STATISTICAL ANALYSIS PLAN

Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of Omecamtiv Mecarbil on Mortality and Morbidity in Subjects with Chronic Heart Failure with Reduced Ejection Fraction

METEORIC-HF
Multicenter **E**xercise **T**olerance **E**valuation of **O**mecamtiv Mecarbil **R**elated to **I**ncreased **C**ontractility in **H**eart **F**ailure

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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	03APR2018	Original version based on the Original Protocol (16JUL2018)
Amendment 2 (v2.0)	30JUL2020	Updates made per Protocol Amendment 1 1. **7.5 Subgroup Analyses** Deleted the subgroup by paced rhythm at peak exercise on baseline CPET 2. **8 Interim Analyses and Early Stopping Guidelines** • Changed conditional power from 0.2 to 0.1 to strop the study due to futility • Added ECG data interim analysis 3. **Appendix C Average Daily Activity Units over Two-Week Intervals** • Included awake time definition based on usual awake time recorded on the eCRF at the end of each wearing period. • Removed the daily activity units endpoints defined using 20 hours wearing criteria Updates made related to COVID-19 4. **3.2 Sample Size** Included the possible COVID-19 impact into the consideration of sample size resize condition to overcome the loss of information due to important protocol deviations due to COVID-19 per Protocol Amendment 1 5. **7.5 Subgroup Analyses** Added a subgroup of subjects who completed planned titration to enable evaluation of treatment effect in subjects who have gone through planned titration 6. **10.2 Subject Accountability** **10.3 protocol deviation** **10.6.1 Adverse Events** **10.6.6 Exposure to Investigational Product** Added descriptive analyses to summarize COVID-19 related subjects early termination from treatment and study, COVID-19 related protocol deviations, COVID-19 Adverse events and COVID-19 impact to the extend expose.

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
		7. **10.5 Efficacy Analyses** **10.5.1 Efficacy Analyses of Primary Efficacy Endpoint** **10.5.3 Efficacy Analyses of Exploratory Endpoints** **10.7 COVID-19 Related Analyses** **10.7.1 Analyses of Efficacy Endpoints** **10.7.2 Identification of Protocol Deviations** To assess the impact of COVID-19, the following additional analyses are included: • Repeating the primary analysis after censoring Week 20 data from subjects who were infected (positive COVID-19 test with or without symptoms) prior to Week 20 CPET • Repeating the primary analysis after censoring Week 20 CPET collected after 24 weeks from randomization • Repeating the primary analysis after censoring Week 20 CPET from subjects with important protocol deviation (per Protocol Amendment 1) due to COVID-19 • Adding supportive analysis to evaluate the potential impact of shelter in place (SIP) in secondary endpoints of daily activity units and KCCQ Total Symptom Score Other updates 8. **10.6.5 Electrocardiogram** Added the ECG data analysis per the Cardiac ECG analysis plan.

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Amendment 3 (v 3.0)	30SEP2021	**1. Remove Amgen throughout the document** **2. 7.5 Subgroup Analyses** added subgroups of • ARNi Use (Y/n) • Region (US/Canada vs. the rest) • CRT use (Y/N) Removed beta blocker user/no use as 95% subjects are in beta blocker use group **3. 10.5 Efficacy Analyses** • added baseline weight in the primary analysis ANCOVA model as covariate • added tipping point analysis for the primary and secondary endpoints per FDA review comments of the SAP • specified missing data will be imputed for the secondary endpoints • specified invalid or non-physiologic CPET will be treated as missing in the analysis • finalized the imputation model. • specified that the primary analysis will report the rank-based p-value in case severe deviation from normal assumption is observed per FDA SAP review comment • added supportive analyses • added actigraphy units endpoints including at least one weekend per FDA SAP review comments **4.** Appendix D Sample SAS code • added SAS code to evaluate treatment effect as function of baseline LVEF as continuous variable
Version 4.0	05JAN2022	**1.** added subgroup analysis by IND site status to comply with SOPs **2.** fixed typo of in the scope of subgroup analyses.

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Table of Abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
BID	Twice a day
COVID-19	Coronavirus disease 2019
CPET	Cardiopulmonary exercise testing
$C_{predose}$	Plasma concentration prior to the investigational product administration
CRT	Cardiac resynchronization therapy
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of study
FAS	Full analysis set
HF	Heart failure
NYHA	New York Heart Association
IBG	Independent biostatistical group
IND	Investigational new drug
IP	Investigational product
IWRS	Interactive web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LSM	Least squares mean
LVEF	Left ventricular ejection fraction
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
OM	Omecamtiv mecarbil
PK	Pharmacokinetic
pVO_2	Peak oxygen uptake
QTcF	Fridericia corrected QT
RER	Respiratory exchange ratio
SAS	Safety analysis set
SD	Standard deviation

SIP	Shelter in place
TSS	Total symptom score
VE/VCO_2	Ventilatory efficiency
$VO_2/logVE$	Oxygen uptake efficiency
WHO Drug	World Health Organization Drug Dictionary

1. Introduction

The purpose of this Statistical Analysis Plan is to provide details of the statistical analyses that have been outlined within the protocol for omecamtiv mecarbil (OM) study CY 1031 (original dated 16 July 2018, protocol amendment 1 dated 31July 2019 and protocol amendment 2 dated 31July 2020). The scope of this plan includes the interim analyses and the final analysis that are planned and will be executed by the Biostatistics department unless otherwise specified.

2. Objectives

2.1 Primary

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

2.2 Secondary

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

2.3 Exploratory

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

2.4 Safety

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

3. Study Overview

3.1 Study Design

This is a randomized, placebo-controlled, double-blind, parallel group, multicenter study in subjects with heart failure (HF) with reduced ejection fraction. 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 subjects with persistent atrial fibrillation at screening will be capped at approximately 20% and subjects with paroxysmal atrial fibrillation will be excluded. Investigational product (IP) will be started at 25 mg orally 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. All subjects will be managed with standard of care HF therapies consistent with regional clinical practice guidelines.

