Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Effect of Omecamtiv Mecarbil on Exercise Capacity in Subjects with Heart Failure with Reduced Ejection Fraction and Decreased Exercise Tolerance

Product:	Omecamtiv Mecarbil [AMG 423
Protocol Number:	CY 1031
EudraCT Number:	2018-001233-40
Study Name:	**M**ulticenter **E**xercise **T**olerance **E**valuation of **O**mecamtiv Mecarbil **R**elated to **I**ncreased **C**ontractility in **H**eart **F**ailure (METEORIC-HF)
Study Sponsor:	
:	Cytokinetics, Inc. 280 East Grand Avenue South San Francisco, CA 94080 Telephone: 1-650-624-3000
Original Protocol Date:	16 July 2018
Amendment 1	31 July 2019
Amendment 2	31 July 2020
Amendment 3	30 June 2021

Study Identification

Sponsor

07/15/2021

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Investigator's Agreement

I have read the attached protocol entitled **A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Effect of Omecamtiv Mecarbil on Exercise Capacity in Subjects with Heart Failure with Reduced Ejection Fraction and Decreased Exercise Tolerance**, dated **30 June 2021**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub-investigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Cytokinetics.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Effect of Omecamtiv Mecarbil on Exercise Capacity in Subjects with Heart Failure with Reduced Ejection Fraction and Decreased Exercise Tolerance

Study Phase: 3
Indication: Heart failure with reduced ejection fraction (HFrEF)
Study Name: **M**ulticenter **E**xercise **T**olerance **E**valuation of **O**mecamtiv Mecarbil **R**elated to **I**ncreased **C**ontractility in **H**eart **F**ailure (METEORIC-HF)

Primary Objective:

- To evaluate the effect of treatment with omecamtiv mecarbil (OM) compared with placebo on exercise capacity as determined by cardiopulmonary exercise testing (CPET) following 20 weeks of treatment with OM or placebo

Secondary Objective:

- To evaluate the effect of treatment with OM compared with placebo on daily activity as determined by accelerometry

Exploratory Objective:

- To evaluate the relationships between exercise capacity (determined by CPET), daily activity (determined by accelerometry), and symptoms (determined by Kansas City Cardiomyopathy Questionnaire [KCCQ])

Safety Objective:

- To evaluate the safety and tolerability of OM compared with placebo, as measured by subject incidence of reported adverse events

Primary Endpoint:

- Change in peak oxygen uptake (pVO_2) on CPET from baseline to Week 20

Secondary Endpoints:

- Change in total workload during CPET from baseline to Week 20
- Change in ventilatory efficiency (VE/VCO_2 slope) during CPET from baseline to Week 20
- Change in the average daily activity units measured over a 2-week period from baseline to Week 18-20

Exploratory Endpoints:

- Change from baseline to Week 20 in oxygen uptake efficiency slope (VO_2/logVE slope), ventilatory threshold (by the V-slope method), VO_2 recovery kinetics, percent predicted pVO_2, circulatory power (VO_2 × systolic blood pressure [BP]), and exercise duration
- Change from baseline in the average daily activity units at Week 6-8 and at Week 12-14
- Change from baseline in the KCCQ Total Symptom Score and its sub-domains from baseline to Week 20

Safety Endpoint:

- Subject incidence of reported adverse events and serious adverse events. Major adverse cardiovascular (CV) events will be adjudicated by a clinical events committee (CEC), including: all-cause death, CV death, major cardiac ischemic events (myocardial infarction, hospitalization for unstable angina, percutaneous coronary intervention and coronary artery bypass graft), heart failure (HF) events and stroke.

Study Design:

This is a randomized, placebo-controlled, double-blind, parallel group, multicenter study in subjects with heart failure with reduced ejection fraction (HFrEF). Approximately 270 eligible subjects will be randomized in a 2:1 ratio to receive either OM or placebo, respectively. Randomization will be stratified based on the respiratory exchange ratio (RER) on the baseline CPET (<1.15, ≥1.15) and persistent atrial fibrillation at screening (Y/N). The number of patients with persistent atrial fibrillation at screening will be capped at approximately 20% and patients with paroxysmal atrial fibrillation will be excluded. Investigational product (IP) will be started at 25 mg orally (PO) twice a day (BID), titrated based on the Week 2 and Week 6 predose plasma concentrations to doses of 25, 37.5, or 50 mg BID and continued for a total of 20 weeks. In instances where a subject cannot complete the Week 20 CPET as planned due to COVID-19, those subjects may continue on IP until the visit can be completed for up to an additional 12 weeks (total of up to 32 weeks on IP), and only after approval from the medical monitor. Additionally, the investigator should attempt to complete the Week 20 visit with the CPET as close as safely possible to the originally planned date (Appendix D). All subjects will be managed with standard of care (SoC) HF therapies consistent with regional clinical practice guidelines.

Inclusion Criteria:

101. Subject has provided informed consent
102. Male or female, ≥ 18 to ≤ 85 years of age at signing of the informed consent form (ICF)
103. History of chronic HF, defined as requiring continuous treatment with medications for HF for a minimum of 3 months before screening
104. New York Heart Association (NYHA) class II or III at screening
105. Left ventricular ejection fraction (LVEF) ≤ 35%, per subject's most recent medical record or an echocardiogram at screening. The qualifying LVEF must be the most recent assessment of LVEF in the chronic, stable setting and must be within 12 months prior to screening.
106. On maximally tolerated SoC HF therapies consistent with regional clinical practice guidelines, if not contraindicated and according to investigator judgment of the subject's clinical status. Beta blocker dose must be stable for 30 days prior to randomization.
107. N-terminal prohormone- brain natriuretic peptide (NT-proBNP) level ≥ 200 pg/mL at screening assessment by the central laboratory.
108. Peak VO_2 ≤ 75% of the predicted normal value with RER ≥ 1.05 on the screening (Week -2) CPET, confirmed by CPET core laboratory.
109. Satisfied all Screening assessments, including at least 7 days of the Screening actigraphy wear period (see Section 7.2.1).

Exclusion Criteria:

Concomitant diseases or conditions

201. Severe uncorrected valvular heart disease
202. Paroxysmal atrial fibrillation or flutter documented within the previous 6 months prior to randomization requiring treatment (e.g., anti-coagulation or antiarrhythmic therapy),

direct current (DC) cardioversion or ablation procedure for atrial fibrillation within 6 months, or plan to attempt to restore sinus rhythm (with drug therapy, ablation, or DC cardioversion) within 6 months of randomization. Subjects with persistent atrial fibrillation and no sinus rhythm documented in the prior 6 months are permitted.

203. Untreated severe ventricular arrhythmias
204. Symptomatic bradycardia, second-degree Mobitz type II, or third-degree heart block without a pacemaker
205. Recipient of a major organ transplant (e.g., heart, lung, liver, bone marrow, renal) or ventricular assist device, or anticipated transplantation or chronic mechanical circulatory support within 12 months from randomization
206. Malignancy within 5 years prior to randomization with the following exceptions: localized basal or squamous cell carcinoma of the skin, cervical intraepithelial neoplasia, stage 1 prostate carcinoma, breast ductal carcinoma in situ
207. Known sensitivity to any of the products or components to be administered during dosing
208. History of gastrointestinal bleeding requiring hospitalization, urgent procedure or transfusion in the prior year, or received intravenous (IV) iron, blood transfusion, or an erythropoiesis-stimulating agent (ESA) within 3 months prior to screening, or planned blood transfusion or ESA use during the study screening or treatment period. Chronic, stable use of oral iron is permitted.
209. Ongoing or planned enrollment in cardiac rehabilitation
210. Requires assistance to walk or use of mobility assistive devices such as motorized devices, wheelchairs, or walkers. The use of canes for stability while ambulating is acceptable if the subject is deemed capable of performing CPET.
211. Clinically significant comorbid disease, disorder, condition or behavioral or other limitation (including ongoing substance abuse) that, in the opinion of the investigator or medical monitor, if consulted, is expected to:
    - Reduce life expectancy to < 2 years
    - Pose a risk to subject safety by participating in the study
    - Substantially limit exercise testing
    - Interfere with study evaluation, procedures, compliance (including study medication and procedures) or completion

Recent or planned medical events

212. Major medical event or procedure within 3 months prior to randomization, including hospitalization, surgery, renal replacement therapy or cardiac procedure. This includes episodes of decompensated HF that require IV HF treatment. Minor hospitalizations or procedures that are not expected to impact the safety of the subject or the integrity of the study results, per investigator, are allowed.
213. Scheduled major surgery or procedure in the next 6 months. Minor surgeries or procedures that are not expected to impact the safety of the subject, the ability to perform CPET, or the integrity of the study results are allowed.

*Screening assessments **

214. Resting systolic BP > 140 mmHg or < 85 mmHg, or diastolic BP > 90 mmHg (mean of triplicate readings) at screening
215. Resting heart rate > 90 beats per minute, or < 50 beats per minute (mean of triplicate readings) at screening

216. Room air oxygen saturation < 90% at screening
217. Hemoglobin <10.0 g/dL at screening
218. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 (by the modified Modification of Diet in Renal Disease equation) at screening
219. Hepatic impairment defined by a total bilirubin (TBL) ≥ 2 × the upper limit of normal (ULN), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3×ULN at screening. Patients with documented Gilbert syndrome and TBL ≥ 2×ULN due to unconjugated hyperbilirubinemia, without other hepatic impairment, are permitted.

* Vital signs, hemoglobin, and liver function test screening assessments may be repeated once and the new results used to determine eligibility in some cases (see Section 7.2.2).

Screening CPET

220. Significant adverse finding (e.g., exercise-induced early ischemic changes, abnormal decrease in BP [systolic BP falls by more than 10 mmHg], unexpected arrhythmia or other serious finding) during CPET at screening that precludes safe participation in the study, per investigator
221. Chronotropic incompetence (including inadequate pacemaker rate response) during CPET at screening, defined as a maximum heart rate <55% of the maximum predicted heart rate

Prior investigational studies

222. Previous or current participation in a study of OM
223. Currently participating in another investigational device or drug study, or received an investigational device or drug < 1 month (or 5 half-lives for drugs, whichever is longer) prior to screening. Other investigational procedures while participating in this study are not permitted.

Pregnancy

224. Male subject with a female partner of childbearing potential and not willing to inform his partner of his participation in this clinical study.
225. Female subject is pregnant or breastfeeding or is planning to become pregnant or planning to breastfeed during treatment with IP (OM or placebo) or within 5 days after the end of treatment with IP.
226. Female subject of childbearing potential who does not practice true sexual abstinence (the reliability of sexual abstinence must be evaluated by the investigator and be the preferred and usual lifestyle of the subject) **AND** not willing to inform her partner of her participation in this clinical study or use 2 acceptable methods of effective birth control during treatment with IP (OM or placebo) and for an additional 5 days after the last dose of IP. If the female subject or her sole male partner has had a surgical contraceptive method (bilateral tubal ligation/occlusion or vasectomy with medical assessment of surgical success), additional contraceptive methods are not required.

    - A female is considered of childbearing potential unless she has had a hysterectomy, bilateral oophorectomy, or bilateral salpingectomy or she is postmenopausal. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Females on HRT and whose menopausal status is in doubt will be required to use 2 of the non-hormonal acceptable methods of

effective contraception if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

- Two acceptable methods of effective birth control include the following options:
  - intrauterine device (IUD) and a barrier method with spermicide, IUD and a hormonal birth control method, hormonal birth control method and a barrier method with spermicide, intrauterine hormonal-releasing system (IUS) and a barrier method with spermicide,
  - 2 barrier methods (each partner must use 1 barrier method except a female condom) and the female partner must also use spermicide (a male and female condom may not be used together due to the risk of tearing)
- Hormonal methods of birth control include oral, intravaginal, transdermal, injectable, or implantable. Barrier methods of birth control include diaphragm with spermicide, cervical cap with spermicide, male or female condom with spermicide, and contraceptive sponge with spermicide. If spermicide is not commercially available in the local country/region a barrier method without spermicide is acceptable.
  - Note: If additional medications (including SoC HF therapies) are given during treatment, the investigator is to review the prescribing information/summary of product characteristics (SmPC) for all concomitant therapy, as they may alter the contraceptive requirements. These additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized after the last dose of protocol-required therapies. The investigator is to discuss these changes with the study subject.

Subjects who do not meet all eligibility criteria at their Initial Screening Visit may be rescreened (see Section 7.2.3). If a subject fails screening due to disruptions in study conduct because of COVID-19, then an additional rescreening may be included (one Initial Screening visit and up to two re-screenings in this instance only). This must also be approved by the Medical Monitor prior to the second rescreening. Rescreened subjects must first be registered as screen failed in the interactive web response system (IWRS) and subsequently registered as rescreened. Subjects will maintain the originally assigned subject identification number. For rescreening, a new ICF must be signed. Rescreened subjects will repeat all screening procedures.

Investigational Product Dosage and Administration:

OM or placebo will be administered PO BID (approximately 12 ± 3 hours apart) in the morning and evening and can be taken under fasted or fed conditions. Subjects randomized to OM will initiate administration at 25 mg BID. Blood samples will be collected at study visits on Weeks 2, 6, and 20 from all subjects to determine the predose OM plasma concentration. The results will be blinded to investigators, Cytokinetics and study subjects. For subjects randomized to OM, the Week 2 predose OM plasma concentration (steady-state for the initial 25 mg BID dose) will guide a dose adjustment at Week 4, as below, and subjects will continue the adjusted OM dose for the remainder of the study (Appendix B). For subjects who are randomized to placebo, identical blood samples will be collected to maintain study blinding. A new IP supply will be provided to all subjects per protocol, regardless of randomized treatment group and result of the OM plasma concentration assessment, to maintain the blind.

If normal site procedures are disrupted due to COVID-19, sites may need to institute alternate means of IP dispensing. Sites may provide IP to the patient either directly at the study site or have IP shipped to the patient if permitted locally and approved by the Sponsor.

For subjects randomized to OM, the predose plasma concentration at Week 2 will guide the dose adjustment at the Week 4 visit as follows:

- Subjects with plasma concentration < 200 ng/mL will have their dose increased to 50 mg BID.
- Subjects with plasma concentration ≥ 200 and < 300 ng/mL will have their dose increased to 37.5 mg BID.
- Subjects with plasma concentration ≥ 300 and < 1000 ng/mL will maintain their dose of 25 mg BID.
- Subjects with plasma concentration ≥ 1000 ng/mL will start administration of placebo BID.

Study Duration for Subjects:

After signing the ICF, subjects should be randomized within 6 weeks. The length of treatment is approximately 20 weeks, but may be up to 32 weeks in the case of disruptions to study conduct due to COVID-19 only after approval by the medical monitor (Appendix D) and follow-up is 4 weeks. Therefore, the duration of the study for an individual subject will be approximately 26 to 42 weeks, depending on the time spent in screening and whether COVID-19 has impacted the timing of the subject's Week 20 visit.

