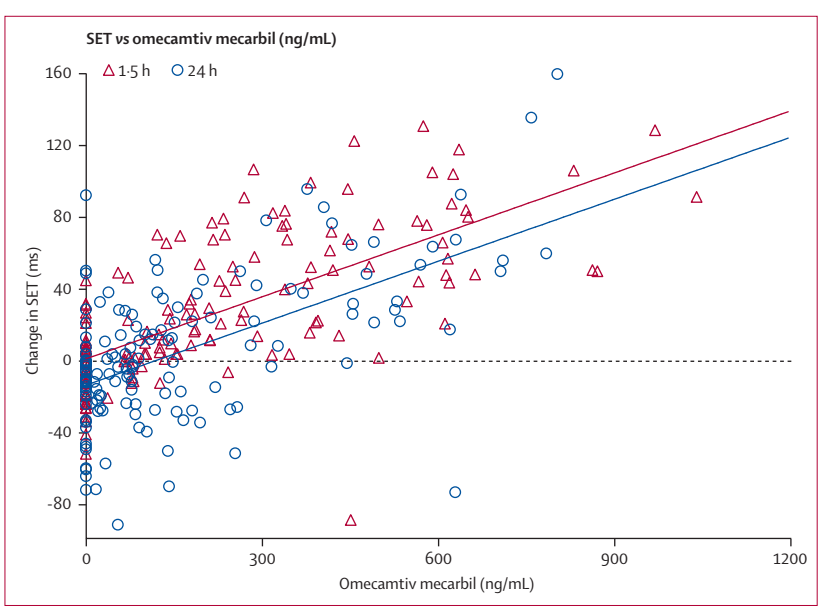

Figure 2: **Concentration-dependent increase in systolic ejection time in cohorts 1–5 at 1·5 h and 24 h**
Absolute changes from baseline plotted for each observation. Lines represent best fit for least squares linear regression. SET=systolic ejection time.

See Online for webappendix

100 ng/mL increments. This analysis pooled all timepoints by omecamtiv mecarbil plasma concentration (where available) and treated the pooled bins as separate groups. Seven concentration bin groups were investigated: placebo, 0 to ≤100, >100 to ≤200, >200 to ≤300, >300 to ≤400, >400 to ≤500, and >500 ng/mL.

Patients with missing baseline values were excluded from the statistical analysis. Echocardiogram data obtained after premature discontinuation of study drug infusion were not included in the analysis of echocardiogram measures (four patients, affecting ten of 574 planned echocardiograms). A 95% CI was calculated for treatment differences at each timepoint between active dose concentration and placebo. No adjustment for multiple comparisons was done. If the 95% CI for the least squares treatment difference did not include zero, then the treatments were regarded as significantly different.

This study is registered at ClinicalTrials.gov, NCT00624442.

Role of the funding source

The study was designed by the authors in collaboration with Cytokinetics, who sponsored the study. Data collection and data analysis were done by ICON Development Solutions (Manchester, UK) under the supervision of the sponsor. The interpretation of the study results was accomplished in cooperation between the authors and the study sponsor. The corresponding author had access to the final data and wrote the first and subsequent drafts of the report, which were commented on by co-authors and representatives of Cytokinetics and Amgen. Authors who were not employed by the sponsor had the ultimate editorial authority.

Results

45 patients in the UK (n=29), Russia (n=11), the USA (n=3), and Georgia (n=2) had 151 infusions of omecamtiv mecarbil. Table 3 shows baseline clinical characteristics. An echocardiogram and simultaneous plasma concentration were measured on 564 occasions. Of 45 patients, 38 were given all the planned doses, two were predicted to achieve higher than intended plasma concentrations at their highest assigned dose and therefore repeated their middle dose, and five did not complete all scheduled dosing periods, including one who was inadvertently given a drug overdose (webappendix p 1).

Table 4 shows the effects of omecamtiv mecarbil on cardiac function according to plasma concentration. In this concentration bin analysis, echocardiogram data were paired with coincidentally measured plasma concentrations of omecamtiv mecarbil grouped in 100 ng/mL increments. Systolic ejection time, stroke volume, and fractional shortening increased in a concentration-dependent manner. Plasma concentrations of omecamtiv mecarbil greater than 100 ng/mL increased systolic ejection time and fractional shortening as compared with placebo. Stroke volume (mean at baseline, 68·5 mL) increased by 5–10 mL at plasma concentrations higher than 200 ng/mL, reaching a plateau at concentrations greater than 400 ng/mL. Plasma concentrations higher than 300 ng/mL were associated with an increase in left ventricular ejection fraction; reductions in left ventricular end-systolic and end-diastolic volume were significant at 500 ng/mL. Transmitral A wave velocity and duration were increased

	Baseline*	Omecamtiv mecarbil (ng/mL)†						p value for correlation‡
		>0–100	>100–200	>200–300	>300–400	>400–500	>500	
Supine vital signs								
SBP (mm Hg)	124 (19, n=44)	0·4 (0·8, n=354), p=0·64	−0·4 (0·8, n=362), p=0·61	−0·5 (1, n=233), p=0·57	−0·9 (1, n=150), p=0·38	−3·9 (1, n=128), p=0·0006	−2·7 (1, n=163), p=0·014	0·0004
DBP (mm Hg)	75 (12, n=44)	0·5 (0·6, n=354), p=0·44	−0·2 (0·6, n=362), p=0·75	−0·2 (0·7, n=233), p=0·75	−0·8 (0·8, n=150), p=0·32	−0·7 (0·8, n=128), p=0·41	0·7 (0·8, n=163), p=0·34	0·57
HR (bpm)	69 (12, n=44)	−0·6 (0·5, n=354), p=0·18	−0·8 (0·5, n=362), p=0·088	−2·0 (0·5, n=233), p<0·0001	−3·0 (0·6, n=150), p<0·0001	−2·3 (0·6, n=128), p=0·0003	−2·7 (0·6, n=163), p<0·0001	<0·0001
Standing vital signs								
SBP (mm Hg)	125 (18, n=31)	2·6 (1, n=129), p=0·049	−0·8 (1, n=126), p=0·54	−3·5 (1, n=91), p=0·012	−2·8 (2, n=54), p=0·090	−3·3 (2, n=54), p=0·051	−7·3 (2, n=67), p<0·0001	<0·0001
DBP (mm Hg)	78 (14, n=31)	2·5 (1, n=129), p=0·011	1·1 (1, n=126), p=0·25	−0·8 (1, n=92), p=0·44	−0·5 (1, n=57), p=0·70	−1·6 (1, n=57), p=0·19	−2·9 (1, n=70), p=0·018	0·0006
HR (bpm)	76 (11, n=31)	0·6 (1, n=129), p=0·53	−1·0 (1, n=125), p=0·25	−2·1 (1, n=92), p=0·034	−3·9 (1, n=57), p=0·0011	−2·6 (1, n=57), p=0·027	−1·5 (1, n=70), p=0·22	0·0002
Orthostatic vital signs								
SBP (mm Hg)	−1·6 (11, n=31)	−0·6 (1, n=129), p=0·59	−1·0 (1, n=126), p=0·38	−1·4 (1, n=91), p=0·25	−0·8 (2, n=54), p=0·60	−0·7 (2, n=54), p=0·65	−1·1 (2, n=67), p=0·45	0·30
DBP (mm Hg)	1·0 (8, n=31)	1·1 (1, n=129), p=0·22	1·6 (1, n=126), p=0·058	0·3 (1, n=92), p=0·75	1·3 (1, n=57), p=0·23	−1·2 (1, n=57), p=0·30	−1·0 (1, n=70), p=0·38	0·14
HR (bpm)	4·7 (6, n=31)	1·3 (1, n=129), p=0·18	−0·4 (1, n=125), p=0·63	0·5 (1, n=92), p=0·65	0·4 (1, n=57), p=0·77	0·6 (1, n=57), p=0·63	−0·5 (1, n=70), p=0·66	0·32
Corrected QT interval§								
QTcB (ms)	445 (33, n=43)	−0·3 (2, n=185)	−3·3 (2, n=149)	−1·3 (2, n=108)	−4·1 (2, n=65)	−7·3 (2, n=66)	−5·6 (2, n=99)	0·0003
QTcF (ms)	438 (30, n=43)	−0·4 (2, n=185)	−2·1 (2, n=149)	1·5 (2, n=108)	−0·2 (2, n=65)	−4·9 (2, n=66)	−2·8 (2, n=99)	0·07

SBP=systolic blood pressure. DBP=diastolic blood pressure. HR=heart rate. bpm=beats per min. NS=non-significant. PK/PD=pharmacokinetic/pharmacodynamic. *Baseline values are mean (SD, n). †Data are placebo-corrected least square mean differences from baseline (SEM, n). ‡The p value for correlation tests the hypothesis that the slope of the regression line for the PK/PD relationship is non-zero—ie, that a PK/PD correlation is present. §QT interval adjusted for heart rate with Bazett's formula (QTcB) or Fridericia's formula (QTcF).