3.2 Sample Size

Assuming a difference in change from baseline of peak oxygen uptake (pVO_2) of 1.0 mL/kg/min for OM versus placebo, a standard deviation (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 subjects 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 and before the potential interim analysis, if the missing data rate or pooled SD is larger than expected Cytokinetics 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 approximately 400 and the decision of whether to increase the sample size based on blinded information will be documented. More specifically, if the overall pooled SD is > 2.5 mL/kg/min, >15% of randomized subjects are missing Week 20 CPET data points, or the total number of Week 20 CPET data points in subjects with important protocol deviations (per Protocol Amendment 1) due to Coronavirus disease 2019 (COVID--19) is >10% of the total number of randomized subjects, then the sample size may be adjusted.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Endpoint

- Change in pVO_2 on CPET from baseline to Week 20

4.1.2 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

4.1.3 Exploratory Endpoints

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

4.1.4 Safety Endpoints

- Subject incidence of reported AEs and serious AEs. Major adverse cardiovascular (CV) events will be adjudicated by a clinical events committee, 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 stoke

4.2 Planned Covariates

Baseline covariates include, but are not limited to the stratification factors based on the RER on the baseline CPET (<1.15, ≥1.15), persistent atrial fibrillation at screening (Y/N), age, sex, hemoglobin level, and baseline measurements.

5. Hypotheses

The null hypothesis for the primary endpoint is that the treatment difference (OM – placebo) of mean change from baseline of pVO_2 at Week 20 is 0 and the alternative hypothesis is that the treatment difference is > 0 (favors OM). The tests will be reported with two-sided p-values, but only the direction favoring OM direction will be considered success.

6. Definitions

6.1 Study Endpoints

KCCQ Scores

Algorithms for deriving the scores for the KCCQ instrument at each time point are in Appendix B.

Daily activity units

Algorithms for deriving the average daily activity units measured over a 2-week period are in Appendix C.

6.2 Study Time Points

Randomization Date

The randomization date for each subject is the date the investigator (or designee) confirms in the Interactive Web Response System (IWRS) that the subject has met all eligibility criteria and is randomized and will be captured on the electronic case report form (eCRF).

First Dose Date of Investigational Product

For each subject, the first dose date of IP is defined as the date of the first administration of IP (OM or placebo).

Last Dose Date of Investigational Product

For each subject, the last dose date of IP is defined as the date of the last administration of IP (OM or placebo).

Study Day 1

The date of the first IP administration or the date of randomization for subjects who are not administrated any dose of IP.

Study Day

For each subject and a given date of interest, study day is defined as the number of days since Study Day 1:

Study day = (date of interest – study day 1 date) + 1

If the date of interest is prior to the study day 1:

Study day = (date of interest – study day 1 date).

Subject-level End of Study Date

For each subject, the end of study (EOS) date is the date recorded on the End of Study eCRF.

Data Cutoff Date for Interim Analyses

The data cutoff date for the interim analysis will be determined with the data monitoring committee (DMC) if results from Study 20110203 become available prior to the completion of this study.

6.3 Demographics and Baseline Related Definitions

Baseline values include pVO_2 on CPET, total workload, ventilatory efficiency (VE/VCO_2 slope), 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), exercise duration, average daily activity units, KCCQ TSS and its sub-domains, laboratory parameters, vital signs, electrocardiogram (ECG), and New York Heart Association (NYHA) class. Baseline value of average daily activity units is the average of non-missing daily activity units from the 2-week interval prior Study Day 1 (Appendix C). Safety baseline values are the last non-missing value collected prior to or on Study Day 1. Other efficacy baseline values are the last non-missing value collected prior to or on Study Day 1. For laboratory parameters, only measurements assessed by the central laboratory will be used for baseline.

Baseline Estimated Glomerular Filtration Rate

The baseline estimated glomerular filtration rate (eGFR) will be calculated from demographic information and baseline serum creatinine by the Modification of Diet in Renal Disease formula (Levey 2006):

eGFR (mL/min/1.73 m^2) = 175 x $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if black), where S_{cr} is serum creatinine measured mg/dL.

For subjects where the calculation cannot be performed due to missing data, the last locally assessed serum creatinine screening measurement will be used in the calculation.

Randomization Stratification Factors

The stratification variables of RER and persistent atrial fibrillation will be those recorded at randomization in IWRS and integrated to the eCRF page. RER at baseline from CPET

data transfer and persistent atrial fibrillation collected on the HF/atrial fibrillation eCRF page will be used for subgroup analyses.

Change from Baseline

The arithmetic difference between a post-baseline value and baseline for a given time point:

Change from baseline = (post-baseline value – baseline value)

6.4 Other Study Related Definitions

Analytical Study Week Assignments

Analytical windows will be used to assign parameters to study weeks. The algorithm is provided in Appendix A.

Actual Treatment Group

A subject's actual treatment group is the randomized treatment group, unless the subject receives treatment throughout the study that is different than the randomized treatment group assignment, in which case the actual treatment group is the treatment received.

Actual Dose Group

Subjects in the OM actual treatment group will be identified as 25 mg BID, 37.5 mg BID, or 50 mg BID, or discontinuing IP prior to dose adjustment based on the dose assigned at Week 8. If a subject discontinues IP prior to the start of Week 8 (IWRS Week 8 dispensation), then the subject will be identified as discontinued IP prior to dose adjustment. The actual dose group may be used in select safety displays.

Investigational Product Exposure Period

For subjects dosed with IP:

[(Last IP administration date – date of Study Day 1) + 1]/ 365.25 * 12 (in months)

[(Last IP administration date – date of Study Day 1) + 1]/7 (in weeks)

Study Exposure Period

For each randomized subject:

Study Exposure Period = (EOS Date - First IP Dose Date + 1)/ 365.25 * 12 (in months)

Study Exposure Period = (EOS Date - First IP Dose Date + 1)/ 7 (in weeks)

Treatment-emergent Adverse Event

For the purpose of reporting, an investigator-reported event starting on or after first dose of IP and up to and including 30 days after the last dose date of IP will be labeled as a treatment-emergent AE.

