Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): A Phase 2, Pharmacokinetic, Randomised, Placebo-controlled Trial

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Summary:

Background: Impaired contractility is a fundamental abnormality in heart failure with reduced ejection fraction (HFrEF). We evaluated the pharmacokinetics of chronic therapy with the cardiac myosin activator omecamtiv mecarbil as well as its effect on cardiac function and structure in such patients.

Methods: In this randomised, parallel-group, double-blind study, 448 patients from 87 sites in 13 countries with stable, symptomatic chronic heart failure and left ventricular ejection fraction d40% were randomly assigned (1:1:1) using an interactive web response system to oral omecamtiv mecarbil (25 mg twice daily; or 25 mg twice daily with pharmacokinetic-guided uptitration to 50 mg twice daily, PK-titration group) or placebo for 20 weeks. The primary endpoint was the maximal omecamtiv mecarbil plasma concentration (C_{max}); secondary endpoints were changes from baseline in cardiac function and dimensions, heart rate and NT-proBNP at week 20. (ClinicalTrials.gov, NCT01786512)

Findings: In patients enrolled from March 17, 2014 through March 5, 2015, C_{max} (mean ± SD) at 12 weeks was 200±71 and 318±129 ng/mL in the 25 mg (n = 147) and PK-titration (n = 141) groups, respectively. Differences were seen in all secondary endpoints by 20 weeks in the PK-titration group (n = 149) compared to placebo (n = 149): systolic ejection time [least square mean difference (95% CI); +25 (18, 32) msec, p<0·0001], stroke volume [+3·6 (0·5, 6·7) mL, p=0·0217], left ventricular end-systolic and end-diastolic dimensions [-1·8 (-2·9, -0·6) mm, p=0·0027; -1·3 (-2·3, 0·3) mm, p=0·0128, respectively], heart rate [-3·0 (-5·1, -0·8) bpm, p=0·0070] and NT-proBNP [-970 (-1672, -268) pg/mL, p=0·0069). The maximum changes from baseline in plasma troponin-I concentrations were greater in patients assigned to omecamtiv mecarbil [PK-titration: 0·020 ng/mL, (0·005, 0·038); median (Q1, Q3), p<0·0001] than placebo

[0·010 ng/mL (0·000, 0·020)]. No important differences in adverse clinical events were observed.

Interpretation: In patients with chronic HFrEF, pharmacokinetic-guided dosing of omecamtiv mecarbil achieved plasma concentrations associated with improvements in cardiac performance and ventricular dimensions.

Funding: Amgen in collaboration with Cytokinetics.

Introduction

For over a century scientists have sought treatments to increase cardiac contractility[1,2] assuming that improvement in ventricular systolic performance may blunt deleterious neurohormonal activation and reverse adverse ventricular remodelling leading to improved clinical outcomes. Currently available pharmacologic agents that increase cardiac contractility have concomitant vascular effects (e.g. dobutamine, milrinone, levosimendan, dopamine) and may provoke important adverse clinical effects such as tachycardia, hypotension, arrhythmias and myocardial ischaemia, which may increase morbidity and mortality and confound their utility in testing the above assumption.[3] These adverse effects may be a consequence of their mechanisms of action (adrenergic activation or phosphodiesterase inhibition) which increase myocardial cytoplasmic calcium or activate second messenger signalling resulting in pleiotropic effects on cardiac and vascular tissue rather than due to a direct consequence of the restoration of contractility.

Omecamtiv mecarbil is a novel selective cardiac myosin activator that, in pre-clinical studies, increased myocardial systolic function and systolic ejection time, but did not increase intracellular calcium or the rate of change in left ventricular pressure (dP/dt), nor have any direct effect on vascular tissue, cardiovascular receptors or ion channels.[4,5] In clinical studies with an intravenous formulation, omecamtiv mecarbil increased systolic ejection time and stroke volume while decreasing ventricular dimensions starting at plasma concentrations from 100-200 ng/mL.[6-8] In early dose-finding studies, the dose-limiting effect was excessive prolongation of systole with a resultant decrease in coronary blood flow during diastole leading to myocardial ischaemia, occurring in some patients with plasma concentrations above 1,200 ng/mL.[6,7] At well tolerated doses, a small increase in troponin concentration has been

noted in the absence of other clinical evidence of myocardial ischaemia.[8] The Chronic Oral Study of Myosin activation to Increase Contractility in Heart Failure (COSMIC-HF; ClinicalTrials.gov NCT01786512) was designed to test the hypothesis that administration of oral omecamtiv mecarbil for 20 weeks using a pharmacokinetic-guided dose titration strategy would result in effective and well-tolerated plasma concentrations that improve ventricular systolic function and favourably decrease ventricular dimensions.

Methods

Study design

COSMIC-HF was an international, multicentre, randomised, parallel group, placebo-controlled, double-blind study conducted at 87 sites in 13 countries (see Supplementary Appendix for listing of sites). Ethics committees approved the study at each centre. The study protocol (see Supplementary Appendix) is available with the full text of this article at thelancet.com.

Patients

All patients provided written informed consent. Eligible patients were aged 18 to 85 years with chronic heart failure (NYHA class II or III) treated with stable, optimal pharmacological therapy for at least 4 weeks, and had an N-terminal-B-type natriuretic peptide (NT-proBNP) of at least 200 pg/mL (e1200 pg/mL if in atrial fibrillation at presentation) and left ventricular ejection fraction d40% with acceptable image quality as determined by central reading of the screening echocardiogram. Patients were excluded if they had recent acute myocardial infarction, unstable

angina, or persistent angina at rest, were receiving treatment with chronic antiarrhythmic therapy (except amiodarone), or had severe chronic kidney disease (estimated glomerular filtration rate < 30 mL/min/1·73 m^2 at screening). Randomisation was stratified by presence of atrial fibrillation with the proportion of patients with atrial fibrillation limited to approximately 20% of study population. Complete eligibility criteria are listed in the Supplementary Appendix.

Randomisation and Masking

Eligible patients were randomised via an interactive web response system based on a computer-generated schedule prepared by Amgen before the start of the study stratified by presence or absence of atrial fibrillation/ flutter in a 1:1:1 ratio to three treatment groups: two groups received oral omecamtiv mecarbil [fixed dose group: 25 mg twice daily; pharmacokinetic (PK)-titration group: 25 mg twice daily uptitrated to 50 mg twice daily] or matching oral placebo.