Table 5: **Effect of omecamtiv mecarbil on vital signs and QT interval**

and E wave velocity reduced; consequently, the E/A ratio fell. The duration of left atrial systole, as measured from the left ventricular inflow doppler, also increased. There was no change in the E/E′ ratio or S′.

The onset of effect was evident from the first timepoint measured (1·5 h) and the effects on cardiac function persisted up to 72 h (figure 1). With the 72-h infusion, the decreases in ventricular volumes compared with placebo appeared sustained, whereas differences in stroke volume began to diminish mainly because of an increase in stroke volume during placebo treatment. The omecamtiv mecarbil concentration responses for all patients at either 1·5 h or 24 h were plotted for systolic ejection time, the most sensitive echocardiogram measurement. There was little change in the slope of the relationship between the increase in systolic ejection time and plasma drug concentration at 24 h as compared with 1·5 h (figure 2).

Systolic blood pressure, both supine and upright, fell at high plasma concentrations without orthostatic changes. Supine diastolic blood pressure did not change; there was a small decrease in standing diastolic blood pressure at concentrations higher than 500 ng/mL. Supine and standing heart rate decreased in a concentration-dependent manner. There were no concentration-dependent changes in systolic or diastolic blood pressure or heart rate going from supine to standing position (orthostatic measures). Corrected QT interval decreased slightly (table 5). No effect on concentrations of NT-proBNP after a 24-h or 72-h infusion of drug was noted in this stable heart failure population (data not shown).

Three serious adverse events were reported. These were septicaemia in the setting of a diabetic foot ulcer, pneumonia pre-dating the next scheduled drug infusion, and non-ST elevation myocardial infarction in a patient who received an unintended drug overdose. The first two of these patients completed all four treatment periods. The overdosed patient in cohort 2 received a dose of 2·2 mg/kg per h (four times the intended dose) and after 45 min developed chest pain, sweating, hypotension, and ECG changes that suggested ischaemia. Symptoms resolved rapidly after termination of the infusion. There was a rise in troponin-I to 2·3 ng/mL (laboratory reference upper limit <0·6 ng/mL) and creatine kinase MB to 12 IU/mL (reference upper limit <9 IU/mL). The patient did not complete the study. He was seen 7 weeks afterward and was in his usual state of health. The plasma concentration of omecamtiv mecarbil 15 min before the onset of symptoms was 1456 ng/mL and the predicted plasma concentration at the time of infusion termination was roughly 1750 ng/mL.

In addition to the patient who received an overdose, four other patients discontinued study drug. A patient in cohort 5 developed similar symptoms and signs of cardiac ischaemia to those in the overdosed patient, including a small rise in cardiac troponin; excessive plasma concentrations were subsequently confirmed (maximum 1350 ng/mL). The patient's bodyweight (106 kg with a body-mass index of 38 kg/m²) and low drug clearance (second lowest estimated drug clearance in the study) both contributed to the resulting drug concentration. A patient with a baseline serum creatinine of 248 µmol/L and blood pressure of 182/116 mm Hg in cohort 5 developed an asymptomatic increase in cardiac troponin starting 6 h after initiation of the infusion and peaking 6 h after completion of the 72-h infusion. The peak plasma concentration in this patient was 730 ng/mL. Otherwise, in 148 of 151 infusions, there were no increases in serial troponin measurements. The other two discontinuations were due to observation by the investigator of a new regional wall motion abnormality on echocardiogram in one case, and in the other case of a QTc longer than 500 ms during infusion. These findings were not confirmed by the core echocardiogram or ECG laboratories. For patients tolerant of all study drug infusions, no consistent pattern of adverse events with either dose or duration of infusion emerged (webappendix p 2).

Discussion

Omecamtiv mecarbil has dose-dependent and concentration-dependent effects on cardiac function that appear at plasma concentrations that are well tolerated by patients with stable chronic systolic heart failure. Plasma concentrations greater than 100 ng/mL were associated with an increase in the duration of left ventricular systole—the expected pharmacodynamic signature of omecamtiv mecarbil. By contrast with inotropic agents, there was no increase in mitral annular systolic velocity. These effects were expected and consistent with data from animal models[4] and healthy volunteers (panel).[8]

Despite the central role of cardiac dysfunction in the development of systolic heart failure, positive inotropic treatments aimed at improvement of myocardial function have met with little clinical success so far and might be harmful.[9,10] However, improvement of cardiac function by other means, such as cardiac resynchronisation, can be associated with striking improvement in symptoms and prognosis.[11–13] New pharmacological methods of increasing ventricular contraction could potentially have similar effects if they can address the limitations of inotropic agents. By contrast with inotropic agents, which increase myocardial oxygen consumption,[14] cardiac myosin activators, in preclinical experiments, increase ventricular contraction without increasing myocardial oxygen consumption, thus increasing cardiac efficiency.[4] Since myocardial oxygen supply can often not match consumption in patients with dilated and poorly functioning ventricles, improved cardiac efficiency could translate into clinical benefits for patients.

A potential concern resulting from the prolongation of systole by omecamtiv mecarbil is that it could encroach on diastole leading to inadequate coronary or ventricular filling, or both. Although omecamtiv mecarbil increased the duration of left ventricular systole, possibly as a consequence of the increase in stroke volume and cardiac output, heart rate also slowed and therefore the duration of diastole was only slightly reduced. Conversely, the duration of left atrial systole increased, possibly because of an increase in atrial contractility, emptying of the left ventricle improved, and ventricular end-systolic and end-diastolic volumes decreased. These effects could reduce diastolic wall stress and the effects of pericardial restraint and result in improved left ventricular diastolic function. Clearly, the effects of omecamtiv mecarbil on cardiac function are likely to be complex and can vary depending on the underlying pathophysiology and disease stage.

The reduction in heart rate is not thought to be mediated directly by omecamtiv mecarbil and more likely reflects a reflex action due to increases in stroke volume. Cardiac output, the product of heart rate and stroke volume, was increased by omecamtiv mecarbil to a small extent (roughly 400 mL) at higher plasma concentrations. However, in this study population of patients with stable heart failure, cardiac output was normal at baseline and should have been adequate for their metabolic needs at rest. The effects of ACE inhibitors and β blockers on resting cardiac function are also small[15,16] and yet they exert a striking reduction in morbidity and mortality. The effect of omecamtiv mecarbil on the cardiovascular function of patients with severe heart failure who might have an inadequate cardiac output at rest, or on patients with mild-to-moderate heart failure who might not have an adequate cardiac output during exercise, has yet to be examined.

***Panel:* Research in context**

Systematic review

We searched the PubMed database for articles published in English with the search terms "heart failure", "inotropic", "CK-1827452", and "omecamtiv mecarbil". The last search was done in June, 2011. We selected studies that were relevant to the Introduction and Discussion and that described the preclinical characterisation of omecamtiv mecarbil.

Interpretation

Reduced cardiac contractility is a central feature of systolic heart failure, but existing agents that improve contractility have met with little clinical success so far and might be harmful. This study is the first application of the cardiac myosin activator omecamtiv mecarbil to patients with heart failure. The first study in healthy volunteers is published as a companion to this report.[8] These studies show that infusion of omecamtiv mecarbil prolongs ventricular systole, increases cardiac function, and defines its potential therapeutic window. These initial clinical studies show the translation of this novel mechanism into human beings. Large clinical trials in patients with heart failure will eventually define the clinical benefit and risk profile of cardiac myosin activation for a condition still marked by substantial morbidity and mortality.

This study suggests that omecamtiv mecarbil is generally well tolerated in patients with stable heart failure over a broad range of plasma concentrations. Plasma concentrations of omecamtiv mecarbil as low as 100–200 ng/mL had some effect on cardiac function and the effect on stroke volume seems to plateau above 400 ng/mL. Plasma concentrations greater than 1200 ng/mL were not clinically tolerated in two of three patients who exceeded those levels. The design of future dosing regimens, in part aided by the pharmacokinetic information gathered in this study and subsequent studies in broader patient populations, will aim to achieve and maintain plasma concentrations within this perceived therapeutic window.