7. Analysis Subsets

7.1 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. Subjects will be analyzed according to their randomized treatment group assignment.

7.2 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.

7.3 Pharmacokinetic Analysis Set

The pharmacokinetic (PK) analysis set includes all randomized subjects who have received at least one dose of OM and have at least one PK sample collected. This analysis set will be used for all PK analyses unless associated dosing or sampling information are missing.

7.4 Interim Analyses Sets

If results from Study 20110203, which is concurrently running to Study CY 1031, become available prior to the completion of this study, Cytokinetics may instruct the independent biostatistical group (IBG) to perform a single interim analysis for review by the DMC in the context of the current benefit/risk profile for subjects. For the interim analyses, interim versions of the FAS will be created that include all subjects randomized up to the data cutoff date for the interim analyses.

7.5 Subgroup Analyses

Subgroup analyses will be conducted for the primary and secondary estimands. In case of incorrect randomization stratification information entered to the IWRS by site at randomization, the correct value recorded on the eCRF or from vendor transferred data

(ECG, CPET) will be used for the subgroup analyses. Prespecified subgroups for the analysis include:

- stratification factor RER on baseline CPET (<1.15, ≥1.15)
- RER on baseline CPET (≤ median, > median)
- stratification factor persistent atrial fibrillation (Y/N)
- Region (US/Canada vs rest of world)
- IND site status (IND sites vs. Non-IND sites)
- 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 left ventricular ejection (LVEF) fraction (≤ median, > median)
- baseline N-terminal prohormone brain natriuretic (NT-proBNP) after excluding subjects in atrial fibrillation at screening (≤ median and > median)
- ARNi Use (Y/n)
- 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)
- subjects who completed planned titration (subjects in placebo group will be included regardless of completing planned titration or not)
- Cardiac resynchronization therapy (CRT) use (Y/N)

8. Interim Analyses and Early Stopping Guidelines

An IBG will perform the interim analyses and provide the interim reports to an independent DMC for data review meetings. The DMC will review all available safety and efficacy data periodically. The IBG and DMC will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the DMC and IBG will not have any direct contact with study center personnel or subjects. The DMC will communicate major safety concerns and recommendations regarding study modification or termination based on the safety and efficacy parameters to Cytokinetics in accordance with the DMC charter.

In addition to DMC data review meetings, Cytokinetics may instruct the IBG to conduct interim analysis if results from Study 20110203 become available prior to the completion of this study for review by the DMC in the context of the current benefit/risk profile for subjects. Sample size resize decision must be made prior to this interim analysis. The CY 1031 interim analysis will not occur when the information fraction is less than 50% based on the planned sample size or the re-estimated sample size if the decision is made to increase the sample size. The interim analysis was decided not to happen as the information fraction is less than 50% based on the planned sample size when Study 20110203 results became available in October of 2020.

At this interim assessment, the DMC may recommend stopping this study due to superiority if statistical significance on treatment difference between OM and placebo in the primary endpoint is achieved using a two-sided alpha of 0.0001 following the Haybittle-Peto approach (Haybittle 1971; Peto 1976). The DMC may also recommend stopping the study due to futility if the conditional power is < 0.10. Treatment difference will be calculated based on the interim FAS using the same analysis method for the primary endpoint in Section 10.5.1. Conditional power, assuming future data will follow the same trend at interim analysis, will be calculated as follows:

First obtain the Z test statistic calculated as the least squares mean (LSM) estimate of treatment difference divided by the standard error. Next calculate the conditional power assuming future data follow the same distribution as data used in the interim analysis:

$$CP = \Phi(-z_{1-\frac{\alpha}{2}}(\sqrt{1-I_t})^{-1} + Z_t\sqrt{\frac{I_t}{1-I_t}} + Z_t\sqrt{\frac{1-I_t}{I_t}}),$$

Where $z_{1-\alpha/2}$ is the critical value from normal distribution for two sided α level test and Z_t is the Z test statistic calculated above, $I_t = \frac{(n_a{}^{-1}+n_c{}^{-1})^{-1}}{N_a{}^{-1}+N_c{}^{-1}}$ is the information fraction at time t where n_a and n_c are sample size at interim analysis for OM and placebo groups respectively, N_a and N_c are total sample size for OM and placebo groups, respectively, and $\Phi(z)$ is the standard normal distribution function.

The stopping rules are to be considered non-binding and 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 CY 1031 are being collected to evaluate the effect of omecamtiv mecarbil on the QT interval in the event that the results from the registrational Study 20110203 might support the approval of omecamtiv mecarbil. In the event CY 1031 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. Approximately 50 subjects who complete the protocol specified treatment will be included for this analysis. An independent third party will conduct the QT analysis according to an ECG statistical analysis plan and provide the unblinded report to the Study 20110203 study team while the CY 1031 study team will remain blinded.

Records of all meetings will be maintained as per the DMC charter.

9. Data Screening and Acceptance

9.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

9.2 Data Handling and Electronic Transfer of Data

Cytokinetics Data Management will provide eCRF data collected in the RAVE database. to be used in the planned analyses. Laboratory test data, ECG, adjudicated events, CPET and daily activity units collected on the wearable device will be provided by the data vendor based on data transfer agreements.

9.3 Handling of Missing and Incomplete Data

9.3.1 Patterns of Missing Data

Subjects may be missing specific data points for various reasons. In general, data may be missing due to a subject's early withdrawal from study, a missing visit, or inevaluability of a data point or an endpoint at a particular point in time. All attempts will be made to capture missing or partial data for this trial prior to the database lock.

The frequency and pattern of missing data for the primary endpoint will be assessed through descriptive summaries of the measurements over time.