Procedures

Patients entered a screening period for up to 30 days and had tests including a 12-lead electrocardiogram (ECG), blood samples, and echocardiogram and eligible patients were randomised to one of the three groups. In the PK-titration group, PK-guided dose titration was employed to minimise the possibility of omecamtiv mecarbil plasma concentrations >1,000 ng/mL. Patients in the PK-titration group received 25 mg twice daily for 2 weeks to reach steady-state and if the trough omecamtiv mecarbil plasma concentration ($C_{predose}$) at 2 weeks was <200 ng/mL, then patients were uptitrated at week 8 to 50 mg twice daily, while those with

$C_{predose}$ e200 ng/mL continued on 25 mg twice daily. Study drug was administered for 20 weeks with a week 24 follow-up visit.

Full details of the study procedures are in the Supplementary Appendix. Intensive pharmacokinetic sampling was performed at the end of week 2 and week 12 over a period of 8 hours on each day. After week 8, visits were every 4 weeks until week 24. Transthoracic echocardiographic assessments were performed at screening, week 12 and week 20 (all centrally analysed, blinded to treatment assignment). Blood samples were obtained at specified visits for central analysis, including measurement of troponin I (cTnI; Siemens ADVIA Centaur Ultra Troponin I)[9,10] at baseline, weeks 2, 8, 12, 16, 20 and 24. Investigator-reported events suspicious of myocardial ischaemia or increases in cTnI [if cTnI > 0·04 ng/mL (99%URL) when prior level was undetectable or if cTnI > 0·03 ng/mL (10% CoV) greater than any prior detectable value] triggered an evaluation of possible cardiac ischaemia or infarction by the Clinical Events Committee (CEC).

Outcomes

The primary endpoint was the maximal concentration of omecamtiv mecarbil (C_{max}) during dosing at weeks 2 and 12 and the concentration prior to the morning dose ($C_{predose}$) at weeks 2, 8, 12, 16, and 20. Secondary endpoints were changes from baseline in systolic ejection time (SET), stroke volume, left ventricular end-systolic (LVESD) and end-diastolic (LVEDD) dimensions, heart rate and NT-proBNP at week 20. Additional pre-specified exploratory echocardiographic endpoints included left ventricular fractional shortening (LVFS), end-systolic (LVESV) and end-diastolic (LVEDV) volumes, and ejection fraction (LVEF). The CEC adjudicated all

hospitalizations and deaths, as well as all investigator-reported and troponin-triggered potential episodes of myocardial ischaemia or infarction.

Statistical analysis

The primary endpoints of this study were the pharmacokinetic measures, C_{max} and $C_{predose}$, of omecamtiv mecarbil described above. Assuming the standard deviations (SDs) for C_{max} and C_{min} are in the range of 40 to 140 ng/mL,[6-8,11-13] 142 subjects (assuming 5% subjects were excluded from the pharmacokinetic analysis set) would provide a 2-sided 95% confidence interval with half width of 6.6 to 23 ng/mL, which was considered sufficient for accurate population estimates of these concentrations. From prior work conducted in a similar patient population, "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."[7] Thus, we attempted to achieve C_{max} greater than 200 ng/mL and avoid exposures above 1000 ng/mL. In addition, with 150 subjects in each arm at two-sided alpha of 0·05, the statistical power for detecting a treatment effect on the echocardiographic endpoints of SET, stroke volume and LVESD was greater than 90% (see Supplementary Appendix, Protocol, Section 10.2). Treatment group differences for changes in echocardiographic variables, heart rate as measured by electrocardiogram, and NT-proBNP were estimated using a repeated measures model fitted separately for each variable and included the stratification factor of presence or absence of atrial fibrillation/flutter at randomisation, baseline value, treatment group, visit, and the treatment group by visit interaction. An unstructured covariance matrix was used to account for the correlation between visits within a subject. Least

squares mean differences with 95% confidence intervals (95%CI) of the mean relative to placebo are presented unless otherwise indicated. As the study was hypothesis generating, all p-values are nominal with no multiplicity adjustment.

Role of funding source

The study was funded by Amgen Inc. in collaboration with Cytokinetics. The Executive Committee designed and oversaw the conduct of the study and data analysis in collaboration with Amgen and Cytokinetics. Data were collected, managed, and analysed by the sponsor according to a predefined statistical analysis plan (see Supplementary Appendix). An external independent Data Monitoring Committee evaluated patient safety throughout the trial. The first author, who had unrestricted access to the data, prepared the first draft of the manuscript that was critically reviewed by all authors, who attested to the accuracy and completeness of the analyses and approved the final version of the manuscript for submission.

Results

Study patients

Of 758 patients screened from March 17, 2014 through March 5, 2015 at 87 centres in 13 countries, 448 were randomly assigned to either omecamtiv mecarbil fixed dose (n = 150; 25 mg twice daily), omecamtiv mecarbil PK-titration dose (n = 149) or placebo (n = 149; see Figure 1). The groups were balanced with respect to most baseline characteristics and patients were receiving recommended pharmacologic therapy for chronic heart failure (Table 1). More than 60% had an ICD, CRT-P or CRT-D.

Pharmacokinetics

At week 12, the $C_{predose}$ (mean ± SD) of omecamtiv mecarbil was 165±68 and 263±116 ng/mL and the mean C_{max} was 200±71 and 318±129 ng/mL in the fixed dose and PK-titration groups, respectively (see Table 2). At week 8, 78 of 146 patients in the PK-titration group were up-titrated to 50 mg bid. At Week 12 in patients with measurements available, 63 of 137 (46%) patients in the fixed dose and 110 of 127 (87%) patients in the PK-titration groups had C_{max} greater than or equal to 200 ng/mL. All patients had a C_{max} <1000 ng/mL and only one patient in the PK-titration group had a C_{max} greater than 750 ng/mL. The maximal observed plasma concentration was 453 ng/mL and 831 ng/mL in the fixed dose and PK-titration groups, respectively.