All subjects will be followed according to the Schedule of Assessments from randomization through the date of their final visit irrespective of whether the subject is continuing to receive study treatment, unless the subject has discontinued prematurely from the study or withdrawn consent. An early termination visit will be performed for subjects that discontinue prematurely from the study. Adverse events observed by the investigator or reported by the subject will be collected through the End of Study visit or 30 days after the last dose of IP, whichever is later.

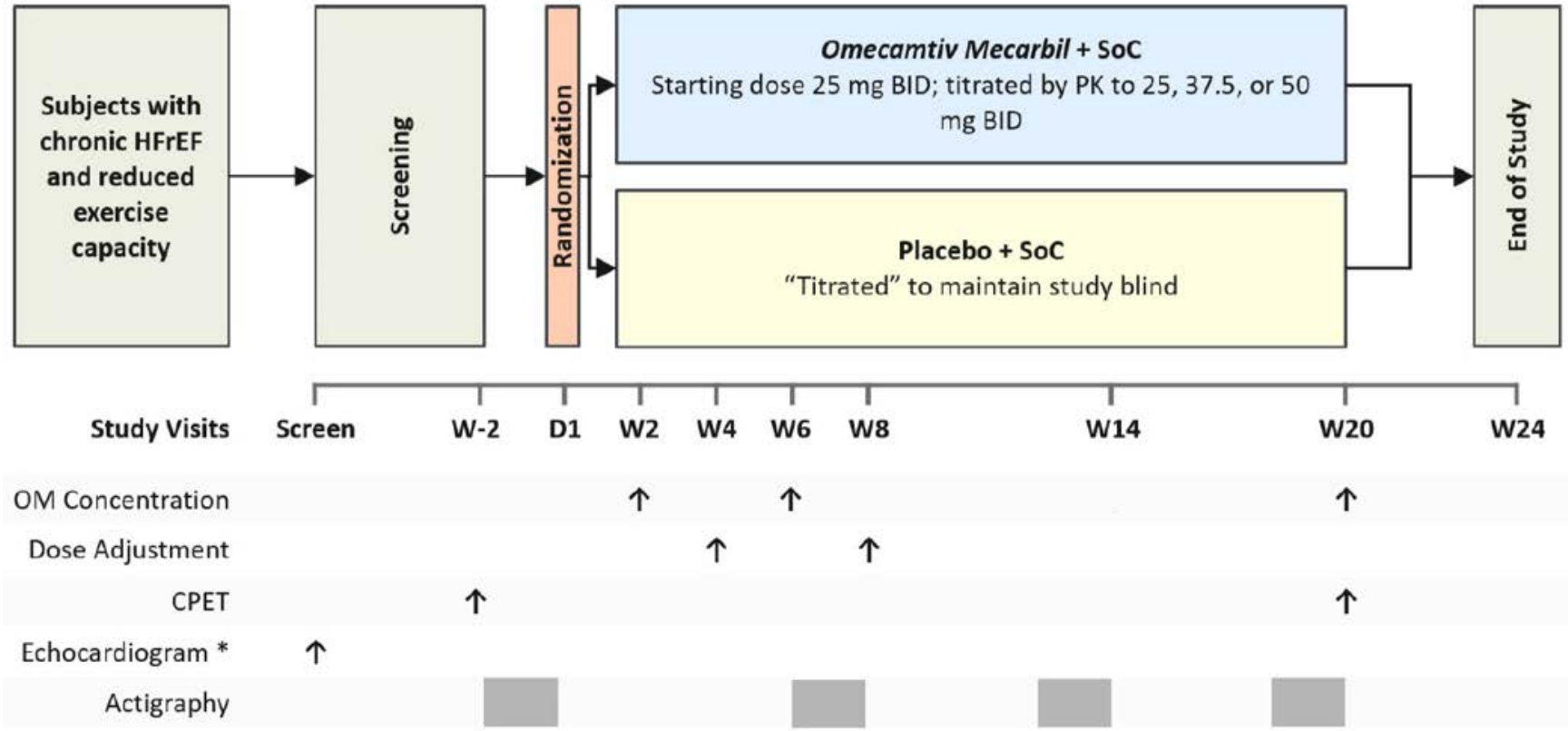
Statistical Considerations:

Sample Size Calculation: Assuming a difference in change from baseline in pVO_2 of 1.0 mL/kg/min for OM compared to placebo, a standard deviation (SD) of 2.5 mL/kg/min in subjects receiving OM and 2.0 mL/kg/min in subjects receiving placebo, and 15% of subjects missing change from baseline data of the primary endpoint, a sample size of 270 subjects (approximately 180 randomized to OM and 90 randomized to placebo) provides 90% power to detect the difference in pVO_2 change from baseline to Week 20 with a 2-sided type I error of 0.05.

Cytokinetics will periodically assess in a blinded fashion the overall pooled SD and missing data rate for the change from baseline in pVO_2 at Week 20. Shortly before enrollment reaches 270 subjects, if the pooled SD or missing data rate of all patients is larger than expected, if a significant amount of subjects (>10%) completed the Week 20 CPET beyond the initially planned Week 20 window as a result of COVID-19, or if the total number of Week 20 CPET data points in subjects with important protocol deviations (per Protocol Amendment 1) due to COVID-19 is > 10% of the total number of randomized subjects, then a one-time consideration may be given to increasing the sample size up to a maximum of 400 randomized patients, in order to maintain 90% power to detect a difference in pVO_2 of 1.0 mL/kg/min.

Unless specified otherwise, efficacy analyses will be performed on the full analysis set (FAS), which includes all randomized subjects who receive at least one dose of randomized study medication, by randomized treatment group. The primary analysis is to test the null hypothesis that there is no treatment difference in the change from baseline in pVO_2 at Week 20 between subjects randomized to placebo and those randomized to OM in the FAS during the placebo-controlled double-blind treatment. As will be detailed in the statistical analysis plan, the analysis will be performed using an analysis of covariance (ANCOVA) model which will include terms of treatment, baseline pVO_2, RER randomization stratum (< 1.15, ≥ 1.15), persistent atrial fibrillation (Y/N), age, sex, and baseline hemoglobin level. The safety analyses will be performed on the safety analysis set, which includes all dosed subjects.

Study Design and Treatment Schema



* Screening echocardiogram is not required if an LVEF assessment performed within 12 months meets the inclusion criteria

BID = twice a day; CPET = cardiopulmonary exercise testing; HFrEF = heart failure with reduced ejection fraction; OM = omecamtiv mecarbil; SoC = standard of care

Shaded boxes indicate actigraphy assessment periods (2 weeks each).

Study Glossary

Abbreviation or Term	Definition/Explanation
ACEi	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
ARNi	angiotensin receptor neprilysin inhibitor
AST	aspartate aminotransferase
BID	twice a day
BNP	B-type natriuretic peptide
BP	blood pressure
CEC	Clinical Events Committee
CK-MB	creatine kinase-MB
COVID-19	Coronavirus disease 2019
CPET	cardiopulmonary exercise testing
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CYP	cytochrome P450
DC	direct-current
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ESA	erythropoiesis stimulating agent
EOS	end of study
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HRT	hormonal replacement therapy

Abbreviation or Term	Definition/Explanation
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
IV	intravenous
IWRS	interactive web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	left ventricular ejection fraction
MRA	mineralocorticoid receptor antagonist
NT-proBNP	N-terminal-prohormone brain natriuretic peptide
NYHA	New York Heart Association
OM	omecamtiv mecarbil
PO	orally
pVO_2	peak oxygen uptake
RER	respiratory exchange ratio
SAP	statistical analysis plan
SAS	safety analysis set
SC	steering committee
SD	standard deviation
SoC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
ULN	upper limit of normal
US	United States
VE/VCO_2	ventilatory efficiency
VO_2	oxygen uptake

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1. OBJECTIVES

1.1 Primary

- To evaluate the effect of treatment with omecamtiv mecarbil (OM) compared with placebo on exercise capacity as determined by cardiopulmonary exercise testing (CPET) following 20 weeks of treatment with OM or placebo

1.2 Secondary

- To evaluate the effect of treatment with OM compared with placebo on daily activity as determined by accelerometry

1.3 Exploratory

- To evaluate the relationships between exercise capacity (determined by CPET), daily activity (determined by accelerometry), and symptoms (determined by the Kansas City Cardiomyopathy Questionnaire [KCCQ])

1.4 Safety

- To evaluate the safety and tolerability of OM compared with placebo, as measured by subject incidence of reported adverse events

2. BACKGROUND AND RATIONALE

2.1 Disease

Heart failure (HF) affects over 26 million people worldwide, with more than 3.5 million people newly diagnosed every year, and is a final pathway for many diseases that affect the heart (Hilfiker-Kleiner et al, 2006). Symptoms of dyspnea, fatigue, increased need to rest, low energy, and difficulty in walking or climbing, correlate with lower quality of life and higher mortality risk (Heo, 2008; Flynn, 2009; Malhotra, 2016; Swank, 2012).

Exercise intolerance, typically manifest by dyspnea and fatigue on exertion, is the predominant chronic symptom of HF and often the first symptom that prompts patients to seek medical care. Assessment of exercise capacity in daily life is widely used to classify the severity of HF, for example the New York Heart Association (NYHA) functional classification and the Canadian Cardiovascular Society functional classification. These assessments are highly prognostic of long-term outcomes. Even small improvements in exercise capacity as measured by CPET correlate with improved survival (Swank, 2012).

Few therapies have demonstrated improvements in exercise capacity. For example, the effect of carvedilol on exercise capacity has been studied in heart failure with reduced ejection fraction (HFrEF) with no improvement seen following 12 months of therapy (Australia/New Zealand Heart Failure Research Collaborative Group, 1997). Currently,

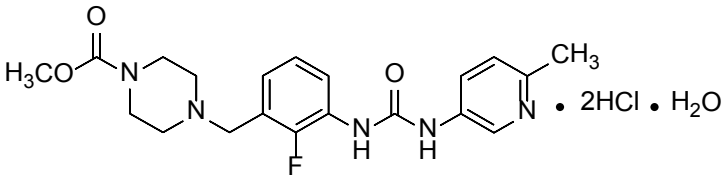
only angiotensin-converting-enzyme inhibitors (ACEis) have product labels that describe a positive effect on exercise capacity in patients with HFrEF.

This study will test the hypothesis that improving cardiac function with the cardiac myosin activator, OM, a drug therapy that directly increases myocardial contractility, will improve exercise tolerance.

2.2 Investigational Product Background

The molecular formula of OM is $C_{20}H_{24}FN_5O_3 \cdot 2HCl \cdot H_2O$ and the chemical structure is provided in Figure 1.

Figure 1. Chemical Structure of Omecamtiv Mecarbil



OM (CK-1827452) is a novel small molecule classified as a cardiac myosin activator that increases cardiac contractility by selectively and directly activating the enzymatic domain of the cardiac myosin heavy chain, the force-generating motor protein of the cardiac sarcomere, without increasing cardiac myocyte intracellular calcium (Malik et al, 2011). OM stabilizes the lever arm of myosin in a primed position prior to contraction, increasing the number of myosin molecules able to bind actin and generate force when systole starts (Planelles-Herrero, 2017). OM increases the left ventricular systolic ejection time without changing the velocity of contraction (dP/dt) or increasing the heart rate. Additionally, in preclinical models, left ventricular filling pressures, left atrial pressures, and total peripheral vascular resistance decreased, providing evidence that prolongation of systolic ejection time and increased systolic function can favorably impact the hemodynamics that drive HF symptoms. The salutary effects of OM were achieved without noticeable effect upon myocardial oxygen uptake, blood pressure (BP), or coronary blood flow (Shen et al, 2010; Malik et al, 2011).

2.2.1 Clinical Experience

OM has been evaluated in 10 phase 1 studies (Studies CY 1011, CY 1013, CY 1015, CY 1016, CY 1111, CY 1211 [20120255], 20080676, 20090229, 20090727, and 20150134), 4 phase 2a studies in subjects with chronic HF (Studies CY 1121, CY 1221, CY 1124, and CY 1021), 1 phase 2b study in subjects with acutely decompensated

HFrEF (Study 20100754), and 2 phase 2b studies in subjects with HFrEF (Studies 20110151 and 20120227). In these studies, the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of OM were evaluated with intravenous (IV) infusions up to 72 hours and oral dosing up to 20 weeks. Information on these studies is in the Investigator Brochure. A phase 3 study, Study 20110203 (GALACTIC-HF), was ongoing at the start of CY 1031 and is intended to assess the efficacy and safety of OM on mortality and morbidity in approximately 8000 subjects with chronic HFrEF receiving standard of care (SoC) therapy. Study 20110203 is now complete and an overview of the results can be found in Section 2.3.

2.2.2 Phase 3 Outcomes Study in Patients with Heart Failure

The clinical program includes the ongoing Phase 3 study (Study 20110203, GALACTICHF; EudraCT number 2016-002299-28), a double-blind, randomized, placebo-controlled, multi-center study to assess the efficacy and safety of OM on mortality and morbidity in subjects with HFrEF. The primary objective is to evaluate the effect of treatment with OM compared with placebo on the time to cardiovascular (CV) death or first HF event, whichever occurs first, in subjects with chronic HFrEF receiving SoC therapy. Secondary objectives are to evaluate the effects of OM on time to CV death; time to HF hospitalization; time to all-cause death; and change in patient-reported outcomes. The study is event-driven and will conclude when approximately 1590 CV death events have occurred. 8256 eligible subjects are randomized in a 1:1 ratio to receive either OM or placebo. The OM dosing regimen is a PK based titration scheme. All subjects were managed with SoC therapies consistent with regional clinical practice guidelines. Approximately 25% or more of the total planned enrollment include subjects who are hospitalized for HF at randomization. An external independent Data Monitoring Committee (DMC) formally reviews the accumulating data from this study to ensure there is no avoidable increased risk for harm to subjects and conducts interim analyses for futility and efficacy.

2.2.3 Dose Selection for Phase 3

The OM dosing regimen selected for this study is identical to that in Study 20110203 and is a PK based titration scheme with three dose levels based on subjects' OM plasma concentration at Week 2. All subjects will receive 25 mg orally (PO) twice a day (BID) at the initiation of treatment. At study visit Week 2 (PK steady-state for initial dose), a predose PK sample will be collected. At Week 4, subjects with Week 2 OM predose

plasma concentrations < 200 ng/mL will have their dose increased to 50 mg BID; subjects with Week 2 predose plasma concentrations ≥ 200 and < 300 ng/mL will have their dose increased to 37.5 mg BID, subjects with Week 2 predose plasma concentrations ≥ 300 ng/mL and < 1000 ng/mL will maintain a 25 mg BID dosing regimen, and subjects with plasma concentration ≥ 1000 ng/mL will stop OM and start administration of placebo BID. All dose adjustments will be done in blinded fashion. PK-based dose adjustment in this study will be used to attain effective steady state concentrations while maintaining OM plasma concentrations < 1000 ng/mL. Please refer to Appendix B for further information on dose adjustment.