9.3.2 Handling of Incomplete Dates

Missing and partially missing dates will be queried. Partial/missing onset dates will be imputed using the following algorithm:

- Set missing year to the randomization date year, missing month to January, and missing day to the 1st
- If after the above, the resulting date is prior to Study Day 1, update the date to Study Day 1

When there is a need to impute partial/missing end dates, the following algorithm will be used.

- Set missing year to the EOS date year, missing month to December, and missing day to the last date of the month
- If after the above, the resulting date is after the subject-level EOS date, update the date to the EOS date

9.4 Detection of Bias

It is not expected that any study conduct procedures will introduce bias in the study results or conclusions. However, potential sources of bias in this study include:

- Major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- Subject level unblinding before final database lock and formal unblinding
- Informative censoring
- DMC related analyses

Major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints will be tabulated in the clinical study report (CSR). Sensitivity analysis may be conducted excluding subjects with major protocol deviations or censoring subjects at the time of the deviations. Examples of protocol deviations that may affect pVO_2 assessments are violation of inclusion or exclusion criteria, using a different exercise modality than that used at baseline, or changing of atrial fibrillation status before being randomized.

Any inadvertent breaking of the blind of individual subjects prior to formal unblinding of the study will be documented in the CSR. The impact of such unblinding on the results will be assessed.

Analyses for the DMC will be provided by the IBG, which is external to Cytokinetics. Details on the DMC are provided in the DMC charter. Any additional unblinding beyond that specified in the protocol will be documented in the CSR. No impact from the DMC review of unblinded data is expected since all DMC members and the IBG supporting DMC are independent to Cytokinetics, the study's Steering Committee and the study sites. Protocol Section 10.3 provides details of access to individual subject treatment assignments by Cytokinetics, or designees.

Reasons for study withdrawal will be summarized in the CSR. If there is a differential study withdrawal rate between treatment groups, then the impact on the primary endpoint will be explored.

Additional sensitivity analyses may be included to assess the impact of the biases on the primary endpoint in Section 10.5.1. If any sensitivity analyses are required to evaluate potential biases in the study's conclusions, then the sources of the potential biases and results of the sensitivity analyses will be documented in the CSR.

9.5 Outliers

Various methods, including univariate summaries, histograms, scatter plots, box plots, and line graphs, may be used to identify outliers in key safety and efficacy variables. Extreme data points will be identified during the blinded review of the data prior to database lock. Such data points will be reviewed with Cytokinetics Data Management to ensure accuracy. The primary analyses will include outliers in the data. Sensitivity analyses may be undertaken if extreme outliers for a variable are observed.

9.6 Distributional Characteristics

The primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model. Model assumption will be assessed by graphical examination of residuals. Section 10.5.1 describes alternative methods when severe deviation from normal assumption or large heterogeneity of residual variance are observed. The use of alternative methods from the planned primary analysis methods will be fully justified in the CSR.

9.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current statistical programming and quality control procedures.

Statistical analyses will be performed using the version 9.4 or later of SAS® on Microsoft Windows operating system.

10. Statistical Methods of Analysis

10.1 General Principles

Efficacy analyses will be performed in the FAS by randomized treatment group and safety analyses will be performed in the SAS by actual treatment group.

If the study is terminated early due to superiority, the data cut used for the interim analysis will be used for the primary efficacy analyses and sensitivity analyses including all data up to the EOS will be conducted. The alpha for testing all primary and secondary

endpoints when terminating early for superiority will be two-sided 0.0001. Exploratory endpoints will be assessed using a nominal alpha level of 0.05 and will not have multiplicity adjustments.

Unless otherwise specified, all hypothesis tests will be reported as 2-sided p-values 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.

Multiplicity Adjustment

In order to preserve an overall type I error rate for the primary and secondary endpoints, primary endpoint and second endpoints in the FAS will be tested in the following pre-specified order using a closed testing procedure. Alpha of 0.0001 (one-sided p-value of 0.00005) will be used to assess superiority at the interim analysis. If the study continues to its planned completion, alpha of 0.05 will be used. Within an analysis, the corresponding alpha will apply to all primary and secondary endpoint hypothesis tests.

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 corresponding alpha 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 corresponding alpha 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 corresponding alpha 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 2-week period from baseline to Week 18-20 in the FAS will be tested at the corresponding alpha level.

10.2 Subject Accountability

The number and percent of subjects who were randomized, received IP, completed IP, discontinued IP and reasons for discontinuing, completed study, and discontinued study and reasons for discontinuing will be summarized by randomized treatment group. A summary of subjects who discontinued treatment/study due to COVID-19 will be provided.

10.3 Important Protocol Deviations

Important Protocol Deviation categories are defined by the protocol deviation classification committee and updated during the Important Protocol Deviation reviews throughout the study prior to database lock. These definitions of Important Protocol Deviation categories, sub-category codes, and descriptions will be used during the course of the study. Subject incidence of Important Protocol Deviation will be summarized by treatment group for all randomized subjects. A summary of protocol deviations due to COVID-19 will be provided separately.

10.4 Demographic and Baseline Characteristics

Demographic (i.e., age, age group [< 65, ≥ 65 and ≥ 75], sex, race, region [North America, Western Europe and Eastern Europe], and ethnicity), stratification variables, and baseline disease characteristics (HF history, characteristics, etiology, and device usage) will be summarized by treatment group and overall using descriptive statistics. Other related medical history will be summarized using appropriate descriptive statistics. Descriptive statistics of regimens will be produced to describe the baseline HF standard of care therapies by treatment group and overall.

10.5 Efficacy Analyses

Table 1 summarizes the primary and secondary efficacy endpoints and planned analysis method.