Outcomes

All pre-specified secondary efficacy endpoints were significantly different from placebo in the omecamtiv mecarbil PK-titration group at week 20 (Figure 2). There were placebo-corrected increases in systolic ejection time of 11 (95%CI; 5, 18) msec (p=0·0007) in the fixed omecamtiv mecarbil 25 mg bid dose group and 25 (18, 32) msec (p<0·0001) in the PK-titration group at week 20. Additionally, there were placebo-corrected increases from baseline in stroke volume in the fixed dose and PK-titration groups [5 (2, 8) mL, p=0·0036; 4 (1, 7) mL, p=0·0217, respectively]. Left ventricular end-systolic and end-diastolic dimensions, as well as heart rate were reduced by omecamtiv mecarbil compared to placebo at week 20 only in the PK-titration group. Reductions in the plasma concentrations of NT-proBNP at 20 weeks were observed both

in patients assigned to the fixed dose [-822 (-1516, -127) pg/mL; p=0·0205] and PK-titration [-970 (-1672, -268) pg/mL, p=0·0069] groups.

In pre-specified exploratory analyses, placebo-corrected reductions in NT-proBNP persisted four weeks after stopping omecamtiv mecarbil [fixed: -1327 (-2056, -597) pg/mL, p=0·0004; PK-titration: -1306 (-2046, -566) pg/mL, p=0·0006]. Additionally, in the PK-titration group, there were reductions in left ventricular end-diastolic and end-systolic volumes, as well as increases in fractional shortening at week 20 compared to placebo (Supplementary Appendix, Table).

Safety

Similar percentages of patients in the three groups completed study drug administration (Table 3). Adverse events, serious adverse events, and deaths were similar across randomised groups. Approximately one-quarter of the patients in the study had cardiac troponin I (cTnI) plasma concentrations above the 99th percentile upper reference limit (0·04 ng/mL) at baseline with no difference between the groups. At week 20, increased concentrations of cTnI compared to placebo were noted in patients receiving omecamtiv mecarbil; median change from baseline was 0·001 and 0·006 ng/mL in the fixed and PK-titration dose groups, respectively whereas there was no median change in the placebo group (Table 3). An analysis of the maximum change from baseline troponin at any time during the 20 weeks of treatment demonstrated that there was a significant increase in troponin in both the 25 mg bid (p=0·0029) and PK-titration (p<0·0001) groups compared to placebo. Over 92% of these increases were <0·1 ng/mL and 97% were <0·2 ng/mL in patients assigned to omecamtiv mecarbil as compared to 95% and 97% in patients assigned to placebo, respectively. Plasma concentrations of cTnI returned to baseline levels

within 4 weeks of discontinuing omecamtiv mecarbil. A patient's maximum concentration of omecamtiv mecarbil was poorly predictive of their maximum change from baseline in troponin (Figure 3; r^2=0·017). There were 278 potential events triggered by an increase in troponin that were submitted to the CEC for adjudication. Of these, none were adjudicated as an episode of myocardial ischaemia or a myocardial infarction.

Discussion

In COSMIC-HF, oral administration of omecamtiv mecarbil to patients with chronic heart failure with reduced ejection fraction achieved target plasma concentrations; almost twice as many patients in the pharmacokinetic (PK)-guided titration group attained target concentrations than in the fixed dose group. Patients in the PK-titration group had increased duration of ventricular systole and stroke volume, reduced ventricular dimensions and volumes and decreased NT-proBNP and heart rate. These effects on cardiac function were similar to those seen in earlier preclinical [4,5] and clinical studies [6-8] using short-term intravenous omecamtiv mecarbil. Unlike currently available inotropes and inodilators, no increases in clinical episodes of tachycardia, hypotension, atrial or ventricular arrhythmia, cardiac ischaemia, or myocardial infarction were observed. The incidence of clinical adverse events was similar with placebo and omecamtiv mecarbil though limited by small sample size, and patients receiving omecamtiv mecarbil had small increases in plasma concentrations of troponin that returned to baseline after omecamtiv mecarbil was discontinued. These findings from COSMIC-HF support the hypothesis that direct and selective augmentation of systolic function can reduce myocardial wall stress (as suggested by the decrease in NT proBNP) and possibly sympathetic activation (as suggested by the

decrease in heart rate), and promote favourable ventricular remodelling in patients with chronic heart failure with reduced ejection fraction.

Omecamtiv mecarbil is a selective cardiac myosin activator that binds to the motor domain of myosin and increases its probability of engaging the actin filament productively to produce force during systole.[4] This mechanism of action directly improves cardiac contractility by specifically modulating the function of the sarcomere. In preclinical studies, omecamtiv mecarbil did not increase the calcium transient in cardiac myocytes, and has no known activity other than its action on cardiac myosin that could account for its effects on cardiovascular function. In animals[4,5] and humans,[6-8] the pharmacodynamic signature of omecamtiv mecarbil is an increase in the systolic ejection time. This finding is a reflection of the mechanism of action of omecamtiv mecarbil; the increase in the number of myosin heads interacting with actin filaments facilitates a longer duration of systole, even as cytoplasmic calcium concentrations fall in the myocyte.

Since the 1960s, it has been recognized that systolic ejection times are shortened by 10-70 msec in patients with systolic heart failure compared to healthy controls.[14] The exact mechanism of this decreased systolic ejection time is unknown although it is proportional to the decrease in stroke volume. In a recent analysis of 2,077 patients from the ARIC study, decreased systolic ejection time was directly related to decreased fractional shortening and predicted the future risk of heart failure.[15] Consistent with studies of intravenous administration in healthy volunteers and patients with acute and chronic heart failure,[6-8] in this study of chronic oral administration of omecamtiv mecarbil, systolic ejection times were increased on average from 11-25 msec, effectively extending the systolic ejection time toward normal.