This study focused on the safety, tolerability, and effects of omecamtiv mecarbil on cardiac function. Further studies are needed to establish whether the observed effects on cardiac function translate into benefits related to symptoms, quality of life, exercise capacity, morbidity, or mortality. A phase 2b trial with a planned enrolment of 600 patients with acute heart failure and left ventricular systolic dysfunction is now underway (NCT01300013). Future studies of intravenous and oral formulations are being planned to evaluate this question in the context of acute and chronic heart failure.

Contributors

JGFC contributed to the design and implementation of the study; enrolment and follow-up of patients; collection and assembly of data; interpretation of results; and drafting of the report. JRT contributed to the design and implementation of the study; collection and assembly of data; interpretation of results; and drafting of the report. RS contributed to the design and implementation of the study; enrolment and follow-up of patients; collection and assembly of data; interpretation of results; and drafting of the report. EMN contributed to the enrolment and follow-up of patients; and collection and assembly of data. JJVM contributed to the design and implementation of the study; enrolment and follow-up of patients; collection and assembly of data; interpretation of results; and drafting of the report. CCL contributed to the design and implementation of the study; enrolment and follow-up of patients; collection and assembly of data; interpretation of results; and drafting of the report. VAT contributed to the enrolment and follow-up of patients; and collection and assembly of data. BHG contributed to the design and implementation of the study; enrolment and follow-up of patients; collection and assembly of data; interpretation of results; and drafting of the report. JM contributed to the enrolment and follow-up of patients; collection and assembly of data; and interpretation of results. DPF contributed to the enrolment and follow-up of patients; collection and assembly of data; interpretation of results; and drafting of the report. TS contributed to the enrolment and follow-up of patients and collection and assembly of data. MM contributed to the enrolment and follow-up of patients; collection and assembly of data; and interpretation of results. MS contributed to the enrolment and follow-up of patients; collection and assembly of data; and interpretation of results. LN contributed to the design and implementation of the study; enrolment and follow-up of patients; collection and assembly of data; and interpretation of results. SMW contributed to the design of the study; interpretation of results; and drafting of the report. JHL contributed to the design and implementation of the study; collection and assembly of data; and administrative, technical, or logistical support; and drafting of the report. KGS contributed to the design and implementation of the study; collection and assembly of data; and administrative, technical, or logistical support; interpretation of results; statistical expertise; and drafting of the report. CPC contributed to the design and implementation of the study; enrolment and follow-up of patients; collection and assembly of data; administrative, technical, or logistical support; interpretation of results; and drafting of the report. JHG contributed to the design and implementation of the study; administrative, technical, or logistical support; interpretation of results; and drafting of the report. AAW contributed to the design and implementation of the study; administrative, technical, or logistical support; interpretation of results; and drafting of the report. FIM contributed to the design and implementation of the study; collection and assembly of data; administrative, technical, or logistical support; interpretation of results; and drafting of the report. All authors have reviewed the Article and agree with its contents.

Conflicts of interest

JGFC, JRT, JJVM, and BHG have received research grants and consulting fees from Cytokinetics and Amgen, which is a licensee of omecamtiv mecarbil. RS, EMN, CCL, VAT, JM, DPF, TS, MM, MS, and LN have received research grants and consulting fees from Cytokinetics. SMW is an employee of Amgen. CPC is an employee of ICON Development Solutions (formerly Medeval, Manchester, UK). JHG is an employee of ICON Clinical Research, and formerly of ICON Medical Imaging, the echocardiogram core laboratory for this study. JHL, KGS, AAW, and FIM are employees of Cytokinetics, the sponsor of this study.

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Dose-dependent augmentation of cardiac systolic function with the selective cardiac myosin activator, omecamtiv mecarbil: a first-in-man study

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Summary

Background Decreased systolic function is central to the pathogenesis of heart failure in millions of patients worldwide, but mechanism-related adverse effects restrict existing inotropic treatments. This study tested the hypothesis that omecamtiv mecarbil, a selective cardiac myosin activator, will augment cardiac function in human beings.

Methods In this dose-escalating, crossover study, 34 healthy men received a 6-h double-blind intravenous infusion of omecamtiv mecarbil or placebo once a week for 4 weeks. Each sequence consisted of three ascending omecamtiv mecarbil doses (ranging from 0·005 to 1·0 mg/kg per h) with a placebo infusion randomised into the sequence. Vital signs, blood samples, electrocardiographs (ECGs), and echocardiograms were obtained before, during, and after each infusion. The primary aim was to establish maximum tolerated dose (the highest infusion rate tolerated by at least eight participants) and plasma concentrations of omecamtiv mecarbil; secondary aims were evaluation of pharmacodynamic and pharmacokinetic characteristics, safety, and tolerability. This study is registered at ClinicalTrials.gov, number NCT01380223.

Findings The maximum tolerated dose of omecamtiv mecarbil was 0·5 mg/kg per h. Omecamtiv mecarbil infusion resulted in dose-related and concentration-related increases in systolic ejection time (mean increase from baseline at maximum tolerated dose, 85 [SD 5] ms), the most sensitive indicator of drug effect (r^2=0·99 by dose), associated with increases in stroke volume (15 [2] mL), fractional shortening (8% [1]), and ejection fraction (7% [1]; all p<0·0001). Omecamtiv mecarbil increased atrial contractile function, and there were no clinically relevant changes in diastolic function. There were no clinically significant dose-related adverse effects on vital signs, serum chemistries, ECGs, or adverse events up to a dose of 0·625 mg/kg per h. The dose-limiting toxic effect was myocardial ischaemia due to excessive prolongation of systolic ejection time.

Interpretation These first-in-man data show highly dose-dependent augmentation of left ventricular systolic function in response to omecamtiv mecarbil and support potential clinical use of the drug in patients with heart failure.

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Introduction

Since the discovery of adrenaline more than 120 years ago, scientists have actively sought to develop drugs that improve cardiac performance[1] and the need for such drugs has increased. An estimated 20 million patients have chronic heart failure with at least 4 million admissions to hospital each year in the USA and Europe alone,[2,3] and major surgery requiring inotropic support has also increased. Currently available inotropes, such as dobutamine, dopamine, and milrinone, improve contractility by increasing cardiac myocyte intracellular calcium, a mechanism of action that inextricably links the haemodynamic benefits of these drugs to their recognised adverse effects.[4,5] Raised intracellular calcium not only increases heart rate and myocardial oxygen consumption, exacerbating myocardial ischaemia, but can also cause atrial and ventricular arrhythmias, all of which contribute to increased morbidity and mortality.[6,7] Several early studies of another inodilator, levosimendan, suggested potential clinical efficacy, although neither of the large phase 3 studies[8,9] confirmed a survival benefit, and REVIVE[8] showed significantly increased adverse events compared with placebo, including hypotension, atrial and ventricular arrhythmias, and possibly early mortality. Furthermore, these positive inotropes have significant vasoactive effects, which have additionally restricted their clinical use.

To address these clinical liabilities, omecamtiv mecarbil, a selective, small molecule, cardiac myosin activator, was developed.[10–12] Consistent with its biochemical mechanism of action, omecamtiv mecarbil increased contractility without affecting the calcium transient in cardiac myocytes.[11] In a conscious dog model of heart failure, this sarcomere-directed therapy increased left ventricular systolic performance and cardiac output, and decreased filling pressures and heart rate without increased myocardial oxygen consumption.[13] Underlying these effects on systolic function was an increase in systolic ejection time in the absence of changes in the rate of left ventricular pressure

development (dP/dt), a pattern distinctly different from existing inotropic drugs. At doses exceeding its maximum effects on cardiac contractility, the systolic ejection time progressively increases and both coronary blood flow and cardiac filling can become impaired, defining the preclinical dose-limiting effect of omecamtiv mecarbil.[11] Thus, this drug's unique pharmacological profile warranted evaluation in human beings.

See Online for webappendix

The primary objective of this first-in-man study was to establish the maximum tolerated dose and plasma concentrations of omecamtiv mecarbil administered as a 6-h intravenous infusion in healthy volunteers. Secondary objectives included evaluation of its pharmacodynamic (including its effect on left ventricular systolic function as assessed by echocardiogram) and pharmacokinetic characteristics, safety, and tolerability.

Methods

Participants

This study was a single centre, double-blind, placebo-controlled, dose-escalating, four-way crossover study in healthy men. The protocol was approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) and independent research ethics committee in Manchester, UK, and the study took place at the residential clinical unit of ICON Development Solutions (formerly Medeval; Manchester, UK). All participants provided written informed consent before enrolment. Healthy men aged 18–50 years were enrolled if they were judged to be in good health on the basis of history, physical and laboratory examination, electrocardiograph (ECG), and a screening echocardiogram showing normal cardiac function with no significant valvular regurgitation or stenosis and good quality images (see webappendix pp 1–2).