Refer to the Investigator's Brochure for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s) of OM.

2.3 Benefit/Risk Assessment

The following benefit-risk assessment supports the conduct of this clinical study. Reference should be made to the Investigator's Brochure for further data on OM.

2.3.1 Benefits

The primary evidence of potential benefit in subjects with chronic HF comes from Study. 20110203 (GALACTIC-HF) which was a Phase 3 randomized, placebo-controlled, double-blind, parallel-group, multicenter study designed to evaluate the effect of OM, when administered with optimized SoC HF therapies, on CV outcomes in subjects with HFrEF. This study included subjects currently hospitalized for HF or with a history of HF hospitalization or ED visit within 1 year prior to enrollment. When used with current SoC treatments, OM when compared with placebo resulted in a statistically significant risk reduction of the primary composite endpoint of CV death or HF events, which was driven by the reduction in HF events. Overall incidences of adverse events similar to placebo, including ventricular arrhythmias and adjudicated myocardial ischemic events and there were no adverse effects on blood pressure, heart rate, creatinine, potassium, or liver function. The prespecified PK-based dose selection strategy, the same strategy being used in METEORIC-HF, successfully prevented excessive exposures to OM and resulted in the majority of study subjects being assigned to the 50 mg BID dose.

Mortality and morbidity for patients with symptomatic HF remains high with half of the patients dying within 4 years, and in patients with severe disease, more than half dying within 1 year (Swedberg et al, 2005). The findings in Study 20110151 suggest that OM improves cardiac function leading to decreases in cardiac volumes and NT-proBNP. Decreases in cardiac volumes and NT-proBNP are correlated with improvements in clinical outcomes (Kramer et al, 2010; Zile et al, 2016). Thus, the data from Study 20110151 are supportive of a potential clinical benefit of OM on clinical outcomes. A phase 3 cardiovascular outcomes study (Study 20110203) in 8256subjects with a history of chronic HFrEF to assess the effect of OM on HF events, symptoms, and cardiovascular mortality recently completed. No new safety issues were identified in this study.

Besides excess mortality and morbidity, patients with HFrEF commonly suffer from physical limitation and exercise intolerance on a daily basis, due in large part to insufficient cardiac output. Although several therapeutic modalities have reduced mortality and HF events, almost none have been shown to improve exercise capacity. By directly activating myosin to increase cardiac contraction and increasing cardiac function, as shown in Study 20110151, OM may provide a therapeutic approach to improve exercise capacity which would provide a benefit to patients with HFrEF.

2.3.2 Key Risks

Myocardial ischemia and infarction have been observed in healthy subjects and patients with HF, and are identified risks of OM. Excessive exposure to OM may result in prolongation of the systolic ejection time to an extent that reduces diastolic coronary blood flow. The reduced coronary blood flow could precipitate myocardial ischemia or infarction. Signs and symptoms of myocardial ischemia or infarction can include but are not limited to electrocardiographic changes consistent with myocardial ischemia (ST-segment depression), angina, chest or throat tightness, palpitations and/or tachycardia, lightheadedness, dizziness, hypotension, dyspnea, premature ventricular contractions, and troponin elevation.

Steps have been taken to mitigate the risk of myocardial ischemia or infarction to subjects during the study. These include a PK-based dose adjustment (piloted in the Phase 2b study 20110151, and verified in the Phase 3 study 20110203) in patients with chronic HF) employed in this trial (see Section 6.2.1.2 and Appendix B for details of the PK-based dose adjustment).; the utilization of an oral modified release formulation; and

educating investigators on how to minimize the risk by describing the risk, providing information about myocardial ischemia and infarction symptoms and actions that should be taken in the events that such symptoms are experienced, and providing administration instructions for OM to reduce the risk of excessive exposure. Safety assessments include adverse event monitoring, electrocardiograms (ECGs), clinical examination, vital signs, and clinical chemistry including assessments for myocardial injury. In addition, an independent and external data monitoring committee has been established to monitor safety and tolerability.

2.4 Clinical Hypotheses

The primary hypothesis is that when added to SoC, OM is superior to placebo in improving exercise capacity in subjects with chronic HFrEF and is well tolerated. An additional hypothesis is that OM increases daily activity, compared to placebo.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a randomized, placebo-controlled, double-blind, parallel group, multicenter study in subjects with HFrEF. Approximately 270 eligible subjects will be randomized in a 2:1 ratio to receive either OM or placebo, respectively. Randomization will be stratified based on the respiratory exchange ratio (RER) achieved during the baseline CPET (<1.15, ≥1.15) and persistent atrial fibrillation at screening (Y/N). The number of patients with persistent atrial fibrillation at screening will be capped at approximately 20% and patients with paroxysmal atrial fibrillation will be excluded. OM will be started at 25 mg PO BID, titrated based on the Week 2 and Week 6 predose plasma concentrations to doses of 25, 37.5, or 50 mg BID and continued for a total of 20 weeks. In instances where a subject cannot complete the Week 20 CPET as planned due to COVID-19, those subjects may continue on IP until the visit can be completed for up to an additional 12 weeks (total of up to 32 weeks on IP), and only after approval from the medical monitor. Additionally, the investigator should attempt to complete the Week 20 visit with the CPET as close as safely possible to the originally planned date (Appendix D). All subjects should be managed with maximally tolerated SoC therapies for HF consistent with regional clinical practice guidelines.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

Approximately 90 sites globally will participate in this study.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects.”

Approximately 270 subjects will be randomized. The number of subjects randomized may increase during the conduct of the study, up to a maximum of 400 subjects, based on the results of blinded analysis of the aggregate pooled missing data rate and overall pooled standard deviation (SD) for the change in peak oxygen uptake (pVO_2) at Week 20 (Section 10.2).

3.4 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

After signing the informed consent form (ICF), subjects should be randomized within 6 weeks. The length of treatment is 20 weeks and follow-up is 4 weeks. Therefore, the duration of the study for an individual subject will be 26 to 30 weeks, depending on the time spent in screening. While the intended maximal length of the study is 30 weeks, in the event that COVID-19 impacts the ability to conduct the Week 20 visit, there may be instances, and only after approval from the medical monitor, when subjects may remain on IP for up to 32 weeks (please refer to Appendix D for guidance). In this instance, the maximum study duration will be 38 to 42 weeks.

All subjects will be followed according to the Schedule of Assessments from randomization through the date of their final visit irrespective of whether the subject is continuing to receive study treatment, unless the subject has discontinued prematurely from the study or withdrawn consent. An early termination visit will be performed for subjects that discontinue prematurely from the study.

3.5.2 End of Study

Primary Completion: The primary completion is the date when the last subject is assessed or receives an intervention for the collection of the primary endpoint (i.e., last subject Week 20 visit), for the purposes of conducting the primary analysis, whether the study concluded according to the prespecified protocol or was terminated.

End of Study: The end of study (EOS) is when the last subject has completed the EOS assessments (i.e., last subject last visit). If the study concludes prior to the time point originally planned in the protocol (i.e., early termination of the study), then the EOS will be the date when the last subject is assessed or receives an intervention for evaluation in the study.

3.6 Study Organization

The study organization will include an independent DMC, steering committee (SC), clinical events committee (CEC) and CPET core laboratory.

An external independent DMC will be established to formally review the accumulating data from this study to ensure there is no avoidable increased risk for harm to subjects. The independent DMC members will have access to treatment assignments and subject level data from the clinical trial database.

A SC will contribute to trial design, implementation, data analysis, and communication of trial results and will consist of experts external to Cytokinetics who are qualified by their medical and scientific expertise and experience. The responsibilities of the SC are described in an SC charter.

An external independent CEC blinded to treatment assignment will adjudicate all major CV adverse events using standardized definitions, including all-cause death, CV death, major cardiac ischemic events (myocardial infarction, hospitalization for unstable angina, percutaneous coronary intervention and coronary artery bypass graft), HF events and stroke.

An external independent CPET core laboratory blinded to treatment assignment will assess all CPET data and determine the final results to be used for subject eligibility and study endpoints. The CPET core laboratory will also qualify study sites.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (e.g., date of screening). Before any study-specific activity/procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

101. Subject has provided informed consent
102. Male or female, ≥ 18 to ≤ 85 years of age at signing of the ICF
103. History of chronic HF, defined as requiring continuous treatment with medications for HF for a minimum of 3 months before screening
104. NYHA class II or III at screening
105. Left ventricular ejection fraction (LVEF) ≤ 35%, per subject's most recent medical record or an echocardiogram at screening. The qualifying LVEF must be the most recent assessment of LVEF in the chronic, stable setting and must be within 12 months prior to screening.
106. On maximally tolerated HF SoC therapies consistent with regional clinical practice guidelines, if not contraindicated and according to investigator judgment of the subject's clinical status. Beta blocker dose must be stable for 30 days prior to randomization.
107. N-terminal prohormone- brain natriuretic peptide (NT-proBNP) level ≥ 200 pg/mL at screening assessment by the central laboratory.
108. Peak VO_2 ≤ 75% of the predicted normal value with RER ≥ 1.05 on the screening (Week -2) CPET, confirmed by CPET core laboratory
109. Satisfied all Screening assessments, including at least 7 days of the Screening actigraphy wear period (see Section 7.2.1)

4.1.2 Exclusion Criteria

Concomitant diseases or conditions

201. Severe uncorrected valvular heart disease
202. Paroxysmal atrial fibrillation or flutter documented within the previous 6 months (prior to screening or randomization) requiring treatment (e.g., anti-coagulation or antiarrhythmic therapy), direct-current (DC) cardioversion or ablation procedure for atrial fibrillation within 6 months, or plan to attempt to restore sinus rhythm (with drug therapy, ablation, or DC cardioversion) within 6 months of randomization. Subjects with persistent atrial fibrillation and no sinus rhythm documented in the prior 6 months are permitted.
203. Untreated severe ventricular arrhythmias
204. Symptomatic bradycardia, second-degree Mobitz type II, or third-degree heart block without a pacemaker
205. Recipient of a major organ transplant (e.g., heart, lung, liver, bone marrow, renal) or ventricular assist device, or anticipated transplantation or chronic mechanical circulatory support within 12 months from randomization
206. Malignancy within 5 years prior to randomization with the following exceptions: localized basal or squamous cell carcinoma of the skin, cervical intraepithelial neoplasia, stage 1 prostate carcinoma, breast ductal carcinoma in situ

207. Known sensitivity to any of the products or components to be administered during dosing
208. History of gastrointestinal bleeding requiring hospitalization, urgent procedure or transfusion in the prior year, or received IV iron, blood transfusion, or an erythropoiesis-stimulating agent (ESA) within 3 months prior to screening, or planned blood transfusion or ESA use during the study screening or treatment period. Chronic, stable use of oral iron is permitted.
209. Ongoing or planned enrollment in cardiac rehabilitation
210. Requires assistance to walk or use of mobility assistive devices such as motorized devices, wheelchairs, or walkers. The use of canes for stability while ambulating is acceptable if the subject is deemed capable of performing CPET.
211. Clinically significant comorbid disease, disorder, condition or behavioral or other limitation (including ongoing substance abuse) that, in the opinion of the investigator or medical monitor, if consulted, is expected to:
    - Reduce life expectancy to < 2 years
    - Pose a risk to subject safety by participating in the study
    - Substantially limit exercise testing
    - Interfere with study evaluation, procedures, compliance (including study medication and procedures) or completion

Recent or planned medical events

212. Major medical event or procedure within 3 months prior to randomization, including: hospitalization, surgery, renal replacement therapy or cardiac procedure. This includes episodes of decompensated HF that require IV HF treatment. Minor hospitalizations or procedures that are not covered above and not expected to impact the safety of the subject or the integrity of the study results, per investigator, are allowed.
213. Scheduled major surgery or procedure in the next 6 months. Minor surgeries or procedures that are not expected to impact the safety of the subject, the ability to perform CPET, or the integrity of the study results are allowed.

*Screening assessments **

214. Resting systolic BP > 140 mmHg or < 85 mmHg, or diastolic BP > 90 mmHg (mean of triplicate readings) at screening
215. Resting heart rate > 90 beats per minute, or < 50 beats per minute (mean of triplicate readings) at screening
216. Room air oxygen saturation < 90% at screening
217. Hemoglobin <10.0 g/dL at screening
218. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 (by the modified Modification of Diet in Renal Disease equation) at screening
219. Hepatic impairment defined by a total bilirubin (TBL) ≥ 2 × the upper limit of normal (ULN), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × ULN at screening. Patients with documented

Gilbert syndrome and TBL ≥ 2 × ULN due to unconjugated hyperbilirubinemia, without other hepatic impairment, are permitted.

* Vital signs, hemoglobin, NT-proBNP, liver function test screening assessments may be repeated once, and the new results used to determine eligibility in some cases (see Section 7.2.2).

Screening CPET

220. Significant adverse finding (e.g., exercise-induced early ischemic changes, abnormal decrease in BP [systolic BP falls by more than 10 mmHg], unexpected arrhythmia or other serious finding) during CPET at screening that precludes safe participation in the study, per investigator
221. Chronotropic incompetence (including inadequate pacemaker rate response) during CPET at screening, defined as a maximum heart rate <55% of the maximum predicted heart rate

Prior investigational studies

222. Previous or current participation in a study of OM
223. Currently participating in another investigational device or drug study, or received an investigational device or drug < 1 month (or 5 half-lives for drugs, whichever is longer) prior to screening. Other investigational procedures while participating in this study are not permitted.

Pregnancy

224. Male subject with a female partner of childbearing potential and not willing to inform his partner of his participation in this clinical study.
225. Female subject is pregnant or breastfeeding or is planning to become pregnant or planning to breastfeed during treatment with investigational product (IP; OM or placebo) or within 5 days after the end of treatment with IP.
226. Female subject of childbearing potential who does not practice true sexual abstinence (the reliability of sexual abstinence must be evaluated by the investigator and be the preferred and usual lifestyle of the subject) AND not willing to inform her partner of her participation in this clinical study or use 2 acceptable methods of effective birth control during treatment with IP (OM or placebo) and for an additional 5 days after the last dose of IP. If the female subject or her sole male partner has had a surgical contraceptive method (bilateral tubal ligation/occlusion or vasectomy with medical assessment of surgical success), additional contraceptive methods are not required.