In a contemporary model of the pathogenesis of heart failure, decreased systolic function leads to multiple pathophysiological adaptations, including activation of the renin-angiotensin-aldosterone (RAAS) and sympathetic systems and adverse ventricular remodelling resulting in deteriorating cardiac function and worsening symptoms. This hypothesis has been supported by multiple trials demonstrating the ability of RAAS and sympathetic blockade (e.g. ACE inhibitors, ARBs, MRAs, and beta blockers) or augmentation of vasodilating peptides (e.g. neprilysin inhibitors) to slow or prevent the progression of heart failure. However, to date, no pharmacological therapy has been available to test the hypothesis that directly and selectively augmenting cardiac function can also delay progression of heart failure. While this study was not designed to specifically test this hypothesis, 20 weeks of omecamtiv mecarbil administration reduced left ventricular end-diastolic dimensions and volumes consistent with favourable cardiac remodelling. Although ventricular dimensions were not reassessed after discontinuation of omecamtiv mecarbil, the persistent decrease in NT-proBNP suggests that the effects on cardiac dimensions do not merely reflect a direct short-term effect on systolic function. The decreased heart rate observed in patients assigned to omecamtiv mecarbil in this study, as well as earlier preclinical [4,5] and clinical studies,[6-8] is also consistent with reduced sympathetic activation. These findings from COSMIC-HF may support the hypothesis that directly improving systolic function can reverse maladaptive structural changes associated with progression of heart failure.

In several prior studies, therapies that improve ventricular remodelling have also had beneficial effects on clinical outcomes. In a meta-analysis of the relationship between drug- or device-related changes in ventricular volumes and subsequent mortality,[16] therapies that decreased end-diastolic or end-systolic volumes by 11 mL were associated with a 65-75% likelihood of the therapy having a favourable effect on mortality. In the MADIT-CRT trial, a 5%

reduction in ventricular volumes was associated with an approximately 14-20% decrease in the combined endpoint of death or heart failure hospitalizations.[17] Plasma concentrations of natriuretic peptides have also been a strong predictor of adverse clinical outcomes, including cardiovascular death, [18,19] and in some studies are stronger predictors of clinical outcomes than left ventricular ejection fraction or volumes.[20] Similar changes in these measures were observed in COSMIC-HF following treatment with omecamtiv mecarbil warranting further investigation of its effects on cardiovascular outcomes.

COSMIC-HF was a pharmacokinetic study that compared two dosing strategies with a goal of achieving effective and well-tolerated plasma concentrations. The PK-titration group was able to achieve the target plasma concentration of >200 ng/mL in 87% of the patients, compared to 46% in the fixed dose group, and importantly, no patients in either group had plasma concentrations above 1,000 ng/mL. However, a small, though potentially concerning increase in plasma troponin concentration was noted temporally associated with administration of omecamtiv mecarbil, but not correlated with maximal omecamtiv mecarbil plasma concentrations, similar to findings in a previous study of patients with acute heart failure.[8] The magnitude of this troponin release is similar to the range of those experienced by healthy endurance athletes[21] and are within the limits of diurnal variation for patients without heart failure.[22] None of the increases in troponin were adjudicated as myocardial ischaemia in the current trial and occurred in the context of improving systolic function, decreasing ventricular volumes and declining NT-proBNP. Whether these troponin elevations are related to myocardial damage or other mechanisms (e.g. exosomal trafficking[23]) is unknown and its impact on clinical events can only be addressed by a large outcomes trial.

COSMIC-HF was designed as a Phase 2, pharmacokinetic study without formal hypothesis-testing, and consequently, the echocardiographic findings should be considered hypothesis-generating. While the study was prospectively powered for the secondary efficacy endpoints of SET, stroke volume and LVESD and all pre-specified secondary efficacy endpoints were significantly different than placebo in the PK-titration group, there were no adjustments for multiple comparisons. With these caveats, the results of COSMIC-HF support the hypothesis that directly and specifically improving cardiac systolic function with a cardiac myosin activator results in favourable ventricular remodelling. However, its effects on long-term morbidity and mortality remain untested and the risks and benefits of omecamtiv mecarbil can only be determined by a large outcomes trial.

Research in context

Evidence before this study

This study incorporated three major lines of evidence in its inception and design. The first line of evidence was that a central defect in heart failure with reduced ejection fraction (HFrEF) is a decrease in systolic function. The question emerges as to whether selectively improving systolic function can reverse some of the other pathophysiologic processes in HFrEF and result in improved clinical outcomes. The second line of evidence emerged from a review of the literature of clinical studies of oral positive inotropes in patients with heart failure [PubMed, see Supplementary Appendix]. Review of this literature revealed many agents given to improve systolic function whose mechanism of action directly or indirectly increased intracellular calcium and that acted on both the myocardium and vasculature. The poor clinical outcomes of oral agents that did eventually advance to Phase III trials, such as milrinone, vesnarinone, enoximone, and flosequinan, were also evident. In addition, this review established that, to-date, the hypothesis of whether a pharmacologic agent that worked solely upon cardiac contractility could favourably influence ventricular remodelling had not been tested. The third line of evidence is derived from the studies performed with omecamtiv mecarbil to date,[6-8,11-13] which demonstrated that plasma concentrations of 100-200 ng/mL and above of intravenous omecamtiv mecarbil could acutely improve cardiac function and dimensions and provided information on the pharmacokinetics and pharmacodynamics of intravenous omecamtiv mecarbil, as well as preliminary data on the pharmacokinetics of oral formulations. These data provided the foundation for selecting the target plasma concentration ranges used in COSMIC-HF, as well as for the hypothesis that oral omecamtiv mecarbil could chronically improve cardiac performance and perhaps favourably influence ventricular remodelling.

Added value of this study

COSMIC-HF demonstrated that using a PK-titration strategy, the great majority of patients achieved the targeted omecamtiv mecarbil plasma concentrations, avoiding excessive drug concentrations where prior adverse effects had been noted. However, an increase in circulating troponins was also noted which were poorly related to maximum plasma omecamtiv mecarbil concentrations. This study provided evidence that omecamtiv mecarbil may improve cardiac function associated with favourable reverse ventricular remodelling and reduced NT-proBNP.

Implications of all the available evidence

The results of COSMIC-HF support advancing omecamtiv mecarbil into a Phase III trial by providing essential data on the dosing strategy and supporting the hypothesis that selectively increasing cardiac function can result in improved ventricular remodelling. The extension of this hypothesis, that this improvement in ventricular function can also result in improved clinical outcomes, needs to be tested in a prospectively powered outcomes trial.

Contributors:

All authors contributed to the interpretation of the results, writing or revision of the manuscript, and approved the decision to submit the article for publication. JRT, GMF, JJVM, SDS, KFA, JGFC, JAE, AG, PM, MM, VM, PP, PS, JS, JT, HJV, AAV were investigators in this study. JJ, MLM and NM are employees of Amgen, and FIM is an employee of Cytokinetics, Inc. JRT, GMF, JJVM, SDS, JJ, MLM, FIM and NM were involved in the study design. JRT wrote the first draft of the article with input from the other authors.