Procedures

Volunteers were enrolled in four successive cohorts, each consisting of a minimum of eight participants. Each participant received three active treatments of intravenous omecamtiv mecarbil (Cytokinetics Inc, South San Francisco, CA, USA) in ascending-dose order with placebo treatment randomised into the sequence (webappendix p 3); each infusion was administered at least a week apart. Active doses ranged from 0·005 to 1·0 mg/kg per h for 6 h with matching placebo. The starting dose of cohorts 2–4 was the same as the previously well tolerated highest dose from the preceding cohort. On day 1 of each dosing period, all participants received a 2-h (single-blind) intravenous placebo infusion (infusion 1) in a semirecumbent position during which baseline measures were obtained, immediately followed by a 6-h (double-blind) intravenous infusion of omecamtiv mecarbil or placebo (infusion 2). Blood samples for omecamtiv mecarbil pharmacokinetics and safety laboratories were obtained at intervals before and after initiation of infusion 2 (webappendix p 4).

Volunteers had an echocardiogram with standard two-dimensional, M-mode, colour, and tissue doppler imaging at screening, 1 h before each dose, at 1, 3, 6, 7, 8, 10, and 24 h after the start of infusion 2, and at the post-study visit. To preserve masking, clinical personnel were not immediately present during the echocardiogram examinations, to the extent allowed by safety considerations. Trained, masked, experienced sonographers read all echocardiograms (webappendix p 4). Baseline and 6-h echocardiograms and their respective measurements were over-read by a panel of expert external cardiologists. Biplane method-of-discs atrial volumes at baseline and 6-h timepoints for the participants treated with the maximum tolerated dose and placebo were also measured post-hoc by a trained, masked investigator.

The primary goal of this study was to establish the maximum tolerated dose, which was protocol specified as the highest infusion rate tolerated by at least eight participants. A dose was intolerable if: (1) the pattern of intolerance clearly distinguished active drug from placebo; or (2) the number of participants intolerant of the dose in question was at least three more than the

	Placebo* (n=28)	Omecamtiv mecarbil dose (mg/kg per h)									
		0·005 (n=6)	0·015 (n=6)	0·025 (n=12)	0·0625 (n=6)	0·125 (n=14)	0·25 (n=8)	0·5 (n=16)	0·625 (n=5)	0·75 (n=2)	1·0 (n=2)
Cohort 1 (N=10)	P	X	Y	Z	..	..	..	..	..	..	..
Cohort 2 (N=9†)	P	..	..	X	Y	Z	..	..	..	..	..
Cohort 3 (N=8)	P	..	..	..	..	X	Y	Z	..	..	..
Cohort 4 (N=8)	P	..	..	..	..	..	..	X	Z′	Z	Y
C_{max} (SD; ng/mL)	NA	8·7 (2·2)	25·6 (3·0)	46·7 (8·9)	121 (19)	236 (33)	459 (46)	905 (183)	1203 (232)	1136, 1403‡	1338, 1333‡

N=number of participants randomised. n=number of given doses administered. X, Y, and Z denote ascending doses of omecamtiv mecarbil. Simultaneous echocardiogram and pharmacokinetic timepoints were obtained at –1, 1, 3, 6, 7, 8, 10, and 24 h after double-blind study drug initiation. C_{max}=maximum plasma concentration. NA=not applicable. *A placebo infusion (P) was randomised into each participant's treatment sequence. †One participant was withdrawn because of unsuitable venous access before receiving study drug. ‡Individual values reported since only two participants received dose.

Table 1: **Dosing scheme**

number of participants intolerant of placebo. Safety was monitored by physical examination, vital signs, and laboratory measurements consisting of serum chemistries, liver function tests, troponins, routine haematological testing, and urinalysis. 12-lead ECGs were also obtained at multiple timepoints and then transmitted for central ECG measurements (Gentiae, San Bruno, CA, USA), including QT_c intervals. Cardiac rhythm was monitored by continuous ECG during the infusions and up to 6 h after completion of infusions. Any adverse or unexpected events, signs, or symptoms were fully recorded.

Statistical analysis

WinNonlin Professional (version 5.0.1) was used for pharmacokinetic analysis, producing geometric means and coefficients of variation for pharmacokinetic measures and assessments of dose-proportionality of area under the curve (AUC_∞) and maximum concentration (C_{max}). We computed summary statistics for all echocardiogram and safety measurements (arithmetic means [SD]) and changes from baseline in pharmacodynamic measures were compared between active dose concentrations from 0·005 to 0·625 mg/kg per h and placebo for the 6-h timepoint, using an ANCOVA procedure. A concentration bin analysis was done with ANCOVA, with treatment dose replaced with concentration bin group. In this analysis, echocardiogram data were paired with the plasma concentration of omecamtiv mecarbil measured at the time of the echocardiogram. The data were then binned by omecamtiv mecarbil concentration in 100 ng/mL increments. This analysis pooled all timepoints by omecamtiv mecarbil plasma concentration (where available) and treated the pooled bins as separate groups. All computations were completed with SAS (version 8.2). For safety evaluation, changes from baseline in vital sign and ECG data were compared between active dose concentrations and pooled placebo with a repeated measures ANCOVA procedure.

Role of the funding source

The design of the study protocols was the responsibility of the authors and Cytokinetics (the sole funder of the study). All statistical analyses were done by ICON Development Solutions and Cytokinetics. All authors have reviewed the report and related documents in full, and approved submission. The authors not employed by the sponsor had ultimate editorial authority and the corresponding author had full access to the study data and was responsible for submission of the report.

Results

Of 175 volunteers screened, 34 men (29 white, three Afro-Caribbean, one white/Afro-Caribbean, and one Asian) were included in the study and received the study drug (table 1; webappendix p 5). Participants were aged between 19 and 47 years (mean 27·1 [SD 6·7] years) with mean body-mass index of 23·56 (SD 2·62) kg/m² and body surface area of 1·94 (SD 0·11) m². 16 participants tolerated omecamtiv mecarbil at a dose of 0·5 mg/kg per h for 6 h. At the next protocol-specified dose (1 mg/kg per h), two participants did not complete the infusion; in the next treatment period, the dose was reduced to 0·75 mg/kg per h and one of two participants did not

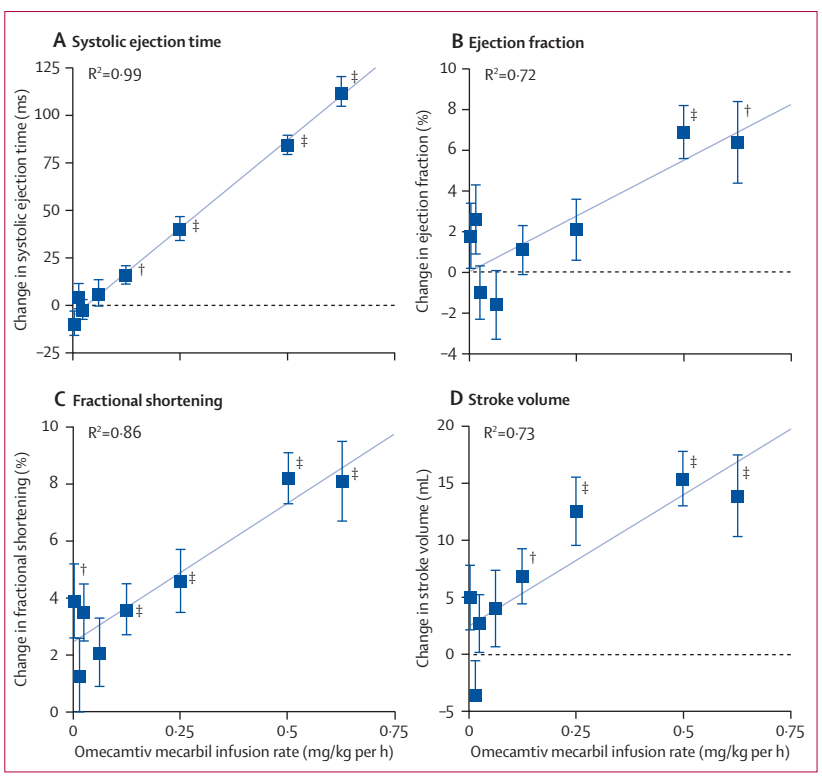

Figure 1: **Dose-dependent changes in echocardiogram measures by omecamtiv mecarbil dose***
Placebo-corrected change in (A) systolic ejection time, (B) ejection fraction, (C) fractional shortening, and (D) stroke volume by omecamtiv mecarbil dose (mg/kg per h after 6 h of infusion). Error bars show SEM. *p<0·0001 for all associations. †p<0·01. ‡p<0·0001.