    - A female is considered of childbearing potential unless she has had a hysterectomy, bilateral oophorectomy, or bilateral salpingectomy or she is postmenopausal. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Females on HRT and whose menopausal status is in doubt will be required

to use 2 of the non-hormonal acceptable methods of effective contraception if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

- Two acceptable methods of effective birth control include the following options:
  - intrauterine device (IUD) and a barrier method with spermicide, IUD and a hormonal birth control method, hormonal birth control method and a barrier method with spermicide, intrauterine hormonal-releasing system (IUS) and a barrier method with spermicide,
  - 2 barrier methods (each partner must use 1 barrier method except a female condom) and the female partner must also use spermicide (a male and female condom may not be used together due to the risk of tearing)
- Hormonal methods of birth control include oral, intravaginal, transdermal, injectable, or implantable. Barrier methods of birth control include diaphragm with spermicide, cervical cap with spermicide, male or female condom with spermicide, and contraceptive sponge with spermicide. If spermicide is not commercially available in the local country/region a barrier method without spermicide is acceptable.
  - Note: If additional medications (including SoC HF therapies) are given during treatment, the investigator is to review the prescribing information/summary of product characteristics (SmPC) for all concomitant therapy, as they may alter the contraceptive requirements. These additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized after the last dose of protocol-required therapies. The investigator is to discuss these changes with the study subject.

Subjects who do not meet all eligibility criteria on the first screening attempt may be rescreened once (a second rescreening is permitted after approval from the Medical Monitor and only in the case of disruptions to study conduct due to COVID-19), for the study (Section 7.2.3). Rescreen subjects must first be registered as screen failed in the interactive web response system (IWRS) and subsequently registered as rescreened. Subjects will maintain the originally assigned subject identification number. For rescreening, a new ICF must be signed. Rescreened subjects who are re-consented will repeat all screening procedures.

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Cytokinetics requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, ICF, and all other subject

information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the ICF before commencement of study-specific activities/procedures.

A subject is considered enrolled when the investigator receives all confirmatory laboratory and CPET screening data, determines that the subject has met all eligibility criteria, and the subject is randomized in the IWRS. Randomization should occur during the Day 1 visit. The investigator is to document the enrollment and date in the subject's medical record and in/on the electronic case report form (eCRF).

Each subject who enters into the screening period for the study (defined as the point at which the subject signs the ICF) receives a unique subject identification number. The subject identification number will be assigned by the IWRS. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

Up to 6 weeks is allowed for screening and subjects can be re-tested if necessary within that 6-week timeframe as detailed in Section 7.2.2. The time between the CPET at the pre-randomization visit and/or randomization will be not more than 3 weeks.

Subjects who do not meet all eligibility criteria on the first screening may be rescreened once (a second rescreening is permitted after approval from the Medical Monitor in the case of disruptions to study conduct due to COVID-19), for the study (see Section 7.2.3).

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

5.1 Randomization/Treatment Assignment

Subjects who meet the eligibility requirements will be randomly assigned to 1 of 2 treatment groups, OM or placebo, in a double-blind manner. Approximately 270 eligible subjects (which could increase up to 400 subjects [see Section 10.2]) will be randomized in a 2:1 ratio to receive either OM or placebo, respectively.

Randomization will be stratified based on the RER on the baseline CPET (< 1.15, ≥ 1.15) and persistent atrial fibrillation (Y/N). The number of patients with persistent atrial fibrillation will be capped at approximately 20%. Subjects can only be randomized once for this study.

Randomization will occur via an IWRS. The local randomization date and time will be documented in the subject's medical record and on the enrollment eCRF.

5.2 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation.

Whenever safe and appropriate, the investigator is strongly encouraged to contact the Medical Monitor before unblinding any subject's treatment assignment. Otherwise they must do so within one working day after the event.

Refer to the Pharmacy Manual for a description regarding how investigators will access treatment information via the IWRS, in the event that there is a need to break the blind.

6. TREATMENT PROCEDURES

6.1 Classification of Product

The IPs used in this study are: OM and matching placebo.

The Pharmacy Manual, a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of OM and placebo.

6.2 Investigational Product

6.2.1 OM and Placebo

OM and placebo will be manufactured and packaged by Amgen Inc. or designee. OM and placebo will be presented as identical tablets. Tablets will be packaged in 14-count blisters. Further details regarding IP storage condition, dispensation, packaging, labeling, and accounting procedures are outlined in the Pharmacy Manual.

6.2.1.1 Dosage, Administration, and Schedule

IP will be administered PO BID (approximately 12 ± 3 hours apart) in the morning and evening by the subjects and can be taken under fasted or fed conditions. IP must be swallowed whole (not chewed, crushed, or split) and taken with water as instructed in the Pharmacy Manual. Each morning and evening administration should be taken at approximately the same time of day. If IP cannot be taken or has not been taken within approximately 12 ± 3 hours from the most recent previous dose, the dose should be missed and the next dose should be taken at the regular time. On study visit days, the time of the dose may be shifted if needed (see Pharmacy Manual).

The amount returned, date dispensed, date returned, and box number of IP are to be recorded on each subject's eCRF.

Subjects randomized to OM will initiate administration at 25 mg BID in a blinded manner. The dose will be adjusted for some subjects based on the OM concentration in predose blood samples (Appendix B), which will be collected for all subjects. If either the Week 2 or Week 6 visit plasma OM concentration is missed, subjects randomized to active treatment will be maintained/returned to their starting dose (OM 25 mg BID).

The results will be blinded to investigators. A new IP supply will be provided to all subjects for the purpose of dose adjustment regardless of randomized treatment group and outcome of the PK assessment in order to maintain the blind.

Subjects randomized to placebo will receive placebo throughout the study and will perform all protocol procedures in order to maintain the blind for the treatment group allocation and IP dose. Subjects should continue to take IP through the morning of the Week 20 Visit.

If normal site procedures are disrupted due to COVID-19, sites may need to institute alternate means of IP dispensing. Sites may provide IP to the patient either directly at the study site or have IP shipped to the patient if permitted locally and approved by the Sponsor.

6.2.1.2 Dosage Adjustments and Missed Doses

All subjects will have predose blood samples to assess OM concentration collected at Week 2 and Week 6 in order to guide possible dose adjustments at Week 4 and Week 8, respectively. The Week 6 OM concentration will reflect the PK results of the previous adjustment. OM concentration will also be assessed at Week 20, but not as part of the PK-based dose adjustment approach (see below). If there are restrictions related to COVID-19, please refer to Appendix D for guidance.

All subjects will discontinue IP after the Week 20 visit. See Appendix B for a summary of dose adjustment rules.

A new IP supply will be provided to all subjects at the Week 4 and Week 8 study visits regardless of randomized treatment group and outcome of the PK assessment in order to maintain the blind. If the Week 2 PK value is not available in time for dose adjustment at Week 4, subjects randomized to OM will continue with the 25 mg BID dose assignment pending the Week 6 PK assessment. If the Week 6 PK value is not available

in time for the dose adjustment at Week 8, subjects randomized to OM will be assigned to the lower dosage regimen (25 mg BID).

In instances where a subject cannot complete the Week 20 CPET as planned due to COVID-19, the subject may continue on IP for up to an additional 12 weeks (up to a total of 32 weeks on study drug), and only after approval from the medical monitor. Additionally, the investigator should attempt to complete the Week 20 visit with the CPET as close as safely possible to the originally planned date. Only in this case, unscheduled visits will be done at 4-week intervals (i.e., temporally occurring at Weeks 20, 24, and 28) until the CPET is performed (designated "Week 20 Visit") to assess vital status, signs and symptoms of ACS, concomitant medications, adverse events, and any interval (such as hospitalizations, medication changes) events. These visits may be conducted remotely/via telephone (see Section 7.2.6). The IWRS will dispense an additional 4 weeks of IP at each visit.

Subjects randomized to placebo will receive placebo throughout the study but will undergo identical PK and resupply procedures.

If IP cannot be taken or has not been taken within approximately 12 ± 3 hours from the most recent previous dose, the dose should be missed and the next dose should be taken at the regular time. On study visit days, the time of the dose may be shifted if needed (see Pharmacy Manual). Subjects who have missed multiple doses of IP should be encouraged to resume BID dosing at the regular times, with no extra doses.

6.2.1.3 Rules for Withholding, Restarting and Permanent Discontinuation

If IP has been discontinued, it may be restarted if the investigator deems it safe and appropriate to do so and the subject and Medical Monitor agree. IP may not be restarted in this study if the subject has experienced:

- a suspected allergic reaction to IP
- certain types of hepatotoxicity (see Section 6.3)
- acute ST-segment elevation myocardial infarction regardless of relatedness to IP
- an acute cardiac ischemic event (e.g., unstable angina) suspected to be related to IP (as determined after IP has been discontinued and the event has resolved)
- pregnancy / lactation

A direct relationship has been observed between the plasma concentrations of OM and increases in systolic ejection time, stroke volume, and left ventricular function (Cleland et al, 2011; Teerlink et al, 2011). Excessive exposure to OM may result in signs

and symptoms of myocardial ischemia or infarction (e.g., increases in heart rate, dizziness, dyspnea, hypotension, chest discomfort or pain, ST-segment depression/elevation on ECG, and/or elevations in troponin I or T). No antidote to OM currently exists. In the event of an overdose, health care providers should be vigilant for signs and symptoms of myocardial ischemia. Standard medical therapies should be used to treat adverse signs or symptoms that do not promptly resolve with discontinuation of the IP.

If a subject experiences clinical signs or symptoms consistent with acute myocardial ischemia or infarction, the subject should receive immediate medical attention according to the institution's usual SoC, and the IP administration should be withheld. Serial cardiac ischemic markers and ECGs should be analyzed locally. Results from local laboratory assessment of troponins (I or T), creatine kinase-MB (CK-MB), and BNP or NT-proBNP should be recorded in the eCRF. A central laboratory PK sample, troponin I, CK-MB, and NT-proBNP should be collected in all subjects experiencing such events as close as possible to the event and the time last IP was taken. The results of the PK assessment, when present, will routinely remain blinded to investigators, Cytokinetics, and study subjects unless the PK is ≥ 1000 ng/mL (other than at Week 4 or Week 8 where subjects are automatically downtitrated as described in Appendix B), in which case the investigator and Cytokinetics will be unblinded and the subject is removed from IP. The DMC, however, will receive unblinded PK data. Cytokinetics should be notified of suspected acute myocardial ischemia or infarction immediately and no later than 24 hours of knowledge of the event.

Restarting IP after a cardiac ischemic event may be considered after appropriate management of the case, and assessment of the likely cause of the event and the potential relatedness of the event to IP. The decision to reinitiate the subject after a cardiac ischemic event that is deemed not to be related to IP should be discussed and agreed upon unanimously by the subject, investigator, and the Medical Monitor.

- **When restarting after ischemic events not suspected to be related to IP, subjects initiate OM 25 mg BID or placebo BID, according to initial randomized allocation, and will not further titrate the dose.**
- **Subjects reinitiating IP after withholding for reasons other than cardiac ischemic events will restart OM or placebo, according to initial randomized allocation, on the same IP dose as established before the event.**

6.3 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (i.e., alkaline phosphatase [ALP], AST, ALT, TBL) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of IP or other protocol-required therapies as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.3.1 Criteria for Permanent Discontinuation of Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

OM **must** be discontinued permanently and the subject should be followed according to the recommendations in Appendix A for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 2 x ULN or INR > 1.5 **AND**
- increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT value	AST or ALT elevation
< ULN	> 3x ULN

- AND no other cause for the combination of the above laboratory abnormalities is apparent; important alternative causes for elevated AST/ALT and TBL values include, but are not limited to:
  - hepatobiliary tract disease
  - viral hepatitis (e.g., Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)
  - right sided HF, hypotension, or any cause of hypoxia to the liver causing ischemia
  - exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
  - heritable disorders causing impaired glucuronidation (e.g., Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (e.g., indinavir, atazanavir)
  - alpha-one antitrypsin deficiency
  - alcoholic hepatitis
  - autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - nonalcoholic Fatty Liver Disease including Steatohepatitis
  - nonhepatic causes (e.g., rhabdomyolysis, hemolysis)

6.3.2 Criteria for Conditional Withholding of Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of IP outlined above and have no underlying liver disease, the following rules are recommended for withholding of IP and other protocol-required therapies:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	> 8x ULN at any time
Any	> 5x ULN but < 8x ULN for ≥ 2 weeks
Any	> 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule
Any	> 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice).

- OR: TBL > 3x ULN at any time
- OR: ALP > 8x ULN at any time

IP and other protocol-required therapies, as appropriate **must** be withheld pending investigation into alternative causes of DILI. If IP is withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.3.3).

6.3.3 Rechallenge of Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject must be discussed and agreed upon unanimously by the subject, investigator, and Medical Monitor. Subjects reinitiating IP after withholding for potential hepatotoxicity will restart OM or placebo, according to initial randomized allocation, on the same IP dose as established before the event and will not further titrate or re-titrate the dose.

If signs or symptoms recur with rechallenge, then OM must be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.3.1) must never be rechallenged.

6.4 Concomitant Therapy

6.4.1 Protocol-required Therapies Other than IP

At randomization, subjects should be optimally managed consistent with HF SoC therapies defined by regional clinical practice guidelines. Oral SoC therapies for chronic HF (e.g., beta blockers, renin-angiotensin-aldosterone system inhibitors, angiotensin receptor neprilysin inhibitor (ARNi), mineralocorticoid receptor antagonists [MRAs]) should be present at appropriate doses, if not contraindicated.

Use of a new agent approved for HFrEF during the conduct of the study will be considered SoC if consistent with regional guidelines or standard clinical practice.

Throughout the study, medications and doses should remain constant whenever appropriate. However, investigators may prescribe or adjust any concomitant medications or treatments deemed necessary to provide adequate supportive care, paying special attention to inhibitors of cytochrome P450 (CYP) 3A4 discussed in Section 6.6.

The dosage of beta blockers, ACEi / angiotensin receptor blocker (ARB) / ARNi, isosorbide dinitrate/hydralazine hydrochloride, diuretics, and MRAs will be recorded at each study visit. If a subject is not taking beta blockers, ACEi/ARB/ARNi, or MRAs, or taking doses below those recommended by local guidelines, investigators should record the reason in the eCRF.

Please refer to Appendix C to see a list of class I and class IIa Guideline Recommended Oral Drugs Commonly Used for Heart Failure with Reduced Ejection Fraction.

All other protocol-required therapies that are commercially available are not provided or reimbursed by Cytokinetics (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies. The investigator is also responsible for reviewing the prescribing information / summary of product characteristics (SmPC) for all concomitant therapy, including ensuring that appropriate contraceptive measures for concomitant therapy are implemented.

Additional details regarding these protocol-required therapies are provided in the Pharmacy Manual.

6.4.2 Other Concomitant Therapies

Throughout the study, medications and doses should remain constant whenever appropriate. However, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, paying special attention to inhibitors of CYP3A4, discussed in Section 6.6.