Table 1 Endpoint Summary Table

Endpoint	Primary Analysis Method	Sensitivity/Subgroup Analysis	COVID-19 Related Analyses
Primary Endpoint: Change in pVO2 on CPET from baseline to Week 20			
Primary estimand[a]	Missing data will be imputed using multiple imputation method (Section 10.5.1). Complete data will be analyzed using an ANCOVA model with fixed effects of treatment, baseline RER randomization strata (<1.15, ≥1.15), persistent atrial fibrillation (Y/N), age, sex, baseline pVO_2 value, baseline hemoglobin level and baseline body weight.	• ANCOVA model will be repeated with missing data from subjects who discontinued OM treatment as if the OM subjects were in the placebo arm. Subgroup analyses for variables in Section 7.5 • Tipping point analysis • ANCOVA model with hemoglobin at Week 20 as additional covariate • Multivariate ANCOVA model to evaluate treatment by covariates interaction; ANCOVA model with significant covariates per model selection • Repeat ANCOVA model for subjects whose Week 20 peak RER ≥ 1.05 • ANCOVA model including baseline LVEF and treatment interaction term evaluating relationship of baseline LVEF and treatment effect. restricted cubit spline is fit to the baseline LVEF. Similarly the relationship of baseline NT-proBNP and treatment effect using the same model will be evaluated.	• Repeat the primary analysis after censoring Week 20 pVO_2 from subjects who were infected (positive COVID-19 test with or without symptoms) prior to Week 20 CPET • Repeat the primary analysis after censoring Week 20 pVO_2 collected after 24 weeks from randomization • Summarize the number of subjects with Week 20 pVO_2 performed out of visit window (≤24 weeks, >24 weeks but ≤28 weeks and >28 weeks from randomization) by treatment groups • Repeat the primary analysis after censoring Week 20 pVO_2 from subjects with important protocol deviation (per Protocol Amendment 1) due to COVID--19 • Summarize observed change from baseline to Week 20 in pVO_2 by Week 20 CPET visit status (Week 20 visit ≤24 weeks, >24 weeks but ≤28 weeks and >28 weeks from randomization) • Summary the number of subjects infected (positive COVID-19 test with or without symptoms) prior to Week 20 CPET

Endpoint	Primary Analysis Method	Sensitivity/Subgroup Analysis	COVID-19 Related Analyses
Secondary estimand[a]	ANCOVA model with fixed effects of treatment, baseline RER randomization strata (<1.15, ≥1.15), persistent atrial fibrillation (Y/N), age, sex, baseline pVO_2 value, baseline hemoglobin level and baseline body weight.	Subgroup analyses for variables in Section 7.5	• Repeat the primary analysis by excluding subjects whose Week 20 pVO_2 are obtained from subjects who were infected (positive COVID-19 test with or without symptoms) prior to Week 20 CPET • Repeat the primary analysis by excluding subjects whose Week 20 pVO_2 collected after 24 weeks from randomization • Repeat the primary analysis after censoring Week 20 pVO2 from subjects with important protocol deviation (per Protocol Amendment 1) due to COVID--19
Secondary Endpoints			
Change in total workload during CPET from baseline to Week 20	Missing data will be imputed using multiple imputation method (Section 10.5.1) and complete data will be analyzed using an ANCOVA model with fixed effects of treatment, baseline RER randomization strata (<1.15, ≥1.15), persistent atrial fibrillation (Y/N), age, sex, baseline total work load, baseline hemoglobin level and baseline body weight	• Tipping point[a] analysis.	• Repeat the primary analysis after censoring Week 20 pVO_2 from subjects who were infected (positive COVID-19 test with or without symptoms) prior to Week 20 CPET • Repeat the primary analysis after censoring Week 20 pVO_2 collected after 24 weeks from randomization • Repeat the primary analysis after censoring Week 20 CPET from subjects with important protocol deviation (per Protocol Amendment 1) due to COVID--19

[a] To be conducted when the primary endpoint is met.

Endpoint	Primary Analysis Method	Sensitivity/Subgroup Analysis	COVID-19 Related Analyses
Change in ventilatory efficiency (VE/VCO_2 slope) during CPET from baseline to Week 20	Missing data will be imputed using multiple imputation method (Section 10.5.1) and complete data will be analyzed using an ANCOVA model with fixed effects of treatment, baseline RER randomization strata (<1.15, ≥1.15), persistent atrial fibrillation (Y/N), age, sex, baseline ventilator efficiency, baseline hemoglobin level and baseline weight	• Tipping point[b] analysis.	• Repeat the primary analysis after censoring Week 20 pVO_2 from subjects who were infected (positive COVID-19 test with or without symptoms) prior to the Week 20 CPET • Repeat the primary analysis after censoring Week 20 pVO_2 collected after 24 weeks from randomization • Repeat the primary analysis after censoring Week 20 CPET from subjects with important protocol deviation (per Protocol Amendment 1) due to COVID-19
Change in the average daily activity units measured over a 2-week period from baseline (Week -2 to Day 1) to Week 18-20	Repeated measures mixed model with terms of treatment, baseline average daily activity units, visit, baseline RER randomization strata (<1.15, ≥1.15), persistent atrial fibrillation (Y/N), as well as interaction terms of treatment-by-visit and baseline-by-visit with an unstructured covariance matrix.	• Repeated measures mixed model will be repeated with missing data imputed if the imputation model for the primary endpoint includes daily activity units (Week 18-20). Missing daily activity units in Week 18-20 interval will be imputed prior to the imputation of the missing primary endpoint. • Sensitivity analysis of average daily activity units derived based on different watch wearing criteria (see Appendix C) by repeating repeated measures mixed model	• Supportive analysis to evaluate effects of group of subjects by the impact of Shelter in Place (SIP) (subjects weren't impacted by the SIP order, subjects with any of the visits impacted by the SIP and subjects enrolled after the re-opening of enrollment, See Section 10.5.2 and Section 10.5.3 for detail), its interaction by treatment, its interaction by visit and treatment in the ANCOVA model. • Repeat the primary analysis after censoring Week 18 - 20 interval data from subjects with important protocol deviation (per Protocol Amendment 1) due to COVID-19

[b] To be conducted when the primary endpoint is met.