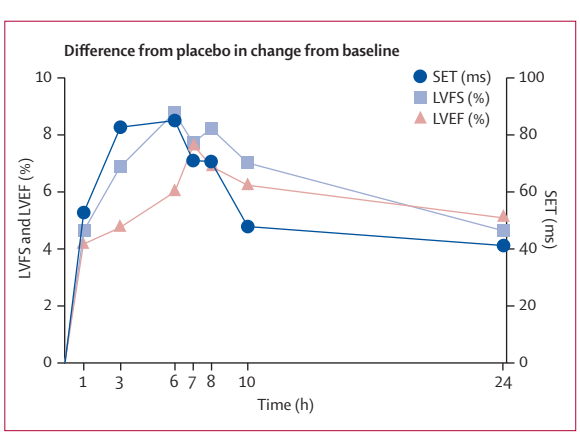

Figure 2: **Change in selected echocardiogram variables over time (omecamtiv mecarbil 0·5 mg/kg per h)**
SET=systolic ejection time. LVFS=left ventricular fractional shortening. LVEF=left ventricular ejection fraction. All points plotted are significant for the difference from pooled placebo in change from baseline (p<0·005).

complete the infusion. A 6-h 0·625 mg/kg per h infusion was well tolerated; however, too few participants (n=6) were treated at that dose for it to be defined as the maximum tolerated dose. Thus, the maximum tolerated dose for omecamtiv mecarbil given to healthy volunteers in this study was a 6-h infusion at 0·5 mg/kg per h.

Since the mean elimination half-life ranged from 17·1 to 21·0 h (webappendix p 6), steady-state concentrations were not achieved during the 6-h infusions administered. Clearance ranged from 132 to 207 mL/h per kg and the volume of distribution was between 3·7 and 5·2 L/kg (mean values) across all doses studied. Omecamtiv

	Baseline*	Omecamtiv mecarbil concentration (ng/mL)†										
		0–100	>100–200	>200–300	>300–400	>400–500	>500–600	>600–700	>700–800	>800–900	>900–1000	>1000
Left ventricular outflow tract doppler												
SET (ms)	310 (22)	6·6 (3·1, n=71), p=0·036	19 (2·7, n=64), p<0·0001	26 (3·1, n=43), p<0·0001	42 (3·1, n=44), p<0·0001	56 (3·6, n=31), p<0·0001	63 (4·0, n=23), p<0·0001	63 (3·7, n=29), p<0·0001	87 (4·3, n=20), p<0·0001	78 (4·8, n=16), p<0·0001	85 (5·1, n=14), p=0·0001	93 (5·4, n=12), p=0·0001
Stroke volume (mL)	83 (15)	0·4 (1·4, n=71), p=0·79	2·1 (1·2, n=64), p=0·081	6·0 (1·4, n=42), p<0·0001	6·3 (1·4, n=43), p<0·0001	9·4 (1·6, n=29), p<0·0001	9·4 (1·8, n=21), p<0·0001	13 (1·7, n=27), p<0·0001	15 (1·9, n=20), p<0·0001	12 (2·1, n=16), p<0·0001	13 (2·3, n=14), p<0·0001	16 (2·4, n=12), p<0·0001
Two-dimensional/M-mode												
LVS (cm)	3·2 (0·4)	−0·05 (0·04, n=71), p=0·16	−0·07 (0·03, n=64), p=0·33	−0·17 (0·04, n=43), p<0·0001	−0·21 (0·04, n=44), p<0·0001	−0·33 (0·04, n=31), p<0·0001	−0·37 (0·05, n=23), p<0·0001	−0·46 (0·04, n=29), p<0·0001	−0·55 (0·05, n=20), p<0·0001	−0·53 (0·06, n=16), p<0·0001	−0·64 (0·06, n=14), p<0·0001	−0·81 (0·06, n=12), p<0·0001
LVD (cm)	4·9 (0·4)	0·002 (0·04, n=71), p=0·97	0·02 (0·03, n=64), p=0·50	−0·03 (0·03, n=43), p=0·44	0·02 (0·04, n=44), p=0·59	−0·04 (0·04, n=31), p=0·26	−0·05 (0·05, n=23), p=0·23	−0·02 (0·04, n=29), p=0·71	−0·06 (0·05, n=20), p=0·23	−0·13 (0·05, n=16), p=0·019	−0·07 (0·06, n=14), p=0·20	−0·25 (0·06, n=12), p<0·0001
FS (%)	35·6 (4·9)	1·3 (0·6, n=71), p=0·044	1·6 (0·6, n=64), p=0·0047	3·0 (0·6, n=43), p<0·0001	4·4 (0·7, n=44), p<0·0001	6·0 (0·7, n=31), p<0·0001	6·7 (0·8, n=23), p<0·0001	8·9 (0·8, n=29), p<0·0001	10 (0·9, n=20), p<0·0001	9·1 (1·0, n=16), p<0·0001	12 (1·1, n=14), p<0·0001	14 (1·1, n=12), p<0·0001
LVESVI (mL/m²)	23·7 (5·2)	−0·2 (0·5, n=70), p=0·69	−1·2 (0·5, n=63), p=0·013	−1·4 (0·5, n=43), p=0·0064	−2·9 (0·5, n=44), p<0·0001	−3·6 (0·6, n=31), p<0·0001	−5·1 (0·7, n=23), p<0·0001	−5·9 (0·6, n=28), p<0·0001	−7·3 (0·7, n=20), p<0·0001	−5·8 (0·8, n=16), p<0·0001	−6·5 (0·9, n=14), p<0·0001	−7·3 (0·9, n=11), p<0·0001
LVEDVI (mL/m²)	61·4 (9·3)	−1·5 (0·9, n=71), p=0·11	−0·8 (0·8, n=63), p=0·30	−0·9 (0·9, n=43), p=0·31	−1·8 (0·9, n=44), p=0·048	−2·1 (1·0, n=31), p=0·038	−3·9 (1·2, n=23), p=0·0010	−3·6 (1·1, n=28), p=0·0010	−4·8 (1·3, n=20), p=0·0002	−6·8 (1·4, n=16), p<0·0001	−5·0 (1·5, n=14), p=0·0009	−7·0 (1·7, n=10), p<0·0001
EF (%)	61·4% (5·7)	−0·6% (0·7, n=70), p=0·37	1·4% (0·6, n=63), p=0·024	1·8% (0·7, n=43), p=0·0088	3·8% (0·7, n=44), p<0·0001	4·7% (0·8, n=31), p<0·0001	6·3% (0·9, n=23), p<0·0001	7·7% (0·8, n=28), p<0·0001	9·8% (1·0, n=20), p<0·0001	6·1% (1·1, n=16), p<0·0001	8·1% (1·1, n=14), p<0·0001	9·1% (1·3, n=10), p<0·0001
Mitral inflow doppler												
Peak E (m/s)	0·81 (0·1)	−0·015 (0·02, n=52), p=0·30	−0·024 (0·02, n=26), p=0·13	−0·038 (0·02, n=23), p=0·020	−0·052, (0·02, n=18), p=0·0042	−0·030 (0·02, n=14), p=0·14	−0·063 (0·03, n=9), p=0·011	−0·098 (0·02, n=9), p<0·0001	−0·11 (0·03, n=7), p=0·0001	−0·11 (0·03, n=9), p<0·0001	−0·085 (0·03, n=8), p=0·0033	−0·15 (0·02, n=11), p<0·0001
Peak A (m/s)	0·48 (0·1)	−0·013 (0·01, n=52), p=0·32	0·006 (0·02, n=26), p=0·67	0·004 (0·02, n=23), p=0·79	0·048 (0·02, n=18), p=0·0051	0·042 (0·02, n=14), p=0·030	0·048 (0·02, n=9), p=0·037	0·074 (0·02, n=9), p=0·0015	0·10 (0·03, n=7), p=0·0001	0·099 (0·02, n=9), p<0·0001	0·092 (0·03, n=8), p=0·008	0·070 (0·02, n=11), p=0·0017
E/A ratio	1·8 (0·4)	0·017 (0·05, n=52), p=0·71	−0·079 (0·05, n=26), p=0·12	−0·079 (0·05, n=23), p=0·14	−0·26 (0·06, n=18), p<0·0001	−0·21 (0·07, n=14), p=0·0019	−0·27 (0·08, n=9), p=0·0008	−0·44 (0·08, n=9), p<0·0001	−0·48 (0·09, n=7), p<0·0001	−0·53 (0·08, n=9), p<0·0001	−0·45 (0·09, n=8), p<0·0001	−0·46 (0·08, n=11), p<0·0001
E-wave deceleration time (ms)	174 (34)	2·3 (4·5, n=52), p=0·61	4·9 (4·9, n=26), p=0·32	11·2 (5·1, n=23), p=0·029	12·5 (5·6, n=18), p=0·027	13·0 (6·5, n=13), p=0·048	11·4 (7·6, n=9), p=0·14	1·7 (7·6, n=9), p=0·82	2·6 (9·6, n=6), p=0·79	19·0 (7·9, n=9), p=0·017	8·1 (9·2, n=7), p=0·38	5·5 (7·9, n=9), p=0·49
A duration (ms)	137 (12)	0·25 (2·3, n=52), p=0·91	−4·3 (2·7, n=26), p=0·11	−2·2 (2·8, n=23), p=0·42	12 (3·1, n=18), p=0·0002	12 (3·5, n=13), p=0·0012	16 (4·1, n=9), p=0·0001	13 (4·1, n=9), p=0·0020	19 (5·2, n=6), p=0·0003	14 (4·2, n=9), p=0·0010	18 (4·9, n=7), p=0·0003	16 (4·2, n=9), p=0·0002
IVCT (ms)	49·8 (11)	−1·7 (1·7, n=51), p=0·31	−1·3 (1·9, n=26), p=0·50	−0·4 (2·0, n=23), p=0·85	−3·7 (2·2, n=18), p=0·091	−5·5 (2·4, n=14), p=0·023	−1·6 (2·9, n=9), p=0·59	−7·2 (2·9, n=9), p=0·015	−18 (3·3, n=7), p<0·0001	−12 (3·5, n=6), p=0·0011	−10 (3·5, n=7), p=0·0048	−9·7 (2·8, n=11), p=0·0006
IVRT (ms)	53·4 (7·5)	1·5 (1·6, n=52), p=0·35	2·2 (1·8, n=26), p=0·24	6·9 (1·9, n=23), p=0·0003	15 (2·1, n=18), p<0·0001	1 (2·3, n=14), p<0·0001	21 (2·8, n=9), p<0·0001	25 (2·8, n=9), p<0·0001	35 (3·0, n=8), p<0·0001	29 (2·9, n=9), p<0·0001	30 (3·2, n=8), p<0·0001	38 (2·6, n=12), p<0·0001