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Declaration of Interests:

Dr. Teerlink received research grants from Amgen, Bayer, Cytokinetics, Mast Therapeutics, Novartis, and Trevena and has served as a consultant to Amgen, Bayer, Cytokinetics, Mast Therapeutics, Novartis, Relypsa, Trevena and ZS Pharma. Dr. Felker has received research grants from Amgen, Roche Diagnostics, Novartis, Otsuka, and NHLBI, and has served as a consultant for Amgen, Novartis, Roche Diagnostics, Singulex, Trevena, Celladon, Bristol Meyers Squibb, Merck, and Medtronic. Dr. McMurray's employer, Glasgow University, has been paid by Cytokinetics/Amgen for his time spent working on the clinical trial program with omecamtiv mecarbil. Dr. McMurray has had travel and accommodation costs paid by Cytokinetics/ Amgen in relation to advisory board and clinical trial meetings about omecamtiv mecarbil. Dr. Solomon has received research support from Amgen for conduct of

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Figure legends:

Figure 1: Trial profile

Figure 2: Efficacy Endpoints

The least squares mean ± SEM change from baseline at week 20 are shown by treatment group of the systolic ejection time (Panel A), stroke volume (Panel B), left ventricular end-systolic (Panel C) and end-diastolic (Panel D) dimensions, heart rate (Panel E), and NT-proBNP (Panel F). The 25 mg group received 25 mg bid for 20 weeks, while the PK-titration group received 25 mg twice daily for 2 weeks to reach steady-state and if the trough omecamtiv mecarbil plasma concentration ($C_{predose}$) was < 200 ng/mL, then patients were uptitrated at week 8 to 50 mg twice daily, while those with $C_{predose}$ ≥ 200 ng/mL continued on 25 mg twice daily. Approximately 60% of patients were up-titrated to 50 mg twice daily. P-values represent comparisons to placebo group using a repeated measures model. The model was fitted separately for each variable and included the stratification factor of presence or absence of atrial fibrillation/flutter at randomisation, baseline value, treatment group, visit, and the treatment group by visit interaction.

Figure 3: Maximum Change from Baseline in Troponin (µg/mL) by Omecamtiv Mecarbil Maximum Concentration (ng/mL)

Shown are the maximal change from baseline in troponin and the maximum omecamtiv mecarbil plasma concentration plotted individually for each patient (n = 429). The linear regression (solid line) demonstrates a very poor correlation of the maximum omecamtiv

534 mecarbil plasma concentration (Max OM) with the maximal change from baseline in troponin

535 (Max Troponin) with $r^2 = 0{\cdot}017$.

Tables

Table 1: Baseline Characteristics of Patients, According to Treatment Group

	Placebo (n = 149)	Omecamtiv Mecarbil 25 mg BID (n = 150)	Omecamtiv Mecarbil Titration Group (n = 149)
Age — years	64±10	63 ±10	63 ±12
Men — no. (%)	119 (80)	127 (85)	125 (84)
White Race — no. (%)	136 (91)	142 (95)	140 (94)
Body Mass Index — kg/m^2	29·7±5·7	28·5±5·6	29·5±6·1
Systolic blood pressure — mmHg	119±14	121±16	119±16
Heart rate — bpm	69±10	67±11	70±12
HF characteristics			
Ischemic heart disease — no. (%)	89 (60)	97 (65)	101 (68)
Years from HF Diagnosis	8·0±7·1	7·7±7·9	7·7±6·5
Hospitalised for HF in past 12 months— no. (%)	38 (26)	51 (34)	38 (26)
NYHA class II/III — no. (%)	105 (70)/ 44 (30)	102 (68)/ 48 (32)	107 (72)/ 42 (28)
Co-morbidities			
Angina — no. (%)	32 (21)	41 (27)	50 (34)
History of:			
Myocardial Infarction — no. (%)	82 (55)	83 (55)	82 (55)
Unstable angina — no. (%)	20 (13)	28 (19)	27 (18)
Coronary angiogram with clinically significant stenosis — no. (%)	70 (47)	73 (49)	78 (52)

	Placebo (n = 149)	Omecamtiv Mecarbil 25 mg BID (n = 150)	Omecamtiv Mecarbil Titration Group (n = 149)
Percutaneous Intervention — no. (%)	62 (42)	61 (41)	63 (42)
CABG — no. (%) *	28 (19)	47 (31)	40 (27)
Persistent A Fib/Flutter — no. (%)	33 (22)	28 (19)	24 (16)
Diabetes mellitus — no. (%)	61 (41)	70 (47)	55 (37)
Hypertension — no. (%)	101 (68)	94 (63)	109 (73)
Dyslipidaemia — no. (%)	111 (74)	95 (63)	99 (66)
Transient ischemic attack — no. (%)	9 (6)	10 (7)	5 (3)
Stroke — no. (%)	14 (9)	15 (10)	14 (9)
Chronic obstructive pulmonary disease — no. (%)	23 (15)	21 (14)	15 (10)
Laboratory variables [a]			
Troponin I — ng/mL, median (Q1, Q3)	0·025 (0·016, 0·041)	0·022 (0·016, 0·039)	0·022 (0·016, 0·042)
NT-proBNP — pg/mL, median (Q1, Q3)	1719 (699, 3242)	1538 (634, 3427)	1719 (881, 3060)
eGFR — mL/min/1·73m^2	65±19	63±19	65±19
Heart Failure Therapies – no. (%)			
ACE inhibitor and/or ARB	140 (94)	142 (95)	137 (92)
ACE inhibitors	106 (71)	104 (69)	97 (65)
ARBs	36 (24)	42 (28)	40 (27)
Beta-blockers	146 (98)	146 (97)	144 (97)
MRAs	88 (59)	87 (58)	94 (63)
Diuretics other than MRAs	125 (84)	128 (85)	134 (90)