6.5 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s) or device(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes OM.

Any product complaint(s) associated with an IP(s) or non-IP(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the Pharmacy Manual.

6.6 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Investigational treatments or procedures other than study-provided IP are prohibited. Medications or foods that are known potent inhibitors of CYP3A4 (see examples provided in Table 1) should be avoided, unless deemed necessary by the investigator. If necessary, the doses should be kept constant throughout the study, however investigators may prescribe or adjust any concomitant medications or treatments deemed necessary to provide adequate supportive care.

Table 1. Examples of Potent Inhibitors of CYP3A4

CYP3A4 Inhibitors	
Amprenavir	Nelfinavir
Cyclosporine	Ritonavir
Clarithromycin	Saquinavir
Delavirdine	Telithromycin
Erythromycin	Verapamil
Grapefruit juice	Voriconazole
Indinavir	Nefazodone
Itraconazole	Ketoconazole

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Screening assessments and study procedures are outlined in this section and in Table 2.

Table 2. Schedule of Assessments

Timepoint/Frequency	Screening: Screen[a]	Screening: Pre-Rand W-2[a]	Rand D1	W2 ±3d	W4[b] ±3d	W6 ±3d	W8[b] ±3d	Phone W12 ±3d	Phone W14 ±7d	Phone W18 ±7d	W20[c] ±7d	EOS F/U[d, e] ±7d	Early Study term. visit[e, f]
GENERAL PROCEDURES & SAFETY ASSESSMENTS													
Informed consent	X												
Registration in IWRS	X												
Medical/Surgical history/Demographics	X												
Vital Signs[g]	X	X	X	X	X	X	X				X	X	X
Weight / height[h]	X	X	X								X	X	X
Adverse events/serious adverse events	X[i]	X[i]	X[i]	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X										X	X	X
ECG[j]	X	X	X	X		X					X		
Echocardiogram[k]	X												
CPET		X									X		
Actigraphy instructions and initiation[l]		X				X		X		X			
Actigraphy data collection			X				X		X		X		X[m]
Randomization			X										
CENTRAL LABORATORY													
Chemistry[n]	X		X								X	X	X
Hematology[n]	X		X								X	X	X
Pregnancy test / Serum FSH[o]	X		X										
Urinalysis	X												
NT-proBNP[p]	X[q]		X								X	X	X
Troponin I[p]	X		X								X	X	X
Biomarkers			X								X		
OM plasma concentration[r]				X		X					X		X

Timepoint/Frequency	Screening: Screen[a]	Screening: Pre-Rand W-2[a]	Rand D1	W2 ±3d	W4[b] ±3d	W6 ±3d	W8[b] ±3d	Phone W12 ±3d	Phone W14 ±7d	Phone W18 ±7d	W20[c] ±7d	EOS F/U[d, e] ±7d	Early Study term. visit[e, f]
PATIENT-REPORTED OUTCOMES AND ASSESSMENTS													
KCCQ[s]			X				X		X		X		
Subject interview[t]		X										X	X
NYHA Class	X	X					X		X		X	X	
ACS signs and symptoms		X	X	X	X	X	X	X	X	X	X	X	X
INVESTIGATIONAL PRODUCT													
Instruction on IP administration			X		X		X		X				
Assessment of IP adherence[u]				X[v]	X	X	X	X	X	X	X		
IP administration[w]			X	X	X	X	X		X		X		
IP dispensation[z]			X		X		X		X				
IP tablet count					X		X				X		X

ACS = acute coronary syndrome; CPET = cardiopulmonary exercise testing; ECG = electrocardiogram; EOS = end of study; FSH = follicle-stimulating hormone; F/U = follow-up; IP = investigational product; IWRS = interactive web response system; KCCQ = Kansas City Cardiomyopathy Questionnaire; OM = omecamtiv mecarbil; NT-proBNP = n-terminal prohormone brain natriuretic peptide; NYHA = New York Heart Association

[a] The screening period between ICF signature and randomization may last from 2 to 6 weeks and the period between the CPET and randomization will be not more than 3 weeks.
[b] May be performed as a home visit at designated sites.
[c] If the subject is temporarily unable to exercise on the treadmill or bicycle (whichever modality was used at baseline) due to an adverse event (e.g., ankle sprain, upper respiratory infection, migraine), but not due to heart failure symptoms, or if the site is unable to perform CPET (e.g., equipment malfunction), then the W20 visit may be postponed by up to 4 weeks. The subject should continue to receive IP until the visit. Sites should contact subjects shortly before the W20 visit and confirm their ability to perform CPET.
[d] The EOS visit will occur at Week 24 (or 4 weeks after a postponed Week 20 visit). It is not required for subjects who discontinue IP more than 4 weeks prior to the Week 20 visit.
[e] Vital status is obtained for all subjects within the limits of local law, including subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date of death should be obtained.
[f] Subjects who withdraw from the study should complete an early termination visit as soon as possible. A safety contact (e.g., phone call) should occur 4 weeks following last dose of IP (vital status, adverse events)
[g] Vital signs include heart rate, respiratory rate and BP. Oxygen saturation to be measured at screening visit only.
[h] Height to be measured at screening visit only
[i] Only adverse events considered related to study procedures (e.g., Week -2 CPET) and serious adverse events are collected during the screening period until randomization (D1). Any adverse event not related to study procedure during this period should be collected as medical history.

[j] ECG to be interpreted locally at the site and electronically transmitted to a central ECG core laboratory.
[k] The screening echocardiogram is not required if an LVEF obtained within 12 months prior to screening meets the inclusion criteria
[l] Instructions on when and how to perform actigraphy will be given at the beginning of every 2-week period of actigraphy. After week 8, this may be done by phone or through digital communication, as long as the subject acknowledges the instructions. When not in use, the accelerometer may be collected at the site or retained by the subject, according to site and subject preference.
[m] Collect any new or ongoing actigraphy data at the early termination visit
[n] Blood samples must be collected before CPET where applicable. Analytes listed in Table 3.
[o] Serum pregnancy in all females of childbearing potential at screening; confirmatory urine or serum pregnancy test performed by a local laboratory within 3 days prior to initiating study drug on Day 1. FSH only if needed. Additional on-treatment pregnancy testing should be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.
[p] Troponin I and NT-proBNP results blinded to subjects, sites and Cytokinetics after randomization
[q] NT-proBNP must be done by the central laboratory for eligibility
[r] All subjects. Blood sample must be collected before the administration of IP.
[s] KCCQ should be obtained prior to other assessments, including CPET and blood draw. KCCQ to be assessed by telephone at Week 14.
[t] Structured subject interviews will be performed by trained personnel during the screening period and the follow-up period. The screening interview may occur any time after the screening CPET and before Day 1. The follow-up interview will occur within 2 weeks after the Week 20 CPET and not after the EOS Visit. They may be performed remotely.
[u] Review with subject IP administration (as per Section 6.2.1.1) and adherence since the last visit.
[v] IP compliance will be recorded as whether or not the subject took at least one dose of IP in the 36 hours prior to the Week 2 visit
[w] On visit days after Day 1, subjects should take their study medication after the blood draw. At Week 20, subjects should take their final dose of IP before the CPET.
[z] For a remote visit, the drug is shipped from the clinical site.

Refer to the applicable supplemental laboratory and ECG manuals for detailed collection and handling procedures.

7.2 General Study Procedures

The procedures performed at each study visit are outlined in Table 2. Details regarding each type of procedure are provided in subsequent sub-sections.

7.2.1 Screening

Screening may be done in 1 combined or 2 separate visits, the Initial Screening Visit and the Pre-Randomization Week −2 Visit. If there are recent pre-screening local subject data (e.g., NT-proBNP, liver function tests, renal function tests, hemoglobin) that meet current inclusion/exclusion criteria, and the investigator believes that these will not have changed significantly, then the screening and pre-randomization visits can be combined and carried out on the same day in order to limit the number of patient visits. Laboratory values obtained at the screening visit and reported through the central laboratory, will be used to determine subject eligibility.

7.2.1.1 Initial Screening Visit

Up to 6 weeks is allowed for screening before the subject must be randomized or screen failed in order to provide flexibility for visit scheduling and potential retesting (see Section 7.2.2).

The following procedures are to be completed for the Initial Screening Visit and at time points designated in the Schedule of Assessments (Table 2). If needed, the assessments below may be performed on separate dates prior to the Pre-Randomization Visit:

- confirmation that the ICF has been signed
- registration in IWRS
- demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.
- physical examination
- medical history
- height and weight
- vital signs (BP, heart rate, respiratory rate, oxygen saturation)
- laboratory assessments (chemistry, hematology, urinalysis, NT-proBNP, troponin I, serum pregnancy [females of childbearing potential only], and FSH [if needed]); laboratory assessments must be performed on the same date

- ECG
- Echocardiogram (if needed)
- NYHA Class
- Adverse event reporting, serious adverse event reporting (only adverse events considered related to study procedures and serious adverse events are reported during the screening period, after signing of the ICF until randomization).
- documentation of concomitant therapy

7.2.1.2 Pre-Randomization Week -2 Visit

The following additional procedures are to be completed during the Pre-Randomization Week −2 Visit as indicated in the Schedule of Assessments (Table 2). It is permitted to combine the Initial Screening Visit and the Pre-Randomization Week −2 Visit (see Section 7.2.1).

- Vital signs (BP, heart rate, respiratory rate)
- ECG (single replicate)
- CPET
- Actigraphy instructions and initiation
- Subject interview
- NYHA Class
- Acute coronary syndrome (ACS) signs and symptoms
- Adverse Event reporting, Serious Adverse Event reporting, Hospitalizations (only adverse events considered related to study procedures and serious adverse events are reported during the screening period, after signing of the informed consent until randomization)
- Documentation of concomitant therapy

The time between the CPET and randomization will be not more than 3 weeks.

7.2.2 Retesting

Vital signs (e.g., BP, heart rate, respiratory rate, oxygen saturation), hemoglobin, NTproBNP, liver function, test screening assessments may be repeated once during screening and the new results used to determine eligibility if:

- The first screening value is worse than the subjects' most recent prior assessment, according to the medical record, or if there is no prior assessment
- In the investigator's judgment, the abnormalities are likely to be transient
- Repeat tests can be evaluated for eligibility and the subject randomized within the allowed screening period

7.2.3 Rescreening

Subjects who do not meet all eligibility criteria on the first screening attempt may be rescreened once for the study when the reason for screen failure is resolved or expected to be resolved. If a subject fails screening due to disruptions in study conduct because of COVID-19, then an additional rescreening may be included (one Initial Screening visit and up to two rescreenings in this instance only). This must also be approved by the Medical Monitor prior to the second rescreening. Rescreened subjects must first be registered as screen failed in IWRS and subsequently registered as rescreened. Subjects will maintain the originally assigned subject identification number. For rescreening, a new ICF must be signed. Rescreened subjects will repeat all screening procedures.

7.2.4 Treatment Period

Subjects who meet all eligibility criteria including confirmation from the CPET core lab, at the end of the screening period will return to the study site for randomization and Day 1 procedures.

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Table 2). IP is to be administered after completion of vital signs, ECG, and blood draw procedures during each visit that these are required. KCCQ should be completed first at each visit, where it is required. The ECG must be performed prior to blood draws or other invasive procedures. CPET should be performed after these assessments, after administration of IP.

- randomization in IWRS
- KCCQ (should be done before other study procedures)
- Review for adverse events/serious adverse events
- ACS signs and symptoms (before CPET)
- NYHA Class
- documentation of concomitant therapy
- Actigraphy
- vital signs (BP, heart rate, respiratory rate)
- weight
- physical examination
- ECG (triplicate ECGs on Day 1, Week 2, Week 6, and Week 20)

- central laboratory assessments (chemistry, hematology, NT-proBNP, troponin I, and biomarkers)
- pregnancy test (performed by local laboratory)
- OM plasma concentration
- Assessment of IP adherence
- Week 2 IP compliance (documented as whether or not subject took at least one dose of IP in the 36 hours prior to the Week 2 visit)
- IP administration at site (after the blood draw and before exercise testing)
- IP dispensation
- IP tablet count
- CPET (Subject visit and ability to perform CPET should be confirmed shortly before the Week 20 Visit)
- Schedule the follow-up subject interview (when applicable)

The Week 20 visit is defined as the end-of-treatment visit and should include a cardiopulmonary exercise test (CPET), the primary endpoint, unless contraindicated. If the subject is temporarily unable to exercise on the treadmill or bicycle (whichever modality was used at baseline) due to an adverse event (e.g., ankle sprain, upper respiratory infection, migraine), but not due to heart failure symptoms, or if the site is unable to perform CPET (e.g., equipment malfunction), then the Week 20 visit may be postponed by up to 4 weeks. During this period, the subject should continue to receive IP until the CPET can be completed within this 4-week period.

If disruptions in site operations due to COVID-19 occur and the in-person Week 20 (+4 weeks) visit with a CPET cannot be scheduled, an Unscheduled Visit must occur (see Section 7.2.6) to extend the treatment duration (Section 6.2.1.2) until the Week 20 visit can be conducted. Extension of the treatment period must be approved by the medical monitor.

Subjects who discontinue IP will be encouraged to continue in the study and perform all assessments according to the Schedule of Assessments, including the Week 20 CPET. If a subject withdraws from the study early, investigators will make every effort to complete and report the observations as thoroughly as possible up to the date of withdrawal. If possible, the early termination procedures should be completed at the time of study withdrawal (see Section 7.2.7).

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date of death should be obtained.

7.2.5 End of Study Visit

The EOS Visit will occur at Week 24 or 4 weeks after the Week 20 Visit (if this is delayed), whichever is later. The following procedures will be completed during the EOS Visit:

- vital signs (BP, heart rate, respiratory rate)
- weight
- review for adverse events/serious adverse events
- NYHA Class
- ACS signs and symptoms
- physical examination as per SoC
- documentation of concomitant therapy
- central laboratory assessments (chemistry, hematology, NT-proBNP, troponin I)
- Confirm completion of the subject interview (when applicable)

For subjects who had discontinued IP more than 4 weeks prior to the Week 20 visit, the EOS Visit is not required (and the Week 20 Visit will be the final visit).