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	Baseline*	Omecamtiv mecarbil concentration (ng/mL)†										
		0–100	>100–200	>200–300	>300–400	>400–500	>500–600	>600–700	>700–800	>800–900	>900–1000	>1000
(Continued from previous page)												
Tissue doppler												
Peak E′ (cm/s)	0·23 (0·04)	–0·002 (0·005, n=51), p=0·72	–0·009 (0·005, n=26), p=0·073	–0·019 (0·005, n=23), p=0·0002	–0·020 (0·006, n=18), p=0·0003	–0·027 (0·006, n=14), p<0·0001	–0·041 (0·008, n=9) p<0·0001	–0·029 (0·007, n=9), p=0·0001	–0·052 (0·010, n=5), p<0·0001	–0·049 (0·008, n=7), p<0·0001	–0·045 (0·010, n=7), p<0·0001	–0·050 (0·008, n=10), p<0·0001
Peak S′ (cm/s)	0·17 (0·03)	0·003 (0·003, n=51), p=0·43	–0·004 (0·004, n=26), p=0·31	–0·010 (0·004, n=23), p=0·011	–0·013 (0·004, n=18), p=0·0019	–0·021 (0·005, n=14), p<0·0001	–0·024 (0·006, n=9), p<0·0001	–0·019 (0·006, n=9), p=0·0011	–0·025 (0·006, n=7), p=0·0002	–0·013 (0·006, n=7), p=0·049	–0·024 (0·007, n=7), p=0·0006	–0·030 (0·005, n=12), p<0·0001
E/E′ ratio	3·7 (0·8)	–0·063 (0·09, n=51), p=0·48	0·044 (0·1, n=26), p=0·64	0·19 (0·1, n=23), p=0·061	0·12 (0·1, n=18), p=0·27	0·41 (0·1, n=14), p=0·0011	0·52 (0·1, n=9), p=0·0006	0·055 (0·1, n=9), p=0·71	0·49 (0·2, n=5), p=0·013	0·27 (0·2, n=6), p=0·13	0·56 (0·2, n=7), p=0·0028	0·32 (0·1, n=10), p=0·32

SET=systolic ejection time. LVS=left ventricular end-systolic dimension. LVD=left ventricular end-diastolic dimension. FS=fractional shortening. LVESVI=left ventricular end-systolic volume index. LVEDVI=left ventricular end-diastolic volume index. EF=ejection fraction. IVCT=isovolumic contraction time. IVRT=isovolumic relaxation time. *Data are absolute arithmetic mean values (SD) for the pooled placebo group (n=28) during single-blind infusion. †Bin data represent placebo-corrected least square mean differences in change from baseline to 6 h after infusion (SEM, n), meaning the least square mean of change from baseline on placebo has been subtracted from each bin.

Table 2: **Placebo-corrected change from baseline in selected echocardiogram variables**

mecarbil had generally dose-proportional pharmacokinetic characteristics. Mean C_{max} values for omecamtiv mecarbil increased in a strictly dose-proportional manner,[14] whereas the increase in AUC_{last} and AUC_{∞} was slightly greater than dose-proportional. C_{max} ranged from 9 to 1203 ng/mL (webappendix pp 6–7), and the mean C_{max} at the maximum tolerated dose of 0·5 mg/kg per h over 6 h was 905 (183) ng/mL.

Administration of omecamtiv mecarbil as a 6-h infusion resulted in dose-dependent increases in the three prespecified primary echocardiogram indices (systolic ejection time, ejection fraction, and fractional shortening), as well as stroke volume (figure 1). Significant increases in systolic ejection time, fractional shortening, and stroke volume were evident at doses of 0·125 mg/kg per h and higher, and improvements in ejection fraction were evident at 0·5 mg/kg per h. Additionally, at the maximum tolerated dose of 0·5 mg/kg per h, there were significant increases in stroke volume with associated decreases in left ventricular end-systolic dimension and volume (webappendix pp 8–10). Serial echocardiograms were done to evaluate the time-effect profile. After initiation of drug infusion, there were rapid increases in the three primary echocardiogram indices of systolic ejection time, fractional shortening, and ejection fraction (figure 2) that peaked in magnitude at or just after the completion of infusion and persisted until the last timepoint at 24 h. This time-effect profile is similar to the pharmacokinetic profiles (webappendix p 7) and suggests a tight correlation between the changes in echocardiogram indices of cardiac function and the plasma concentrations of omecamtiv mecarbil.

The primary indices of cardiac function increased with omecamtiv mecarbil concentration and were highly correlated with drug concentration (all p<0·0001) in an analysis of the effects of omecamtiv mecarbil plasma concentrations on changes in cardiac function using echocardiograms at all timepoints and doses (n=489; table 2, webappendix p 11). Systolic ejection time and fractional shortening were the most sensitive measures of drug effect; significant increases in each were evident at less than 100 ng/mL (p=0·036 for systolic ejection time and p=0·044 for fractional shortening). Similarly, ejection fraction and stroke volume increased in a concentration-dependent manner (p<0·0001) with significant increases evident at more than 100 ng/mL for ejection fraction (p=0·024) and greater than 200 ng/mL for stroke volume (p<0·0001). Improvements in systolic function were associated with significant changes in other echocardiogram measures as well, including decreases in systolic left ventricular volume and dimension, with less prominent decreases in diastolic volume and dimension. As we have noted, the increase in systolic ejection time was most reflective of the mechanism of action and pharmacological effect of omecamtiv mecarbil. These increases in systolic ejection time were associated with improvements in systolic performance with omecamtiv mecarbil administration as assessed by stroke volume, ejection fraction, and fractional shortening (figure 3).