	Placebo (n = 149)	Omecamtiv Mecarbil 25 mg BID (n = 150)	Omecamtiv Mecarbil Titration Group (n = 149)
Digitalis glycosides	31 (21)	24 (16)	32 (22)
Implantable cardiac defibrillator (ICD) only	52 (35)	58 (39)	60 (40)
Cardiac resynchronisation therapy (CRT) without ICD	6 (4)	2 (1)	1 (1)
Cardiac resynchronisation therapy (CRT) with ICD	30 (20)	39 (26)	37 (25)
Echocardiographic Variables			
SET — msec	299±37	305±39	298±33
Stroke volume — mL	52·2±14·9	54·1±15·4	52·4±14·9
LVESD — mm	53·1±9·6	52·4±8·6	53·9±9·1
LVEDD — mm	61·9±9·6	61·2±8·3	62·8±9·0
Fractional Shortening — %	18·9±5·5	18·7±5·5	18·4±5·3
LVESV — mL	155·9±89·0	144·2±61·3	157·1±77·7
LVEDV — mL	215·7±99·2	199·9±69·1	215·9±88·8
Ejection Fraction — %	29·3±7·4	29·3±7·5	29·0±7·3

Note: Mean ± SD, unless otherwise noted. [a] Laboratory variables, heart failure therapies and echocardiographic variables excludes 3 patients who were randomised but not dosed. SET = systolic ejection time, LVESD/ LVEDD = left ventricular end-systolic/ end-diastolic dimension, LVESV/ LVEDV = left ventricular end-systolic/ end-diastolic volume. * $p < 0{\cdot}05$, all others $p > 0{\cdot}05$; P-values provided as a measure of baseline difference and not for statistical testing. Continuous variable p-values are from ANOVA tests and categorical variable p-values from chi-square tests.

Table 2: Pharmacokinetic Primary variables:

	Omecamtiv mecarbil 25 mg (N =147)	Omecamtiv mecarbil PK-Titration Group* (N =141)
$C_{predose}$ (ng/mL)		
Week 2	174±62.2 (35.7)	179±68.8 (38.4)
Week 8	156±69.1 (44.2)	161±74.4 (46.1)
Week 12	165±67.9 (41.3)	263±116 (44.1)
Week 16	155±69.0 (44.6)	240±120 (50.0)
Week 20	149±71.2 (47.8)	239±118 (49.5)
C_{max} (ng/mL)		
Week 2	212±70.4 (33.2)	212±81.0 (38.2)
Week 12	200±71.1 (35.6)	318±129 (40.5)

Values are presented as Mean±SD (CV%); $C_{predose}$ = plasma concentration prior to an OM dose; C_{max} = maximum observed plasma concentration.

*Included 5 subjects who discontinued the study early prior to day 50 and were not treated after week 8; Patients in the PK-titration group received 25 mg twice daily for 2 weeks to reach steady-state and if the trough omecamtiv mecarbil plasma concentration ($C_{predose}$) was <200 ng/mL, then patients were uptitrated at week 8 to 50 mg twice daily, while those with $C_{predose}$ ≥200 ng/mL continued on 25 mg twice daily.

557 **Table 3: Safety Variables and Adverse Events**

No. (%)	Placebo (n = 149)	Omecamtiv Mecarbil 25 mg BID (n = 150)	Omecamtiv Mecarbil Titration Group (n = 146) [a]
Tolerability			
Completed IP	133 (89)	134 (89)	127 (85)
Discontinued IP	16 (11)	16 (11)	19 (13)
Troponin I — ng/mL			
Change to Week 20, median (Q1,Q3)	0·000 (-0·007, 0·004)	0·001 (0·000, 0·012)	0·006 (0·000, 0·024)
Maximum change from baseline, median (Q1, Q3)	0·010 (0·000, 0·020)	0·016 (0·003, 0·034)	0·020 0·005, 0·038)
Change to Week 24, median (Q1,Q3)	0·000 (-0·006, 0·008)	0·000 (-0·002, 0·009)	0·000 (-0·003, 0·010)
Adjudicated Clinical Events			
Hospitalisation	**24 (16)**	**24 (16)**	**26 (18)**
Heart failure	11 (7)	9 (6)	10 (7)
MI	1 (1)	-	1 (1)
Unstable angina	-	1 (1)	-
Chest pain (non-MI/UA)	1 (1)	2 (1)	2 (1)
Other categories	15 (10)	14 (9)	15 (10)
Total MI [c]	2 (1)	-	1 (1)
Death	4 (3)	1 (1)	3 (2)
CV Death	2 (1)	1 (1)	2 (1)
Any Adverse Event	**91 (61)**	**92 (61)**	**95 (65)**
Most-common Adverse Event [b]			

No. (%)	Placebo (n = 149)	Omecamtiv Mecarbil 25 mg BID (n = 150)	Omecamtiv Mecarbil Titration Group (n = 146) [a]
Dyspnoea	8 (5)	11 (7)	13 (9)
Fatigue	4 (3)	14 (9)	9 (6)
Dizziness	6 (4)	8 (5)	10 (7)
Cardiac failure	13 (9)	5 (3)	8 (5)
Nasopharyngitis	5 (3)	8 (5)	5 (3)
AE Leading to study discontinuation	**12 (8)**	**8 (5)**	**12 (8)**
Serious Adverse Events	**30 (20)**	**36 (24)**	**32 (22)**
Cardiac SAEs	**19 (13)**	**18 (12)**	**17 (12)**
Cardiac failure	4 (3)	3 (2)	5 (3)
Cardiac failure acute	1 (1)	3 (2)	3 (2)
Cardiac failure congestive	3 (2)	3 (2)	3 (2)
Angina pectoris	-	3 (2)	1 (1)
Ventricular tachycardia	1 (1)	2 (1)	1 (1)

[a] Tolerability includes 3 additional patients who were randomised but not dosed; [b] Treatment Emergent Adverse Events occurring in ≥5% of patients; [c] Includes 0/278 increased troponin-triggered potential myocardial ischaemia/ infarction events adjudicated by CEC as MI; AE = adverse event; CV = cardiovascular; IP = Investigational product; MI = myocardial infarction; SAE = serious adverse event; UA = unstable angina.