7.2.6 Unscheduled Visit

The following procedures may be completed during an unscheduled visit:

- vital signs (BP, heart rate, respiratory rate) as medically indicated
- review for adverse events/serious adverse events
- physical examination as per SoC as medically indicated
- documentation of concomitant therapy
- ACS signs and symptoms
- central laboratory assessments (chemistry and hematology) as medically indicated
- ECG as medically indicated
- OM plasma concentration
- assessment of IP adherence
- dispense IP (if applicable)

7.2.7 Early Termination Visit

For subjects who discontinue the study prematurely, the following procedures will be completed during an Early Termination visit as soon as possible:

- vital signs (BP, heart rate, respiratory rate)
- weight
- review for adverse events/serious adverse events
- physical examination as per SoC
- documentation of concomitant therapy
- ACS signs and symptoms
- collection of actigraphy device and any new data
- central laboratory assessments: chemistry, hematology, NT-proBNP, troponin I, and OM plasma
- IP tablet count
- when possible, the subject's EOS interview will be conducted before or during the Early Termination Visit
- safety contact (e.g., phone call) 4 weeks following last dose of IP (vital status, adverse events)

7.2.8 Description of Study Procedures

7.2.8.1 Informed Consent

All subjects must sign and personally date the IRB/IEC approved ICF before any study-specific procedures are performed.

7.2.8.2 Demographic Data

Demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

7.2.8.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started prior to enrollment through the screening visit. Medical history will include information on the subject's concurrent medical conditions and significant prior conditions. Record all findings on the medical history eCRF.

7.2.8.4 Vital Signs

The following measurements must be performed: systolic/diastolic BP, respiratory rate, heart rate and oxygen saturation. Use of an automated oscillometric device for BP measurement is preferred and recommended. BP will be recorded in both of the

subject's arms unless a concomitant condition favors the use of a particular arm. The arm with the higher systolic reading will be used for eligibility determination. The appropriate size cuff should be used. The subject's pulse should be measured for 30 seconds and the number multiplied by 2 to obtain heart rate. Heart rate and BP should be measured three times and averaged (mean) to determine eligibility during screening. Oxygen saturation will be obtained once at screening and the measurement can be repeated once if the previous reading is outside of the eligibility range. The repeat oxygen saturation measure should be taken at least 2 minutes following the previous measure.

Subjects should be in supine position in a rested and calm state for at least 5 minutes before BP and heart rate assessments are conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF.

All measurements of vital signs will be entered into the vital signs eCRF.

7.2.8.5 Physical Examination

A focused physical examination will be conducted as per SoC. Breast, genital, and rectal examinations are not required unless specific evaluation is warranted. Physical examination findings should be recorded on the appropriate eCRF (e.g., medical history, adverse event).

7.2.8.6 Height and Weight

Height, in centimeters, should be measured without shoes and at screening only. Weight, in kilograms, should be measured without shoes.

7.2.8.7 Cardiopulmonary Exercise Testing

All subjects will undergo CPET with gas-exchange analysis and the methodology will be standardized across all participating sites, as described in the CPET manual. Testing will include continuous ECG monitoring by trained personnel and be performed in an area that is equipped for cardiopulmonary resuscitation. Cycle ergometry will be the preferred modality for exercise testing. For CPET laboratories that do not perform cycle ergometry, treadmill exercise testing is an acceptable alternative. Exercise protocols for both modalities will be provided in the CPET manual. Subjects must use the same testing modality for all exercise tests during the study. Whenever possible, CPET should be

administered by the same study personnel using the same piece of equipment and performed after the other study procedures on that visit day (including KCCQ, NYHA class, ACS signs and symptoms, vital signs, ECG, blood sampling, IP administration). Patients naïve to exercise protocols (bicycle, treadmill, and measurement of oxygen consumption) will be familiarized with the technique during screening.

All CPET testing will be symptom-limited and subjects will be strongly encouraged to achieve maximal exertion and a RER ≥1.15. The reason(s) for termination of sub-maximal exercise tests will be documented. A test will be identified as being maximal effort if the RER is ≥ 1.15, however subjects will still be eligible for the study as long as they achieve an RER ≥ 1.05 on the pre-randomization CPET.

The Week 20 CPET should be performed at approximately the same time of day (e.g., morning, mid-day, afternoon) as the baseline CPET, at a consistent time after the last dose of beta blocker and IP. Whenever possible, subjects should perform exercise testing between three and ten hours after taking beta blocking agents.

If a life-threatening arrhythmia, early ischemia, severe hypotension or other serious finding is identified by the investigator during CPET, the subject will be asked to stop the exercise test, and his/her physicians will be notified of the results. If the subject is performing the pre-randomization test, s/he will not be randomized to the study. Enrolled subjects who have a non-life-threatening event or finding that stops the test can resume testing when it is safe to do so and after appropriate treatment, per the investigator.

All study sites must be qualified by the CPET core laboratory prior to the initiation of screening. To qualify, sites will perform an exercise test on two healthy adults and submit them for core laboratory review. Centers may be required to submit additional normal exercise tests during the conduct of the study for review by the CPET core lab in order to confirm proper function of testing equipment. Centers may be qualified based on exercise tests recently reviewed by the CPET core laboratory during the conduct of other studies.

7.2.8.8 Electrocardiogram

Subject must be in a supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position as possible. The ECG must be performed prior to blood draws, and as close to the PK sample as possible, or

other invasive procedure. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals, and assessment of cardiac rhythm.

At each time point at which triplicate ECGs are required (Day 1, Week 2, Week 6, and Week 20 visits), 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. The visits prior to randomization (i.e., the screening) and pre-randomization only require a single replicate ECG.

The principal investigator or designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents.

Further detail about the equipment provided and its use for this study will be provided in an ECG Manual distributed to the sites before start of enrollment. Digital ECGs will be submitted to the Central Core Laboratory for analysis.

7.2.8.9 Concomitant Therapy

For all concomitant medications (see Section 6.4), investigators must document whether therapy was being taken at any time point during the study.

The dosage of concomitant medications will be recorded. If a subject is not taking beta blockers, ACEi/ARB/ARNi, or MRA, or taking doses below those recommended by local guidelines, investigators should record the reason in the eCRF.

Initiation of nonpharmacological treatments for HF (e.g., implantable cardioverter defibrillator, cardiac resynchronization therapy) and coronary revascularization will be recorded on the eCRF.

7.2.8.10 Patient-Reported Outcomes

Subjects will be asked to complete the KCCQ questionnaire in a quiet place prior to the medical consultation and prior to undergoing any tests and procedures to avoid biasing their response to the questionnaire. Site staff will be asked to check the questionnaire for completeness before the subject leaves the clinic or hospital. If the subject is unable to complete a visit in-person due to COVID-19 at Week 8, the KCCQ may be completed over the telephone and documented as "assessed by telephone" in the source documentation. At Week 14, the KCCQ will be assessed by telephone.

7.2.8.11 NYHA and ACS Signs and Symptoms

After interviewing the subject, Investigators (or delegates) will record the NYHA class and the presence or absence of ACS signs and symptoms in the medical record and eCRF.

7.2.8.12 Actigraphy

Actigraphy will be collected during 4 sessions throughout the study for 2-week intervals. Instructions on when and how to perform actigraphy will be given to the subject at the beginning of every 2-week session of actigraphy. After Week 8, the instructions and reminders will be given to the subject during the phone visits or through digital communication, as long as the subject acknowledges the instructions. During wear periods, the subjects may be contacted by an outside firm to promote compliance. When not in use, the accelerometer may be collected at the site or retained by the subject, according to site and subject preference. Data will be uploaded per the device specifications. The actigraphy device will be collected at the Week 20 Visit or the Early Termination Visit, whichever is later.

Week -2 until Day 1

Instructions will be given at the Week -2 visit for the actigraphy session that spans from Week -2 until Day 1.

Week 6 until Week 8

Instructions will be given at the Week 6 visit for the actigraphy session that spans from Week 6 until Week 8.

Week 12 until Week 14

Instructions will be given during the Week 12 phone visit for the actigraphy session that spans from Week 12 until Week 14.

Week 18 until Week 20

Instructions will be given at the Week 18 phone visit for the actigraphy session that spans from Week 18 until Week 20.

7.2.8.13 Subject Interview

At participating centers in the US, English language-speaking subjects will have two structured, qualitative subject interviews, one during the screening period and a second at the end of the study during the follow-up period after the Week 20 CPET is completed.

The screening interview may occur any time after the screening CPET and before randomization and will collect information in the patient's words regarding their own perceptions of baseline functionality and impact of HF, symptom burden, activities of daily living and expectations going into the study.

The follow-up interview should occur within 2 weeks after the Week 20 CPET and not after the EOS Visit and will collect information in the patient's words regarding their experience with any change in functionality and impact of HF, symptom burden, activities of daily living and overall treatment experience. The subject interviews may be performed remotely.

7.2.8.14 Laboratory Assessments

The schedule of assessments (Table 2) defines the analytes to be collected at each study visit. The date and time of sample collection will be recorded in the source documents at the site. Table 3 below outlines the specific analytes to be tested and reported.

Table 3. Analyte Listing

Chemistry		Urinalysis	Hematology	Other Labs
Sodium	TIBC[b]	Specific gravity	Hemoglobin	OM plasma concentration (PK)
Potassium	Creatinine	pH	Hematocrit	Pregnancy test[a]
Chloride	Total bilirubin	Blood	RBC	FSH[a]
Calcium	Direct bilirubin	Protein	RDW	NT-proBNP
Magnesium	CK	Glucose	MCV	Troponin I
Phosphorus	ALP	Bilirubin	MCH	
Urea	LDH		MCHC	
Iron[b]	AST (SGOT)		WBC	
Ferritin[b]	ALT (SGPT)		Platelets	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; FSH = follicle-stimulating hormone; LDH = lactic acid dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OM = omecamtiv mecarbil; PK = pharmacokinetic; RBC = red blood cell; RDW = red cell distributions width; TIBC = total iron binding capacity; WBC = white blood cell

[a] A pregnancy test is required for females of childbearing potential; FSH only at screening if needed.

[b] Assessed on Day 1 only.

OM plasma concentrations will be measured using an investigational device, QMS Omecamtiv Mecarbil Immunoassay, developed by Thermo Fisher Scientific. The

investigational assay will be used in accordance with local regulatory and labeling requirements along with the Instructions for Use provided with the investigational device.

7.3 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

Cytokinetics may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to OM.

Blood samples are to be collected for biomarker development at the times indicated in Table 2.

7.4 Pharmacogenetic Studies

In countries where allowed, if the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of OM and/or to identify subjects who may have positive or negative response to OM. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

7.5 Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments (Table 2) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Cytokinetics (or designee) can do additional testing on remaining samples (i.e., residual and back-up) to investigate and better understand HF, the dose response and/or prediction of response to OM, and characterize aspects of the molecule (e.g., mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the ICF.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide Cytokinetics with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. However, information collected from samples prior to the request for destruction, will be retained by Cytokinetics.

Cytokinetics is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (e.g., the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, Cytokinetics owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving IP and/or other protocol-required therapies or procedures at any time during the study and

continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from IP or other protocol-required therapies and must discuss with the subject the option for continuation according to the Schedule of Assessments (Table 2) and collection of data, including endpoints and adverse events. Subjects who have discontinued IP and/or protocol required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow-up that is agreed to by the subject.

Withdrawal of consent for follow-up should be accompanied by documentation of the reason for withdrawal. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up (e.g., medical records checks). Subjects requesting withdrawal should be informed that withdrawal of consent for follow-up will jeopardize the public health value of the study.

Subjects who discontinue IP or withdraw from the study should be asked explicitly about the contribution of possible adverse events to their decision to withdraw consent, and any adverse event information elicited should be documented.

The subject will withdraw consent in writing. If the subject or the subject's representative refuses or is physically unavailable, the site will document and sign the reason for the subject's failure to withdraw consent in writing. The informed consent for the study will note that although a subject is free to leave the study and stop taking study medication, the investigators hope the patient will remain available for follow-up status evaluations.

For subjects who have withdrawn consent for further follow-up, investigators will review public records as permitted by applicable law to determine vital status of the subject before or at the end of the study.

8.2 Investigator or Cytokinetics Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or Cytokinetics can decide to withdraw a subject(s) from IP and/or other protocol required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with IP and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required IP or procedural assessments include any of the following:

- subject request
- safety concern (e.g., due to an adverse event, pregnancy/lactation, poor compliance with IP dosing regimen or study safety procedures)
- death
- lost to follow-up
- decision by Cytokinetics (other than subject request, safety concern, lost to follow-up)
- OM plasma concentration ≥ 1000 ng/mL when assessed at an unscheduled visit

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by Cytokinetics
- withdrawal of consent
- death
- lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (e.g., diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than

anticipated (i.e., more than usual fluctuation of disease) during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Adverse Event eCRF.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative, requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least one of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization," if the event necessitated an admission to a health care facility (e.g., overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event." Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, DILI (see Appendix A for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Adverse Events

9.2.1.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after randomization through the EOS, or 30 days after the last administration of IP, whichever is later, are recorded in the Adverse Event eCRF. Adverse events considered related to study procedures (e.g., Week -2 CPET) and/or serious adverse events that occur during the screening period (after signing of the ICF until randomization) are also reported. Serious adverse events are also reported on an SAE Report Form, per Section 9.2.1.2 below.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity (and/or toxicity per the Common Terminology Criteria for Adverse Events [CTCAE] v4.0),
- Assessment of relatedness to IP or study procedure,
- Action taken with the IP.

It is not acceptable for the investigator to submit photocopies of the subject's medical records in lieu of completion of an SAE Report Form or Adverse Event eCRF page. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission via SAE email or facsimile number as defined in Section 9.2.1.2 below.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

The adverse event grading scale used in this study is CTCAE, described in Appendix A. Because severity (i.e., the criteria for the CTCAE grading scale) differs from the regulatory criteria for serious adverse events, if adverse events correspond to a grade 4

"life-threatening" CTCAE grading scale criteria (e.g., laboratory abnormality reported as grade 4 without manifestation of life-threatening status), it will be left to the investigator's judgment to report the abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event's severity status must be recorded in the subject's medical record. The investigator must assess whether the adverse event is possibly related to IP. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the IP?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The investigator is expected to follow reported adverse events until stabilization, reversibility, or return to baseline.

For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include on the initial SAE Report Form, as per Section 9.2.1.2. However, it is very important that the investigator always make an assessment of causality for every event when reporting the serious adverse event data. The investigator may change his/her opinion of causality, in light of follow-up information received, and send a follow-up SAE Report Form with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

9.2.1.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through EOS /safety follow-up visit, or 30 days after the last administration of IP, whichever is later, are reported immediately (no later than 24 hours) following the investigator's knowledge.

The investigator must update the eCRF page as appropriate.

All serious adverse events must be reported on an SAE Report Formvia one of the following contact methods:

Email: cy1031drugsafety@cytokinetics.com

Facsimile: +1 (650) 745-7375

The investigator should also update the Adverse Event eCRF page as appropriate.

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after EOS. However, these serious adverse events can be reported using the process described in this section. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after EOS. If serious adverse events are reported, the investigator will complete an SAE Report Form and forward via SAE email or facsimile (as per above) immediately and no later than 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to IP.