Endpoint	Primary Analysis Method	Sensitivity/Subgroup Analysis	COVID-19 Related Analyses
Exploratory Endpoints			
Change in KCCQ TSS from baseline to Week 20	Repeated measures mixed model with terms of treatment, baseline KCCQ TSS, visit, baseline RER randomization strata (<1.15, ≥1.15), persistent atrial fibrillation (Y/N), as well as interaction terms of treatment-by-visit and baseline-by-visit with an unstructured covariance matrix	• Repeated measures mixed model will be repeated with missing data imputed if the imputation model for the primary endpoint includes KCCQ TSS at Week 20. Missing KCCQ TSS at Week 20 will be imputed prior to the imputation of the missing primary endpoint.	• Supportive analysis to evaluate effects of group of subjects by the impact of Shelter in Place (SIP) (subjects weren't impacted by the SIP order, subjects with any of the visits impacted by the SIP and subjects enrolled after the re-opening of enrollment), its interaction by treatment, its interaction by visit and treatment in the ANCOVA model. Repeat the analysis by removing any of these factors with a p-value greater than 0.1. • Repeat the primary analysis after censoring Week 20 data from subjects with important protocol deviation (per Protocol Amendment 1) due to COVID-19
Change from baseline in the average daily activity units at Week 6-8 and at Week 12-14	Repeated measures mixed model with terms of treatment, baseline average daily activity units, visit, baseline RER randomization strata (<1.15, ≥1.15), persistent atrial fibrillation (Y/N), as well as interaction terms of treatment-by-visit and baseline-by-visit with an unstructured covariance matrix	• Repeated measures mixed model will be repeated with missing data imputed • Sensitivity analysis of average daily activity units derived based on different watch wearing criteria (see Appendix C) by repeating the primary analysis method	

Endpoint	Primary Analysis Method	Sensitivity/Subgroup Analysis	COVID-19 Related Analyses
Change from baseline in total daily steps at Weeks 6-8, 12-14 and 19-20.	Repeated measures mixed model with terms of treatment, baseline total daily steps, visit, baseline RER randomization strata (<1.15, ≥1.15), persistent atrial fibrillation (Y/N), as well as interaction terms of treatment-by-visit and baseline-by-visit with an unstructured covariance matrix	Sensitivity analysis and subgroup analysis are not planned.	
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), and exercise duration	ANCOVA model with fixed effects of treatment, baseline RER randomization strata (<1.15, ≥1.15), persistent atrial fibrillation (Y/N), age, sex, baseline value, baseline hemoglobin level and baseline body weight	Sensitivity analysis and subgroup analysis are not planned	Repeat the primary analysis after censoring Week 20 CPET from subjects with important protocol deviation (per Protocol Amendment 1) due to COVID-19

[a] See Table 2 for details on the two estimands for the primary endpoint.

10.5.1 Efficacy Analyses of Primary Endpoint

The primary endpoint is change in pVO_2 from baseline to Week 20. The primary analysis will be performed using an ANCOVA model which will include terms of treatment, baseline RER randomization strata (<1.15, ≥1.15), persistent atrial fibrillation (Y/N), age, sex, baseline pVO_2, baseline hemoglobin level and baseline body weight. Table 2 below displays details of the two estimands for the primary endpoint.

Table 2 Estimands for Primary Endpoint

Attributes	Primary Estimand	Secondary Estimand
Population	Target population of potentially treatable OM subjects. Subjects without any dose of IP excluded.	Hypothetical target population of potentially treatable OM subjects continue with treatment and are capable of completing the Week 20 assessment. Subjects with missing Week 20 pVO_2 due to intercurrent events or discontinuing treatment prior to Week 20 will be excluded.
Variable	Change from baseline to Week 20 in pVO_2. Data to be analyzed include all observed Week 20 pVO_2 values regardless of whether subjects complete 20 weeks of treatment and imputed pVO_2 for subjects who don't have Week 20 pVO_2. Imputation details are provided below.	Change from baseline to Week 20 in pVO_2. Data to be analyzed include observed pVO_2 values from subjects who complete 20 weeks of treatment.
Measure of intervention effect	Mean treatment difference regardless of completing 20 weeks of treatment and experiencing intercurrent events.	Mean treatment difference among all subjects who remained on their randomized treatment for 20 weeks.

Subjects will be followed per the schedule of assessments from randomization through their final visit irrespective of whether the subject is continuing to receive study treatment. Intercurrent events of death and hospitalization due to worsening HF may preclude CPET at Week 20. Other intercurrent events such as other CV AEs and non-CV AEs (e.g., orthopedic injury) could also preclude a CPET test at Week 20. Intercurrent events due to COVID-19 may include subjects missing Week 20 visit due to

the stay-at-home measures, subjects' decision to early terminate from the study due to the COVID-19 precautions, site closures, hospitalization due to COVID-19, or COVID-19 symptoms preventing subjects from coming to the Week 20 visit. Reasons for not completing Week 20 CPET will be recorded on eCRF; categories of reasons include adverse events, early termination, equipment failure, investigator decision, subject decision and other. The percentage of missing CPET data at Week 20 and the reasons for the missing data will be tabulated in the FAS. CPET data deemed to be invalid by the CPET core lab will be treated as missing CPET data in the analysis. The reasoning will be summarized and listed. CPET core lab flags the CPET results as invalid when there are:

- patient specific or technical limitations that preclude exercise, including injury (e.g., acute orthopedic injury), inability to cooperate, or technical malfunction of metabolic cart
- mechanical components that preclude the appropriate acquisition of gas exchange data throughout exercise, including malfunctions of the flow sensor, pneumotachography or similar, and oxygen or carbon dioxide gas analyzers
- Major exercise protocol deviations the differ sufficiently between baseline and Week 20 tests and preclude consistent data acquisition

This type of missing data can be considered as missing at random. .