Figure 1: Trial Profile

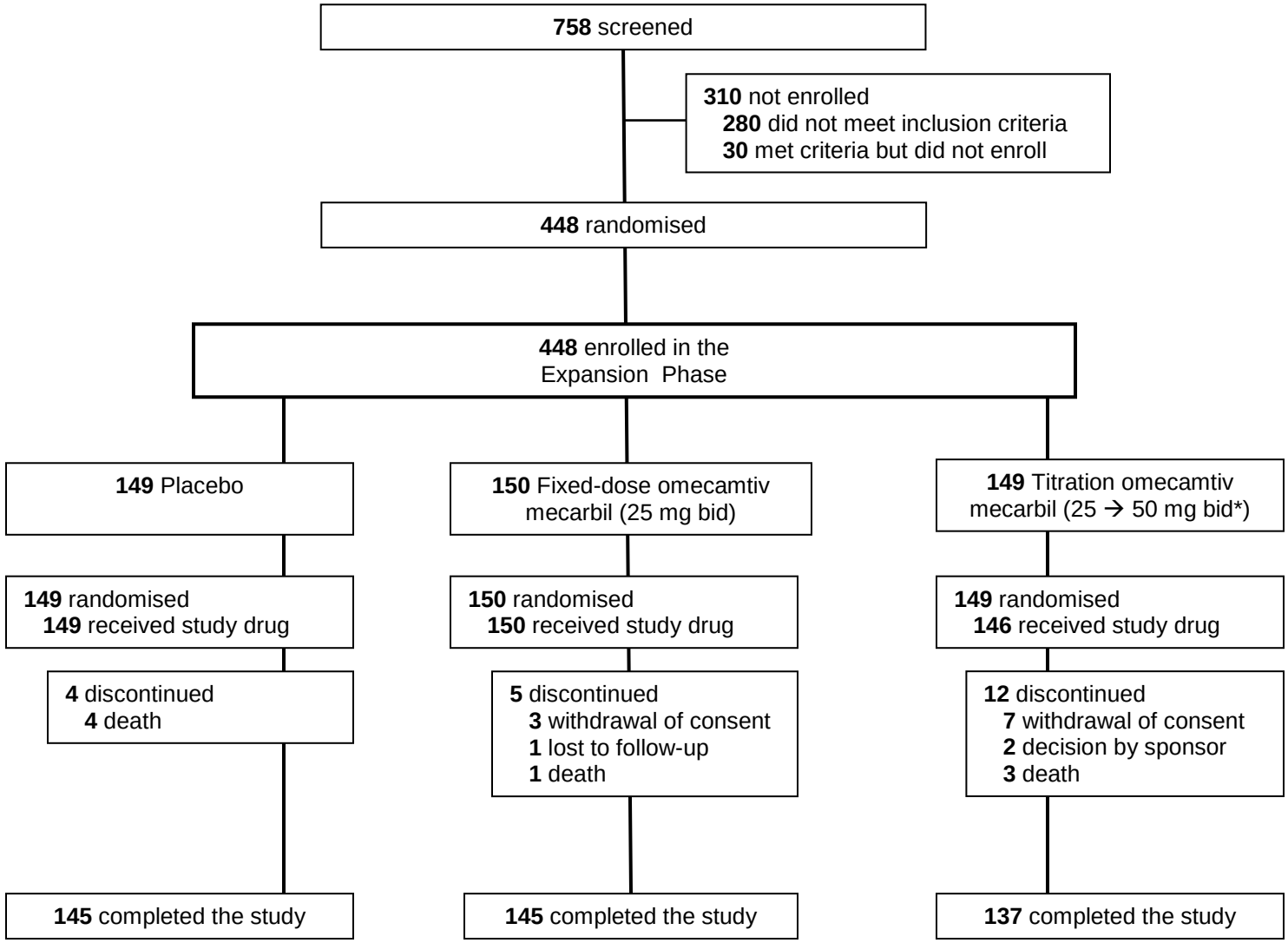


Figure 2: Efficacy Endpoints

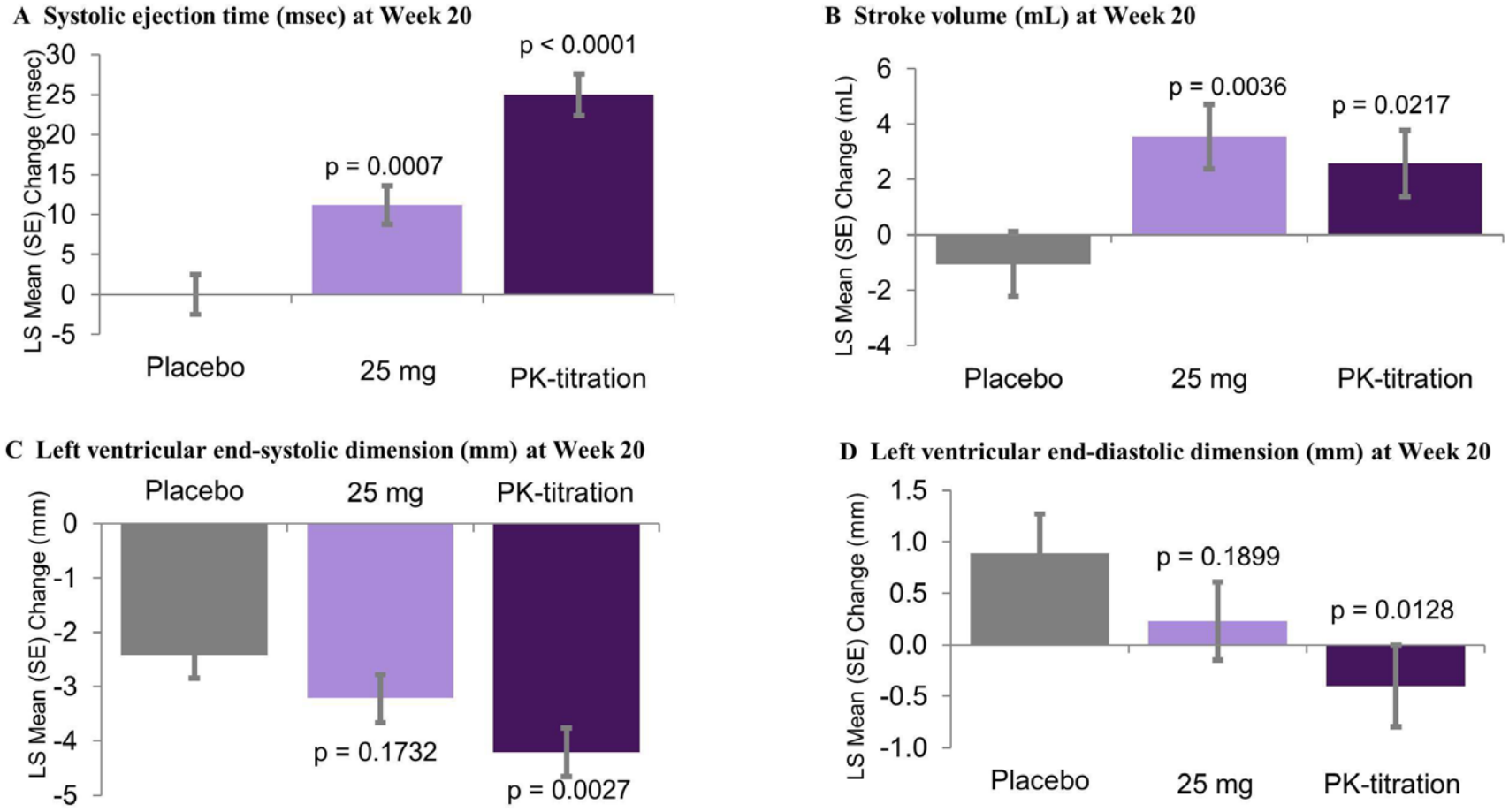
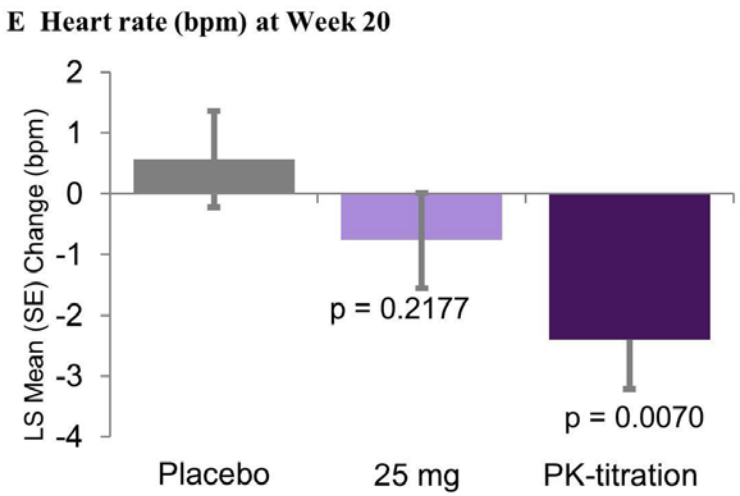