If the EDC system is unavailable to the site staff and an SAE Report form has been sent to Cytokinetics, the site will enter the serious event data into the eCRF as soon as it becomes available. The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure?"

The investigator is expected to follow all reported serious adverse events until stabilization, reversibility, or return to baseline.

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted on an SAE Report Form as per the SAE email or facsimile number provided above.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Cytokinetics (or designee) before submission to regulatory authorities. Investigators will receive blinded notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

Cytokinetics (or designee) will report safety issues and suspected unexpected serious adverse reactions (SUSARs) as required to regulatory authorities and IECs. Cytokinetics (or designee) will report SUSARs to investigators/institutions, and IRBs in compliance with all reporting requirements according to local regulations and good clinical practice (GCP).

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Cytokinetics or designee, in accordance with local procedures and statutes.

9.2.1.3 Follow-up of Adverse Event and Serious Adverse Event

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Cytokinetics or designee to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide a copy of any post-mortem findings including histopathology, if available, to Cytokinetics upon request.

New information relating to a previously reported serious adverse event must be reported to Cytokinetics immediately and no later than 24 hours following the investigator's knowledge of the new information (as described in Section 9.2.1.2). The investigator may be asked to provide additional follow up information, which may include a discharge summary or extracts from the medical record. Information provided about

the serious adverse event must be consistent with that recorded on the Adverse Event eCRF.

9.3 Pregnancy and Lactation Reporting

9.3.1.1 Collection of Pregnancy Information

9.3.1.2 Female Subjects Who Become Pregnant

The investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 5 days after the end of treatment with IP.

Information will be recorded on the Initial Pregnancy Mother Authorization and Questionnaire. The worksheet must be submitted to Cytokinetics immediately and no later than 24 hours following the investigator's learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Initial Pregnancy Mother Authorization and Questionnaire that violates the country or region's local privacy laws). The Initial Pregnancy Mother Authorization and Questionnaire and any additional source documents must be submitted using the instructions for SAE report submission/contact information in Section 9.2.1.2.

After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 5 days after the end of treatment with IP. This information will be forwarded to Cytokinetics. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of pregnancy will be reported to Cytokinetics immediately and no later than 24 hours following the investigator's knowledge of the event, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay on an infant, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Cytokinetics.

If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (e.g., female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.

Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the IP by the investigator will be reported to Cytokinetics immediately, and no later than 24 hours, following the investigator's knowledge of the event on an SAE Report Form, as described in Section 9.2.1.2. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.

Any female subject who becomes pregnant while participating in the study will discontinue IP.

9.3.1.3 Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

In the event a male subject fathers a child during treatment, and for an additional 5 days after discontinuing protocol-required therapies, the investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.

The male subject may continue receiving treatment; however, he must use barrier method (i.e., condom) during sexual intercourse to avoid further fetal exposure. After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. The information will be recorded on the Initial Pregnancy Mother Authorization and Questionnaire. The worksheet must be submitted to Cytokinetics immediately and no later than 24 hours following the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Initial Pregnancy Mother Authorization and Questionnaire that violates the country or region's local privacy laws) as described in Section 9.2.1.2.

Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of the pregnancy will be reported to Cytokinetics regardless of fetal status (presence or absence of anomalies) or indication for procedure as described in Section 9.2.1.2.

9.3.2 Collection of Lactation Information

Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 5 days after the end of treatment with IP.

Information will be recorded on the Lactation Notification Form and submitted to Cytokinetics immediately and no later than 24 hours following the investigator's knowledge of event as described in Section 9.2.1.2.

IP will be discontinued if female subject breastfeeds.

With the female subject's signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the Lactation Notification Form on any female subject who breastfeeds while taking protocol-required therapies through 5 days after the end of treatment with IP after discontinuing protocol-required therapies.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

- Change in pVO_2 on CPET from baseline to Week 20

10.1.1.2 Secondary Endpoints

- Change in total workload during CPET from baseline to Week 20
- Change in ventilatory efficiency (VE/VCO_2 slope) during CPET from baseline to Week 20
- Change in the average daily activity units measured over a 2-week period from baseline (Week -2 to Day 1) to Week 18-20

10.1.1.3 Exploratory Endpoints

- Change from baseline to Week 20 in oxygen uptake efficiency slope (VO_2/logVE slope), ventilatory threshold (by the V-slope method), VO_2 recovery kinetics, percent predicted pVO_2, circulatory power (VO_2 × systolic BP), and exercise duration
- Change from baseline in the average daily activity units at Week 6-8 and at Week 12-14

- Change from baseline in the KCCQ Total Symptom Score and its sub-domains from baseline to Week 20

10.1.1.4 Safety Endpoint

- Subject incidence of reported adverse events and serious adverse events. Major adverse CV events will be adjudicated by a CEC, including: all-cause death, CV death, major cardiac ischemic events (myocardial infarction, hospitalization for unstable angina, percutaneous coronary intervention and coronary artery bypass graft), HF events and stroke.

10.1.2 Analysis Sets

10.1.2.1 Efficacy Analysis Set

Efficacy analyses will be performed on the full analysis set (FAS), which includes all randomized subjects who receive at least one dose of randomized IP, by randomized treatment group. Subjects will be analyzed according to their randomized treatment group assignment.

10.1.2.2 Safety Analysis Set

Safety analyses will be performed on the safety analysis set (SAS), which includes all randomized subjects who receive at least one dose of IP on study. Unless otherwise specified, for safety analyses, subjects will be grouped according to their randomized treatment group assignment with the following exception: if a subject receives treatment throughout the study that is different than the randomized treatment group assignment, then the subject will be grouped by the actual treatment group.

10.1.3 Covariates and Subgroups

Baseline covariates include the randomization stratification factors of the RER on the baseline CPET (<1.15, ≥1.15) and persistent atrial fibrillation (Y/N) as well as age, sex, and hemoglobin level and any additional factors as described in the statistical analysis plan (SAP), which have the potential to impact pVO_2 measures.

Prespecified subgroups for the analysis include, but are not limited to:

- stratification factor RER on baseline CPET (<1.15, ≥1.15)
- stratification factor persistent atrial fibrillation (Y/N)
- age (< 65 years, ≥ 65 years)
- sex (male, female)
- baseline body mass index (≤ median and > median)
- baseline NYHA Class (II, III)
- primary cause of HF (ischemic, non-ischemic)

- baseline LVEF (≤ median, > median)
- baseline NT-proBNP excluding subjects in atrial fibrillation at screening (≤ median and > median)
- baseline use of beta blocker (yes, no)
- CPET modality (treadmill, bicycle)
- pVO_2 on baseline CPET (≤ median, > median)
- total workload on baseline CPET (≤ median, > median)
- VE/VCO_2 slope on baseline CPET (≤ median, > median)
- Change in heart rate (resting to peak) on baseline CPET (≤ median, > median)

The final list of prespecified subgroups for the analysis will be detailed in the SAP.

10.2 Sample Size Considerations

Assuming a difference in change from baseline of pVO_2 of 1.0 mL/kg/min for OM versus placebo, an SD of 2.5 mL/kg/min for OM subjects and 2.0 mL/kg/min (Lewis, 2017) for placebo, and 15% of subjects missing change from baseline data, 270 subjects (approximately 180 randomized to OM and 90 randomized to placebo) provides 90% power to detect the difference in pVO_2 change from baseline to Week 20 with a 2-sided type I error of 0.05. Eligible subjects will be randomized in a 2:1 ratio to receive either OM or placebo, respectively. The 2:1 ratio was selected based on the expected difference in SD between the placebo and active arms, because the SD in the change in pVO_2 increases as the exercise capacity increases (Ismail, 2013). Randomization will be stratified based on the RER on the baseline CPET (<1.15, ≥1.15) and persistent atrial fibrillation at screening (Y/N). The number of patients with persistent atrial fibrillation at screening will be capped at approximately 20%. A treatment difference in pVO_2 of 1.0 mL/kg/min is considered clinically meaningful (Lewis, 2016; Tucker, 2018; Kitzman, 2011).

During the study, Cytokinetics will periodically assess in a blinded fashion the aggregate pooled missing data rate and overall pooled SD for the change from baseline in pVO_2 at Week 20. Shortly before the enrollment reaches 270 subjects, if the missing data rate or pooled SD is larger than expected or there is possible impact from COVID-19 on the assessment of the primary endpoint, for example if 20% of randomized subjects are missing change in pVO_2 at Week 20, >10% of subjects completed the Week 20 CPET beyond the initially planned Week 20 window as a result of COVID-19, or the overall pooled SD is > 2.5 mL/kg/min, then the sponsor may consider increasing the sample

size once in order to maintain 90% power to detect a difference in pVO_2 of 1 mL/kg/min. The maximum number of randomized subjects will be 400.

10.3 Access to Individual Subject Treatment Assignments by Cytokinetics or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators or subjects prior to the study being formally unblinded except as specified (e.g., Section 5.2 and Section 9.2.1.2).

10.4 Planned Analyses

10.4.1 Interim Analyses

This study is running concurrently to Study 20110203 (GALACTIC-HF), an international, phase 3 study designed to assess the efficacy and safety of OM on mortality and morbidity in subjects with chronic HFrEF. If Study 20110203 completes (last patient last visit) or interim results become available (i.e., planned interim analyses yield new information) prior to the completion of this study, the sponsor may instruct the Independent Statistical contract research organization (CRO) to perform a single interim analysis for review by the DMC in the context of the current risk/benefit profile for subjects. At this interim assessment, the DMC may recommend stopping this study due to superiority if a two-sided p-value is ≤ alpha of 0.0001 following the Haybittle-Peto approach (Haybittle et al, 1971; Peto et al, 1976). The DMC may also recommend to stop the study due to futility if the conditional power is < 0.10. The DMC is to make a recommendation to stop or continue the study using their collective judgment and the totality of evidence available.

The ECG data in this study are being collected to evaluate the effect of omecamtiv mecarbil on the QT interval. In the event this study is not yet complete at the time Study 20110203 completes or interim results become available, the sponsor may conduct an interim analysis of the ECG data collected in this study in order to support the potential preparation of a registration dossier. An independent third party will conduct the QT analysis according to an interim statistical analysis plan and the sponsor will receive an aggregated analysis report and may receive individual subject data if required for review. Individual subject data will be available only to a group separate from those involved in the operation of the study. Every effort will to made to maintain the integrity of

data-blinding. Data handled by the independent third party will be restricted to ensure separation from the study team.

10.4.2 Data Monitoring Committee

An external independent DMC will be established to formally review the accumulating data from this study to ensure there is no avoidable increased risk for harm to subjects. The independent DMC is chaired by an external academic cardiologist who is an expert in HF and clinical trials. Analyses for the DMC will be provided by an independent statistical CRO, which is external to Cytokinetics. Details will be provided in the DMC charter. The independent DMC members and the independent statistical CRO will have access to treatment assignments and subject level data from the clinical trial database.

10.4.3 Primary Analysis

The primary analysis will include hypothesis testing for each of the primary and secondary endpoints and include analyses of exploratory endpoints. The primary analysis will occur after all subjects complete the study. At that point, the database will be cleaned, processed and a snapshot will be taken. The study will also be unblinded. Based on the snapshot, unless specified otherwise, efficacy analyses will be performed on the FAS by randomized treatment group and safety analyses will be performed on the SAS. Sensitivity and supportive analyses evaluating the impact to the primary and secondary endpoints due to COVID-19 will be detailed in the SAP.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Unless otherwise specified, all hypothesis tests will be reported as 2-sided and the full study will have an overall type I error rate of 0.05.

Subject disposition, demographics, baseline characteristics, and exposure to IP will be summarized.

Continuous variables will be summarized using descriptive statistics, including the number of observations (n), mean, SD or standard error, median, the first quartile and third quartile, minimum, and maximum. Categorical variables will be summarized using the number and percent of subjects.

All deaths, HF events, major cardiac ischemic adverse events (myocardial infarction, unstable angina hospitalization, and coronary revascularization), and strokes will be adjudicated by an external CEC, using standardized definitions in a blinded manner. The

CEC is external to Cytokinetics and primarily comprises both academic clinical physicians (to include cardiologists) and medical reviewers trained on the clinical trial protocol, the CEC charter, and CEC processes. The chairman of the CEC is responsible for overseeing the operations in conformance with the CEC charter and for supervising the flow of data between the sponsor/data management and the CEC. Committee members are qualified in the appropriate subspecialty and free of conflict of interest. The CEC is blinded to treatment allocation and reviews events according to prespecified criteria defined in the CEC charter.

An HF event is defined as presentation of the patient for an urgent, unscheduled clinic/office/emergency department visit, or hospital admission, with a primary diagnosis of HF, where the patient exhibits new or worsening symptoms of HF on presentation, has objective evidence of new or worsening HF, and receives initiation or intensification of treatment specifically for HF (Hicks et al, 2015). Changes to oral diuretic therapy do not qualify as initiation or intensification of treatment.

10.5.2 Multiplicity Adjustments

The null hypothesis for the primary and secondary efficacy variables in the FAS will be tested in the following pre-specified order using a closed testing procedure. This procedure will maintain the family-wise error rate at 5% for all hypotheses tested in a confirmatory sense.

Step 1. The null hypothesis that there is no treatment difference between OM and placebo in the primary efficacy variable in the FAS will be tested at the 5% significance level. If this hypothesis is rejected, testing will proceed to Step 2; otherwise stop.

Step 2. The null hypothesis of no treatment difference between OM and placebo in the secondary endpoint of change in total workload during CPET from baseline to Week 20 in the FAS will be tested at the 5% significance level. If this hypothesis is rejected, testing will proceed to Step 3; otherwise stop.

Step 3. The null hypothesis of no treatment difference between OM and placebo in the secondary endpoint of change in ventilatory efficiency (VE/VCO_2 slope) during CPET from baseline to Week 20 in the FAS will be tested at the 5% significance level. If this hypothesis is rejected, testing will proceed to Step 4; otherwise stop.

Step 4. The null hypothesis of no treatment difference between OM and placebo in the secondary endpoint of change in the average daily activity units measured over a two-

week period from baseline to Week 18-20 in the FAS will be tested at the 5% significance level.

10.5.3 Primary Efficacy Endpoint

The primary endpoint is the change in pVO_2 on CPET from baseline to Week 20.