Missing pVO_2 at Week 20 regardless of type of intercurrent events will be imputed using multiple imputation methodology under the missing at random (MAR) assumption for the primary analysis of the primary estimand.

The imputation model will use regression multiple imputation which includes treatment arm, baseline RER, persistent atrial fibrillation (Y/N), age, sex, baseline pVO_2, baseline hemoglobin, baseline eGFR, baseline body weight, baseline KCCQ TSS, baseline NYHA, baseline average daily activity units (refers to 10 hours of wearing during the awake time for ≥7 days unless otherwise specified). Categorical variables, i.e., treatment arm, persistent atrial fibrillation (Y/N), baseline NYHA, and sex will be specified in the CLASS statement. Fifty (50) imputed datasets will be generated. Missing baseline daily activity units will be replaced by baseline daily activity units derived using 10 hours of wearing during the awake time for ≥4 days criteria. If baseline daily activity units are still missing after above handling, predicted value from a linear model with the baseline daily

activity units as dependent variable and sex, baseline hemoglobin, baseline eGFR, age, baseline KCCQ TSS and baseline body weight as covariates will be used. Change from baseline in pVO_2 will be calculated based on the observed and imputed data. Each of the imputed datasets will be analyzed using the primary analysis ANCOVA model. LSM treatment difference and the standard error will be combined using Rubin's imputation rules to produce a LSM estimate of the treatment difference, its 95% confidence interval, and p-value for the test of null hypothesis of no treatment effect.

Sensitivity analyses will be performed by exploring missing not at random assumption in the imputation of pVO_2: missing pVO_2 from subjects who discontinued OM treatment or missing pVO_2 from subjects from the placebo arm will be imputed based on the model that is constructed using observed pVO_2 data from the placebo arm. Missing pVO_2 from subjects who remained on OM treatment will be imputed based on the model that is constructed using observed pVO_2 data from OM arm. Tipping point analysis will be performed. Negative shift will be applied to impute missing pVO_2 of subjects in OM group. The same imputation model for pVO_2 for the primary analysis will be used in this sensitivity analysis.

Subgroup analyses will be performed by fitting the same ANCOVA model to each subgroup level separately. If a subgroup variable is also a fixed effect in the primary ANCOVA model, the ANCOVA model used in the subgroup analysis of this variable will have this variable removed. Only summary statistics will be presented for the subgroup level when the number of subjects in either treatment arm is ≤ 15 at this level. LSM estimate of the treatment difference, 95% confidence intervals for the mean treatment difference and nominal p-values will be provided for each subgroup level and repeated for all subgroups in Section 7.5.

In order to mitigate the risk of missing Week 20 CPET due to COVID-19, subjects are allowed a visit window of up to 32 weeks from randomization to perform the Week 20 visit. Supportive analysis for the primary estimand will include presenting the number of subjects by Week 20 visit status (Week 20 visit ≤ 24 weeks, >24 weeks but ≤28 weeks and >28 weeks from randomization) by treatment groups and summary statistics of the observed change from baseline in pVO_2 by visit status and treatment groups will be provided. A sensitivity analysis by repeating the primary analysis after censoring Week 20 CPET data collected outside of 24 weeks from randomization will be conducted.

Subjects who are infected (positive COVID-19 test with or without symptoms) during the study will be summarized by treatment group. A sensitivity analysis will be performed to repeat the primary analysis by setting data as missing from subjects who are infected prior to the Week 20 CPET. Another sensitivity analysis will be performed by repeating the primary analysis after setting the Week 20 pVO_2 from subjects with important protocol deviation (per Protocol Amendment 1) due to COVID-19 to missing.

Supportive analyses will be performed by:

1. Adding hemoglobin level at Week 20 to the ANCOVA model. This analysis is based on the observed data.
2. Repeat primary analysis ANCOVA model including subjects with Week 20 CPET peak RER ≥ 1.05
3. Covariates used to define pre-specified subgroups; these covariates by treatment interaction terms will be included in the ANCOVA model. Covariates measured as continuous will be introduced to the model as continuous variable. Global test of covariates by treatment interactions will be performed. Primary analysis ANCOVA model will also be repeated by adjusting for the significant baseline covariates. Stepwise model selection method will be used based on the default stay or entry level of 0.15. These analyses are based on observed data.
4. Evaluating treatment effect as a function of baseline LVEF as continuous variable. Restricted cubic spline will be fitted to baseline LVEF with knots specified as baseline LVEF values at 10^{th}, 50^{th} and 90^{th} percentile. This analysis is based on the observed data.
5. Evaluating treatment effect as a function of baseline NT-proBNP as continuous variable using same method specified in bullet point 3. Baseline NT-proBNP will be log transformed in the model and will be back transformed in the presentation of the treatment effect as function of baseline NT-proBNP.

The assumptions of the ANCOVA model will be investigated graphically. The scaled residuals will be examined. The analysis will be repeated after transforming pVO_2 data into ranks if severe deviation from the normal assumption are observed. The primary analysis will report the rank-based p-value and provide the treatment effect using the current estimates from the primary analysis based on the original scale. Ranks will be applied to all changes from baseline data after the imputation step. Baseline data will be ranked separately.

The secondary estimand will be analyzed using an ANCOVA model with fixed effects of treatment, baseline RER randomization strata (<1.15, ≥1.15), persistent atrial fibrillation (Y/N), age, sex, baseline pVO_2, baseline body weight and baseline hemoglobin level. Subgroup analysis will be performed following the same method for the primary estimand.

10.5.2 Analyses of Secondary Efficacy Endpoints

The analysis method for secondary CPET efficacy endpoints will be the same for the primary efficacy endpoint. The change in the average daily activity units measured over a 2-week period from baseline (Week -2 to Day 1) to Week 18-20 will be analyzed using a repeated measures mixed model with terms such as treatment, baseline value, 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. LSM of treatment difference, 95% of confidence interval and nominal p-value at each visit interval will be presented.