Figure 2: Efficacy Endpoints (continued)



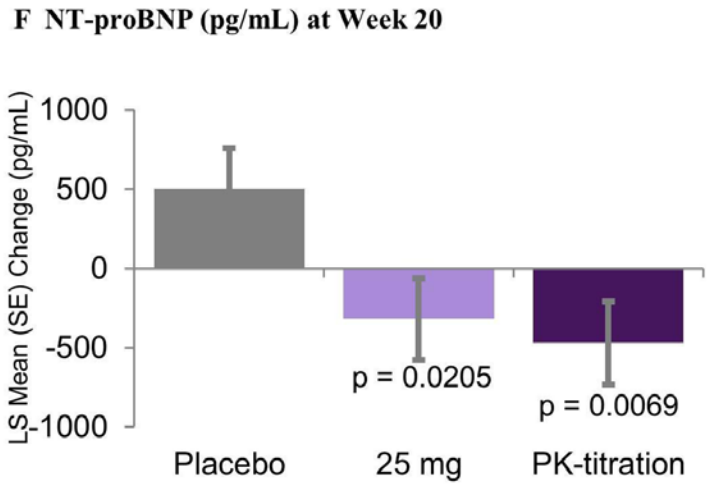
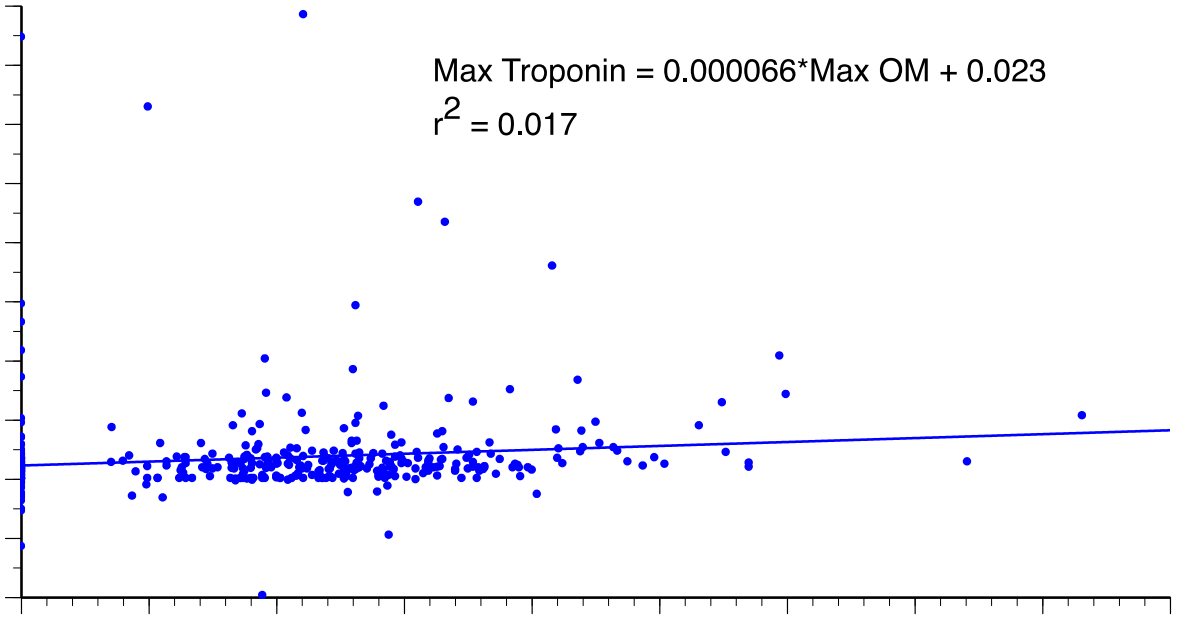


Figure 3: Maximum Change from Baseline in Troponin (µg/mL) by Maximum Concentration of Omecamtiv Mecarbil (ng/mL)



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