There were no clinically meaningful changes in measures of diastolic function (table 2; webappendix pp 8–10), with small increases in peak A wave velocity and decreases in peak E wave velocity with a commensurate increase in E/A ratio. Additionally, there were small increases in mitral valve E-wave deceleration time and isovolumic relaxation time accompanied by partial offsetting of decreases in isovolumic contraction time. Analysis of left atrial function in participants receiving omecamtiv mecarbil 0·5 mg/kg per h (table 3) showed increased duration of atrial contraction (mitral A wave duration) analogous to the increase in left ventricular systolic ejection time and consistent with a pharmacological effect on the atrial

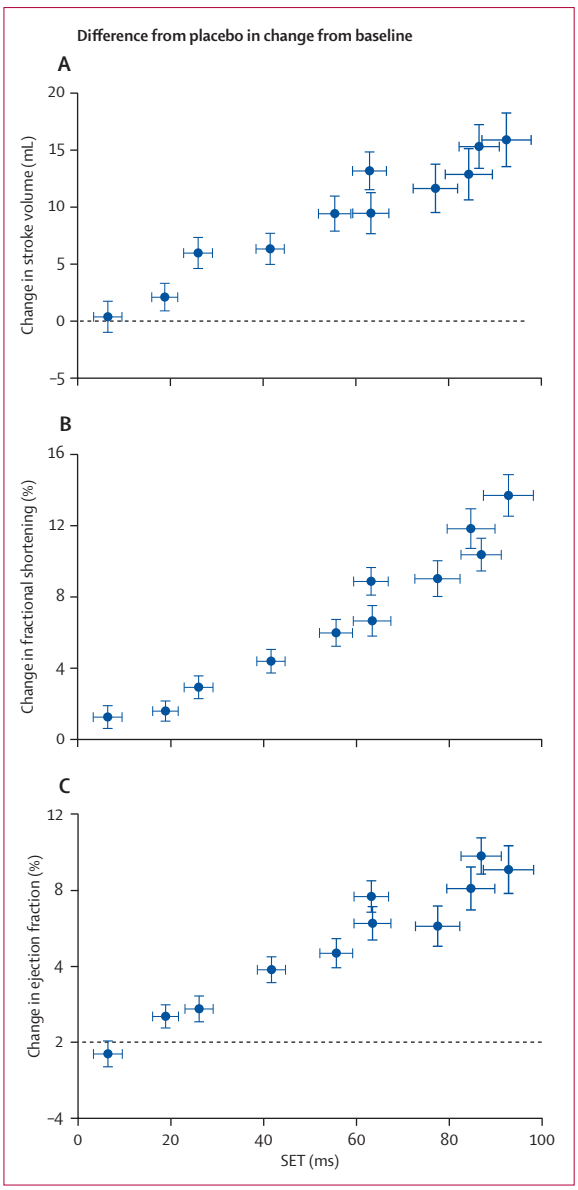

Figure 3: **Relation between changes in systolic ejection time and changes in selected echocardiogram variables**
Placebo-corrected change in (A) stroke volume, (B) fractional shortening, and (C) ejection fraction by change in systolic ejection time. SET=systolic ejection time. Error bars show SEM.

myocardium. This change was associated with increased mitral inflow A wave and A′ velocity, left atrial emptying fraction (p=0·064), and maintained or increased left atrial function index.[15] These findings are most consistent with increased atrial contractile function and relaxation initiating from a reduced end-systolic volume and possibly decreased preload.

The incidence of overall adverse events was not increased for infusions up to the maximum tolerated dose compared with placebo (table 4), except for slightly more frequent catheter-site pain in participants who received omecamtiv mecarbil. There were no deaths during the study. Five participants were withdrawn from the study because of adverse events: one treated with placebo who had postural dizziness; one treated with omecamtiv mecarbil 0·005 mg/kg per h because of non-specific ST and T wave abnormalities, judged to be unrelated to study drug, but precluding effective ongoing assessment of safety; one with ST segment depression judged to be related to study drug after dosing with omecamtiv mecarbil 0·75 mg/kg per h for 3 h 58 min ($C_{3\,h}$=1136 ng/mL; $C_{3\,h\,58\,m\,modelled}$=1346 ng/mL); one with chest discomfort judged related to study drug after dosing at 1·0 mg/kg per h for 3 h 22 min ($C_{3\,h}$=1338 ng/mL); and one participant with chest discomfort, ST segment depression, and mild transient increased troponin concentrations (normal creatine kinase MB) after dosing at 1·0 mg/kg per h for 4 h 12 min ($C_{3\,h}$=1333 ng/mL) without evidence of myocardial infarction, as assessed by gadolinium-enhanced contrast cardiac MRI. Thus, the dose-limiting toxic effect of omecamtiv mecarbil in this study was myocardial ischaemia probably due to excessive prolongation of the ejection time (by more than 110 ms in each of these cases) at plasma concentrations probably exceeding 1200 ng/mL, reducing the time during which diastolic coronary blood flow could occur.

Vital signs obtained after 6 h of infusion showed a pronounced increase in orthostatic heart rate in the placebo-treated participants (17 [13] beats per min; webappendix p 12). At doses of 0·5 mg/kg per h and above, a pattern of dose-related reductions in supine systolic blood pressure versus placebo began to emerge, accompanied by small decreases in supine diastolic blood pressure, occurring at doses of 0·625 mg/kg per h and higher. However, supine heart rate did not seem to be affected at any dose studied. Effects on standing and orthostatic vital signs were less consistent, although standing systolic blood pressure tended to decrease and heart rate to increase at the two highest doses studied. Omecamtiv mecarbil caused no change in ECG intervals, except for dose-related decreases in QT and QT_c (webappendix p 13).

Discussion

In this first-in-man study, the novel cardiac myosin activator omecamtiv mecarbil had highly dose-dependent pharmacokinetic characteristics, was well tolerated up to 0·625 mg/kg per h infusion rates, and increased systolic ejection time with commensurate augmentation of cardiac systolic function in a dose-related and concentration-related manner when administered intravenously to healthy men for 6 h. This study shows that omecamtiv mecarbil is the first member of a novel class of drugs with the ability to improve cardiac function by direct modulation of the contractile apparatus, independent of second messenger systems such as intracellular calcium and cyclic AMP, and provides information for dose selection for future studies.

	Placebo (n=16)		Omecamtiv mecarbil, 0·5 mg/kg per h (n=16)		p value
	Baseline	Change at 6 h	Baseline	Change at 6 h	
Left atrial emptying fraction (%)	65% (8)	+4% (7)	69% (4)	+8% (7)	0·064
Left atrial function index[15]	0·63 (0·14)	+0·17 (0·12)	0·69 (0·13)	+0·19 (0·15)	0·18
Mitral valve A wave peak velocity (m/s)	0·46 (0·09)	+0·02 (0·07)	0·54 (0·07)	+0·07 (0.06)	<0·0001
Mitral valve A wave duration (ms)	137 (12)	−5 (9)	135 (9)	+16 (15)	<0·0001
Mitral annular A′ peak velocity (cm/s)	0·12 (0·02)	−0·01 (0·02)	0·13 (0·02)	+0·01 (0·02)	0·032

This analysis includes only participants who received the maximum tolerated dose of omecamtiv mecarbil (0·5 mg/kg per h).

Table 3: **Echocardiogram assessment of left atrial function**

	Placebo (n=28)	Omecamtiv mecarbil infusion rate (mg/kg per h)									
		0·005 (n=10)	0·015 (n=8)	0·025 (n=13)	0·0625 (n=6)	0·125 (n=14)	0·25 (n=8)	0·5 (n=16)	0·625 (n=5)	0·75 (n=2)	1·0 (n=2)
Postural dizziness	6 (21%)	2 (20%)	2 (25%)	1 (8%)	1 (17%)	1 (7%)	0	5 (31%)	1 (20%)	1 (50%)	1 (50%)
Catheter-site pain	2 (7%)	0	0	1 (8%)	0	3 (21%)	1 (12%)	5 (31%)	2 (40%)	1 (50%)	1 (50%)
Headache	3 (11%)	2 (20%)	1 (12%)	2 (15%)	0	1 (7%)	0	3 (19%)	0	1 (50%)	0
Dizziness	4 (14%)	2 (20%)	0	0	0	1 (7%)	0	2 (12%)	1 (20%)	0	1 (50%)
Chest discomfort	3 (11%)	0	0	1 (8%)	1 (17%)	0	0	0	0	0	2 (100%)
Fatigue	3 (11%)	1 (10%)	0	1 (8%)	0	0	0	0	2 (40%)	0	0
Feeling hot	1 (4%)	0	0	0	0	0	0	0	1 (20%)	2 (100%)	2 (100%)
Palpitations	1 (4%)	0	0	0	0	0	0	0	1 (20%)	2 (100%)	2 (100%)
Catheter site haematoma	1 (4%)	0	0	1 (8%)	0	0	0	1 (6%)	0	0	0
Nasopharyngitis	0	0	1 (12%)	1 (8%)	1 (17%)	0	0	0	0	0	0
Nausea	1 (4%)	1 (10%)	0	0	0	0	0	1 (6%)	0	0	0
Paraesthesia	1 (4%)	0	0	1 (8%)	0	0	0	0	1 (20%)	0	0
Pharyngolaryngeal pain	0	0	1 (12%)	0	1 (17%)	0	0	1 (6%)	0	0	0
Dysgeusia	1 (4%)	0	1 (12%)	0	0	0	0	0	0	0	0
Infusion-site extravasation	1 (4%)	0	0	0	0	0	0	0	1 (20%)	0	0
Rash	1 (4%)	0	1 (12%)	0	0	0	0	0	0	0	0
Any adverse event	17 (61%)	6 (60%)	6 (75%)	7 (54%)	5 (83%)	5 (36%)	1 (12%)	12 (75%)	4 (80%)	2 (100%)	2 (100%)

Data are n (%). Adverse events are listed by preferred term from MedDRA Thesaurus.