The primary estimand is the difference in means of the change from baseline to Week 20 in pVO_2 between OM and placebo for the target population of potentially treatable OM patients despite intercurrent events after a first dose. Subjects without a dose of IP will be excluded from the FAS as they are anticipated to not represent patients from a treatable population defined as patients who would meet the eligibility requirements of this study and are capable and willing to be dosed. The primary analysis is to test the null hypothesis that there is no treatment difference in the change from baseline in pVO_2 at Week 20 between patients in the FAS randomized to placebo and those randomized to OM during the placebo-controlled double-blind treatment. The primary analysis will be performed using an analysis of covariance (ANCOVA) model which will include terms of treatment, baseline pVO_2, baseline RER randomization strata (<1.15, ≥1.15), persistent atrial fibrillation (Y/N), age, sex, and baseline hemoglobin level. Least square mean difference between the two treatment groups and standard errors will be provided. Hypothetically, the OM treatment arm may have fewer intercurrent events of death and hospitalization due to worsening HF, based on the intended mechanism of action of OM, and these events may preclude CPET at Week 20. Other intercurrent events such as other CV adverse events and non-CV adverse events (e.g., orthopedic injury , COVID-19 symptoms) that could preclude a CPET test might not be related to OM and in this case the missing data due to these events are likely to be missing at random. The distribution of missing CPET data at Week 20 and the reasons for the missing data will be tabulated in the FAS. The missing data model for the primary analysis, including the final list of covariates in the model, will be detailed in the SAP before database lock.

The same model above will be used for subgroups of the stratification factors and the other prespecified subgroups.

The secondary estimand is the difference in means of the change from baseline to Week 20 in pVO_2 between OM and placebo due to treatment for the hypothetical target population of potentially treatable OM patients for 20 weeks and capable of completing the Week 20 assessment. Subjects with intercurrent events of missing Week 20 pVO_2 or

discontinuing treatment prior to Week 20 will be excluded from this analysis. This supportive analysis will test the null hypothesis that there is no treatment difference in the change from baseline in pVO_2 at Week 20 between all subjects randomized to placebo and all randomized to OM and have at least one post-randomization CPET measure on treatment during the placebo-controlled double-blind treatment. The supportive analysis will use the same ANCOVA model as the primary analysis described above.

As a sensitivity analysis for the primary analysis, the ANCOVA model will be repeated with missing data imputed as if the OM subjects were in the placebo arm.

10.5.4 Secondary Efficacy Endpoints

The analysis method for secondary CPET efficacy endpoints will be the same for the primary efficacy endpoint. The non-CPET secondary endpoints will be analyzed using a repeated measures mixed model with terms such as treatment, baseline values, visit, RER randomization strata (<1.15, ≥1.15), and persistent atrial fibrillation (Y/N) as well as interaction terms of treatment-by-visit and baseline-by-visit with an unstructured covariance matrix. The exploratory change from baseline endpoints will also be analyzed using the same method as secondary efficacy endpoints. The models and terms will be described in the SAP before database lock.

The correlation between CPET efficacy endpoints and non-CPET efficacy endpoints will be examined regardless of treatment groups and by treatment group. The Spearman correlation coefficients, p-values, and 95% confidence intervals will be provided.

10.5.5 Safety Endpoints

10.5.5.1 Adverse Events

The current Medical Dictionary for Regulatory Activities version at the time of the data lock will be used to code all adverse events to a system organ class and a preferred term.

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from IP, and significant treatment-emergent adverse events will also be provided.

10.5.5.2 Laboratory Parameters

The analyses of safety laboratory values will include summary statistics at each scheduled visit by treatment group.

Shifts in grades or between relevant thresholds of safety laboratory values between baseline and the worst on-study value will be tabulated by treatment group.

10.5.5.3 Vital Signs

The analyses of vital signs will include summary statistics at each scheduled visit by treatment group.

10.5.5.4 Electrocardiograms

Descriptive summaries over time and/or changes from baseline over time will be provided for all ECG parameters by treatment group. Subjects' maximum change from baseline in QTcF will be categorized and the number and percentage of subjects in each treatment group will be summarized. Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects in each treatment group will be summarized.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample ICF is provided for the investigator to prepare the informed consent document to be used at his or her site. The written informed consent document is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any IP(s) is/are administered.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed ICF is to be provided to the subject.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and ICF must be received by Cytokinetics before recruitment of subjects into the study and shipment of IP.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the ICF. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Cytokinetics, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC approval throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Cytokinetics.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Cytokinetics.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the eCRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

- For serious adverse events reported to Cytokinetics, subjects are to be identified by their unique subject identification number, initials (for reports by facsimile, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to = Cytokinetics (e.g., signed ICFs) are to be kept in confidence by the investigator, except as described below.

In compliance with Federal regulations/ International Council for Harmonisation (ICH) Tripartite Guideline on GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Cytokinetics, will be any or all of the following:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Cytokinetics amends the protocol, agreement from the investigator must be obtained. The IRB/IEC must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IRB/IEC to Cytokinetics.

Cytokinetics reserves the right to terminate the study at any time. Both Cytokinetics and the Investigator reserve the right to terminate the Investigator's participation in the study according to the study contract executed to allow conduct of the study by the investigator. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Cytokinetics.

Subjects may be eligible for continued treatment with Sponsor IP(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Sponsor reserves the unilateral right, at its sole discretion, to determine whether to supply Sponsor IP(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Cytokinetics and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed eCRFs, ICFs, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen and Cytokinetics
- IP-related correspondence including Proof of Receipts, IP Accountability Record(s), Return of IP for Destruction Form(s), Final IP Reconciliation Statement, as applicable.
- Non-IP(s) and/or medical device(s) documentation, as applicable.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

The Cytokinetics representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and,

upon request, inspecting the various records of the clinical study (e.g., eCRFs and other pertinent data) provided that subject confidentiality is respected.

Cytokinetics is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Cytokinetics representative is to have access to subject medical records and other study-related records needed to verify the entries on the eCRFs. Should the site be unable to accommodate in-person source document review as a result of COVID-19, Cytokinetics may employ remote document verification tools should this be allowed by the site, is in compliance with Ethics Committee/Institutional Review Board regulations, and consented to by the subject.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Cytokinetics' Quality Assurance function (or designees). Inspection of site facilities (e.g., pharmacy, protocol-required therapy storage areas, laboratories) and review of study related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and readily available.
- Updates to eCRFs will be automatically documented through the software's audit trail.
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Cytokinetics (or designee). During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by a Cytokinetics (or designee) reviewer.
- The investigator signs only the Investigator Verification Form for this EDC study or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that

investigator inspected or reviewed the data on the eCRF, the data queries, and agrees with the content.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 2), the investigator can search publicly available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

eCRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

To coordinate dissemination of data from this study, Cytokinetics encourages the formation of a publication committee consisting of several investigators and appropriate Cytokinetics staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Cytokinetics staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Cytokinetics staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (International Committee of Medical Journal Editors, updated Dec 2017), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity

of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4.

- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the ICF that is available as a separate document.

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Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

Refer to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. When an adverse event cannot be graded by CTCAE Version 4.0, the following severity grade may be used:

Grade	Standard Adverse Event Severity Scoring System
1	MILD: Aware of sign or symptom, but easily tolerated.
2	MODERATE: Discomfort enough to cause interference with usual activity.
3	SEVERE: Incapacitating with inability to work or do usual activity.
4	LIFE-THREATENING: Refers to an event in which the patient was, in the view of the investigator, at risk of death at the time of the event (This category is not to be used for an event that hypothetically might have caused death if it were more severe).
5	FATAL

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of drug-induced liver injury (DILI), cases of concurrent aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin (TBL) and/or international normalized ratio (INR) elevation according to the criteria specified in Section 6.3 require the following:

- The event is to be reported to Cytokinetics as a serious adverse event within 24 hours of discovery or notification of the event (i.e., before additional etiologic investigations have been concluded)
- The Adverse Event eCRF that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Cytokinetics.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.1.2.

Additional Clinical Assessments and Observation

All subjects in whom IP(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Sections 6.3.1 and 6.3.2 or who experience AST or ALT elevations > 3 x ULN are to undergo a repeat test and a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours

- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, bilirubin (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the IP(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count (CBC) with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Obtain serum acetaminophen (paracetamol) levels
  - Obtain a more detailed history of:
- Prior and/or concurrent diseases or illness
- Exposure to environmental and/or industrial chemical agents
- Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
- Prior and/or concurrent use of alcohol, recreational drugs and special diets
- Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Obtain viral serologies
  - Obtain creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for PK analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all IP(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications, and laboratory results must be captured in corresponding eCRFs.

Appendix B. Summary of Dose Adjustment and Action to be Taken Regarding IP Concentration Assessment

Study Visit	Week 2 Plasma Concentration (ng/mL) [a]	Current Dose BID	New Dose BID
Week 4	< 200	25 mg	50 mg
	≥ 200 - < 300		37.5 mg
	≥ 300 - < 1000		no change
	≥ 1000		placebo
Study Visit	**Week 6 Plasma Concentration (ng/mL) [a]**	**Current Dose BID**	**New Dose BID**
Week 8	< 750	Any	no change
	≥ 750 - < 1000	25 mg	no change
		37.5 mg	25 mg
		50 mg	37.5 mg
	≥ 1000	25 mg	placebo
		37.5 mg	25 mg
		50 mg	
Study Visit	**Plasma Concentration (ng/mL)**	**Current Dose**	**New Dose**
Unscheduled Visit [b]	≥ 1000	Any	Withdraw IP

BID = twice a day; IP = investigational product

[a] In the event Week 2 is skipped and/or PK value is not available prior to Week 4 titration visit, subjects randomized to OM will continue with the 25 mg BID until the Week 6 PK assessment. If the Week 6 PK value is not available prior to Week 8 titration visit, subjects randomized to OM will be assigned to the lowest dose (25 mg BID).

[b] For unscheduled visits that are clinically indicated (e.g., chest pain), PK evaluation may be indicated. Unscheduled visits carried out as a result of COVID-19 related Week 20 extension, do not require PK assessment.

Appendix C. List of Class I and Class IIa Guideline Recommended Oral Drugs Commonly Used for Heart Failure with Reduced Ejection Fraction

Adapted from Yancy et al, 2016. American College of Cardiology /American Heart Association / Heart Failure Society of America Focused Update on New Pharmacological Therapy for Heart Failure and Ponikowski et al, 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure.

Drug	AHA/ACC/HFSA Recommended Maximum Daily Dose(s)	ESC Recommended Target Daily Dose(s)
ACE inhibitor		
Captopril	50 mg 3 times	50 mg 3 times
Enalapril	10 to 20 mg twice	10 to 20 mg twice
Fosinopril	40 mg once	NA
Lisinopril	20 to 40 mg once	20 to 35 mg once
Perindopril	8 to 16 mg once	NA
Quinapril	20 mg twice	NA
Ramipril	10 mg once	5 mg twice
Trandolapril	NA	4 mg once
ARB		
Candesartan	32 mg once	32 mg once
Losartan	50 to 150 mg once	150 mg once
Valsartan	160 mg twice	160 mg twice
ARNi		
Valsartan/sacubitril	97/103 mg twice	97/103 mg twice
MRA		
Spironolactone	25 mg once or twice	25 mg once or twice
Eplerenone	50 mg once	50 mg once
Beta-blockers		
Bisoprolol	10 mg once	10 mg once
Carvedilol	50 mg twice	25 to 50 mg twice
Carvedilol CR	80 mg once	NA
Metoprolol succinate extended release	200 mg once	200 mg once
Nebivolol	NA	10 mg once
Other		
Hydralazine and isosorbide dinitrate - Fixed-dose combination	75 mg hydralazine/40 mg isosorbide dinitrate 3 times daily	NA
Hydralazine and isosorbide dinitrate	Hydralazine: 300 mg daily in divided doses and Isosorbide dinitrate: 120 mg daily in divided doses	NA
Ivabradine	5 to 7.5 mg twice	5 to 7.5 mg twice

ACC = American College of Cardiology; ACE = angiotensin-converting enzyme; AHA = American Heart Association; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor neprilysin inhibitor; CR = controlled release; ESC = European Society of Cardiology; HFSA = Heart Failure Society of America; MRA = mineralocorticoid receptor antagonist; NA = not applicable

Appendix D. Study Modifications in Response to COVID-19

It is imperative that in the setting of COVID-19, when subject visits cannot be conducted as planned, the reason for failing to conduct such visits is clearly documented and communicated with the sponsor (e.g., "Week 6 PK lab draw not completed due to site closure as a result of COVID-19 pandemic"). The following adjustments to the visits and schedule are only permitted in the setting of COVID19:

- Screening and Randomization
  - Subjects that have undergone screening, but have yet to be randomized, will be screen-failed if COVID-19 renders participation in the study unsafe or unlikely to be completed per protocol. In this instance and only with approval from the medical monitor, a third screening visit will be permitted (see Section 7.2.3).
  - Subjects having undergone randomization should continue on study, with primary focus being the maintenance of subject safety and with reasonable attempts to maintain study visits per protocol.
  - **Study Assessments:** If, as a result of COVID-19, onsite visits need to be converted to telephone or virtual visits, some study procedures will be missed (for example sample collection or ECG). Please contact the medical monitor, to discuss prior to upcoming study visits. In some instances, it may be possible to conduct the visit and/or study procedures (e.g., blood draw, ECG, vital signs) in the subject's home.
- Visit-specific guidance:
  - **Week 2:** Subjects unable to complete the Week 2 OM plasma concentration blood draw will automatically continue with their initial dose and forgo dose adjustment (i.e., remain on OM 25 mg BID or placebo).
  - **Week 6:** Subjects unable to complete the Week 6 OM plasma concentration blood draw will automatically revert, irrespective of whether the dose was uptitrated at Week 4, back to the starting dose per IWRS (i.e., OM 25mg BID or placebo).
  - **Week 4 & Week 8:** These visits can be conducted as telephone visits per the Schedule of Assessments (see Table 2) if allowed by the site's institution.
  - **Week 12, Week 14 & Week 18:** These visits are telephone visits. No modifications should be needed.
  - **Week 20:** The CPET can be conducted within an additional +4-week window provided the subject remains on IP according to the Schedule of Assessments (see Table 2). In the setting of COVID-19 and only with approval from the medical monitor, additional IP will be supplied in 4 week increments up to 2 times (an additional 8 weeks, totaling to 12 weeks from the original Week 20 visit). It is imperative that the Week 20 visit be conducted in as close proximity to the originally planned Week 20 visit as possible. The Week 20 visit can only be considered complete if the subject underwent a CPET (or this was contraindicated and documented as such) as part of that visit.

- **Week 24:** This visit can be conducted as a telephone visit if necessary. It should occur 4 weeks after the Week 20 visit (CPET) has been completed.
- **Unscheduled Visits**: In instances where a subject cannot complete the Week 20 CPET as planned due to COVID-19, those subjects may continue on IP until the visit can be completed for up to an additional 12 weeks (total of up to 32 weeks on IP), and only after approval from the medical monitor. Additionally, the investigator should attempt to complete the Week 20 visit with the CPET as close as safely possible to the originally planned date. An Unscheduled Visit is required every 4 weeks during this period. This may be completed via telephone and should include at minimum a review for adverse events/serious adverse events, documentation of concomitant therapy, and evaluation for ACS signs and symptoms