Table 4: **Adverse events**

Cardiac myosin is central to the translation of chemical energy into mechanical force that results in myocardial contractility. During myocardial contraction, myosin latches onto actin (cross-bridge formation) and undergoes a power stroke, resulting in fibre shortening. This mechanical action is coupled to a cycle of ATP turnover, in which myosin initially binds and rapidly but reversibly hydrolyses ATP, after which myosin retains the products of hydrolysis (phosphate and ADP), in a weakly bound state to the actin filament. The subsequent transition to the strongly bound cross-bridge state is the slowest step in the myosin cycle; once it occurs, myosin undergoes a force-generating power stroke releasing the bound phosphate.[16]

Omecamtiv mecarbil directly activates cardiac myosin, increasing the probability of the transition from a weakly actin-bound to a strongly actin-bound, force-producing state.[11] During each cardiac cycle, only a few myosins contained within each sarcomere are able to engage the actin filament and complete their cross-bridge cycle before the end of cardiac systole, when the myosins detach allowing the heart to relax.[17] The number of myosin cross-bridges is the primary determinant of the extent of myocardial contraction. An increase in the transition rate of myosin to the force-generating state in the presence of a cardiac myosin activator results in more active force generators during each cardiac systole, analogous to "more hands pulling on the rope", in which myosin heads are the hands and the actin filament is the rope, hence increasing myocardial contraction without additional ATP hydrolysis or calcium handling. In preclinical studies, cardiac myosin activators increased myocardial contraction and stroke volume but did not increase oxygen consumption,[13] thereby increasing myocardial efficiency. Preclinically, this mechanism increases systolic ejection time in the absence of changes in the rate of left ventricular

Panel: **Research in context**

Systematic review

We searched the PubMed database for articles published in English with the search terms "heart failure", "inotrope", "systolic ejection time", "CK-1827452", and "omecamtiv mecarbil." The last search was done in June, 2011. We selected studies that were relevant to heart failure, previous studies of positive inotropes, myocardial mechanics, and those that described the preclinical characterisation of omecamtiv mecarbil.

Interpretation

For more than a century, agents that improve cardiac function have operated through mechanisms that increase intracellular cardiomyocyte calcium fluxes or cAMP, or both, inextricably linking the benefit of improved myocardial function with the risk of myocardial ischaemia, arrhythmias, and death. This first-in-man study shows increased cardiac function through the novel mechanism of cardiac myosin activation with omecamtiv mecarbil, as well as defining the drug's potential therapeutic window and providing the basis for studies in patients with heart failure.[23] Large clinical trials in patients with acute and chronic heart failure will eventually define the clinical benefit and risk profile of cardiac myosin activation for a condition with a compelling unmet therapeutic need.

pressure development;[11,13] in this study, we similarly noted that increases in systolic ejection time were the most sensitive marker of drug effect and seemed to underlie the increases in systolic function.

Systolic ejection times[18] are decreased in heart failure[19] and paradoxically tend to be further decreased by acute administration of both conventional positive inotropes (epinephrine, digoxin, dobutamine, xamoterol, milrinone) and negative inotropes (β blockers). Uniquely, omecamtiv mecarbil could shift this variable in the opposite direction towards normal in patients with heart failure. The tight correlation of changes in the systolic ejection time with the omecamtiv mecarbil dose and plasma concentrations suggests that its pharmacodynamic effects are readily predicted by dose and could be followed clinically.[20,21]

The physiological actions of omecamtiv mecarbil evident in this study support its clinical efficacy as an agent to increase systolic function. The 8–10 percentage points increase in ejection fraction represents a potentially clinically important increase in left ventricular function, and in the absence of substantial changes in afterload and preload, the decreased end-systolic volumes are consistent with direct improvements in end-systolic elastance.[22] The increases in stroke volume, especially in healthy, reflex-intact participants, are also clinically meaningful and relevant, representing a 13% increase above the baseline stroke volume. The absence of increases in heart rate supports the mechanism of action and the concept that there is no increase in myocardial oxygen consumption.

Omecamtiv mecarbil was generally well tolerated in doses up to 0·625 mg/kg per h without evidence of off-target adverse events. Although signs and symptoms of myocardial ischaemia began to emerge at plasma concentrations in excess of 1200 ng/mL, significant increases in ejection time and stroke volume were evident at much lower concentrations (from 0–100 ng/mL for ejection time and >200 ng/mL for stroke volume). Future studies will need to monitor participants carefully for possible excessive pharmacological effects on prolongation of systolic ejection time, which might result in compromised diastolic coronary filling and myocardial ischaemia. In these healthy volunteers, left ventricular diastolic function was preserved with no clinically significant abnormalities, although the small increases in isovolumic relaxation time warrant observation. Left atrial function seemed to also be augmented, suggesting a potential beneficial effect of omecamtiv mecarbil on atrial myocardium.

In conclusion, this study provides the first clinical evidence for the translation into human beings of a novel mechanism to directly improve cardiac function, namely cardiac myosin activation (panel). The pharmacokinetic and pharmacodynamic data from this study will guide the selection of an initial target plasma concentration range (from 100 to 1200 ng/mL) and monitoring of potential dose-limiting effects of excessive prolongation of systolic ejection time as omecamtiv mecarbil is advanced into patients with heart failure,[23] in whom its potential clinical benefits and risks will ultimately be defined.

Contributors

JRT contributed to the conception, design, and implementation of the study; interpretation of results; drafting of the report; statistical expertise; administrative, technical, or logistical support; and collection and assembly of data. CPC contributed to the conception, design, and implementation of the study; interpretation of results; drafting of the report; enrolment and follow-up of patients; administrative, technical, or logistical support; and collection and assembly of data. KGS contributed to the design and implementation of the statistical analysis; interpretation of results; statistical expertise; administrative, technical, or logistical support; and collection and assembly of data. JHL contributed to the conception, design, and implementation of the study; interpretation of results; drafting of the report; administrative, technical, or logistical support; and collection and assembly of data. MMC contributed to the design and implementation of the statistical analysis; interpretation of results; statistical expertise; administrative, technical, or logistical support; and collection and assembly of data. RDE contributed to the conception, design, and implementation of the study; interpretation of results; drafting of the report; administrative, technical, or logistical support; and collection and assembly of data. LE contributed to the interpretation of results; drafting of the report; enrolment and follow-up of patients; administrative, technical, or logistical support; and collection and assembly of data. RB contributed to the interpretation of results; drafting of the report; enrolment and follow-up of patients; administrative, technical, or logistical support; and collection and assembly of data. MRH contributed to the interpretation of results; drafting of the report; administrative, technical, or logistical support; and collection and assembly of data. JHG contributed to the interpretation of results; drafting of the report; administrative, technical, or logistical support; and collection and assembly of data. NBS contributed to the interpretation of results; drafting of the report; administrative, technical, or logistical support; and collection and assembly of data. FIM contributed to the conception, design,

and implementation of the study; interpretation of results; drafting of the report; statistical expertise; administrative, technical, or logistical support; and collection and assembly of data. AAW contributed to the conception, design, and implementation of the study; interpretation of results; drafting of the report; statistical expertise; administrative, technical, or logistical support; and collection and assembly of data. All authors have reviewed the report and agree with its contents.

Conflicts of interest

JRT has received research grants from Amgen, Corthera, Cytokinetics, Merck, Novartis, and Scios; and consulting fees from Bayer, Corthera, Cytokinetics, Merck, Nile Therapeutics, and Novartis. CPC is an employee of ICON Development Solutions (formerly Medeval). LE and RB are employees of ICON Medical Imaging. KGS, JHL, MMC, RDE, FIM, and AAW are employees of Cytokinetics, the sponsor of this study. MRH and NBS received research grants from ICON Medical Imaging. JHG is an employee of ICON Clinical Research, and formerly of ICON Medical Imaging, the echocardiogram core laboratory for this study.

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