Sensitivity analysis for average daily activity units from baseline to the interval of Week 18--20 will be performed using the same method for average daily activity units from baseline to the intervals of Week 6-8 and Week 12-14 as specified in Section 10.5.3.

10.5.3 Analyses of Exploratory Endpoints

The exploratory efficacy endpoints from CPET will be analyzed using the same ANCOVA model for the primary analysis. LSM of the treatment difference, 95% confidence interval and nominal p-values will be reported. Change from baseline in the average daily activity units at Week 6-8 and at Week 12-14 will be analyzed using the same repeated measures mixed model for the change from baseline to Week 18-20. The change from baseline in the KCCQ TSS and its sub-domains from baseline to Week 20 will be analyzed using a repeated measures mixed model with terms such as treatment, baseline value, 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. Mean differences between treatment arms and associated 95% confidence intervals will be provided.

Average daily activity units derived based on different criteria of watch wearing (Appendix C) will be analyzed using the repeated measures mixed model as sensitivity analysis.

The study enrollment was temporarily suspended due to the COVID-19 pandemic on 14 April 2020 and re-initiated in June 2020. Subjects will be grouped based on the impact of the SIP order: subject's Week 20 visit occurred before the first SIP order in the US (16 March 2020), subjects with any visits (from pre-randomization visit until Week 20 visit) that were impacted by a SIP order, and subjects who were screened after the re-opening of enrollment. Supportive analyses for the average daily activity units and KCCQ TSS will be performed by including the class variable to group subjects by the impact of SIP order and its interaction by treatment, its interaction by visit and treatment in the repeated ANCOVA model. Sensitivity analysis will be performed by repeat the primary analysis after censoring Week 20/Week 18 - 20 interval data from subjects with important protocol deviation (per Protocol Amendment 1) due to COVID-19.

Change from baseline in average total daily steps will be calculated following a similar method used in the average daily activity units and analyzed as an exploratory analysis using the same repeated measures mixed model.

Shift of NYHA classification from baseline to post-baseline will be presented by visit and treatment arm.

Other exploratory endpoints e.g., change in NT-proBNP from baseline to each assessment and changes in resting heart rate as measured by ECG from baseline to each assessment, will be summarized. Summary statistics for change from baseline at each scheduled visit by treatment arm will be reported. Mean differences between treatment arms and associated 95% confidence intervals will be provided.

10.6 Safety Analyses

10.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version at the time of the database lock will be used to code all AEs to a system organ class and a preferred term. All AE tables will be summarized by treatment group.

Subject incidence of AEs will be summarized for all treatment-emergent AEs, serious AEs, AEs leading to withdrawal of IP, fatal AEs and AEs of interest.

Summaries of treatment-emergent and serious AEs occurring in at least 1% of the subjects by preferred term in any treatment arm will be provided in descending order of frequency. Summaries of treatment-emergent COVID-19 AEs and treatment-emergent serious COVID-19 AEs will be provided separately.

Subject incidence of all treatment-emergent AEs, serious AEs, AEs leading to withdrawal of IP and fatal AEs will be tabulated by system organ class and preferred term in descending order of frequency. Subject incidence of AEs of interest (structured MedDRA queries and/or customized queries) will also be summarized according to their categories.

10.6.2 Laboratory Test Results

Laboratory results and their change from baseline will be summarized by treatment group and scheduled assessment for a subset of laboratory analytes provided in the protocol, Table 3. These include creatinine, creatine kinase, total bilirubin, direct bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), NT-proBNP, and troponin I.

Shift tables will be provided by treatment group, which will be based on modified (using only the numerical thresholds) Common Terminology Criteria for Adverse Events (CTCAE; v4.03 or later) grades and will compare baseline laboratory values with the most extreme post-baseline values. Summaries of subjects with post-baseline laboratory values with a CTCAE grade ≥ 3, if available, will be provided. The following shift tables will be generated:

- Total bilirubin (blood bilirubin increased)
- ALP (alkaline phosphatase increased)
- AST (SGOT) (aspartate aminotransferase increased)
- ALT (SGPT) (alanine aminotransferase increased)

Number and percentage of subjects of each troponin I status “below lower limit of quantification”, “measurable but below upper reference limit of the assay”, and “above the upper reference limit of the assay” at each scheduled assessment will be summarized overall and by baseline status. Change of troponin status from baseline to the worst post-baseline status will be tabulated. These summaries will be repeated by using different thresholds based on multiples of the upper reference limit (URL): 1xURL, 2xURL, 3xURL, 4xURL, 5xURL, and 10xURL.

Summaries will also be presented by treating troponin as continuous variable. Troponin values below or above the quantifiable limits will be treated as equal to the limits.

10.6.3 Adjudicated Events

All deaths, HF events, major cardiac ischemic AEs (myocardial infarction, unstable angina hospitalization, and coronary revascularization), and strokes will be adjudicated

by an external clinical events committee in a blinded manner. Subject incidence of positively adjudicated events will be tabulated by treatment group and event type.

10.6.4 Vital Signs

The analyses of vital signs (systolic and diastolic blood pressure and heart rate as measured by pulse) will include summary statistics at each scheduled visit by treatment group.

10.6.5 Electrocardiogram

The baseline ECG is defined as the mean of all pre-dose assessments. PR, RR, QRS, QT, and Fridericia corrected QT (QTcF) intervals and their change from baseline will be summarized by treatment group and scheduled assessment. Subjects will be categorized into the following groups per their maximum change from baseline in QTcF. Unscheduled assessments will be included in the determination of the maximum change. The number and percentage of subjects in each group will be summarized.

- ≤30 msec
- >30 – 60 msec
- >60 msec

Subjects will also be categorized into the following groups per their maximum post baseline QTcF. Unscheduled assessments will be included in the determination of the maximum post baseline value. The number of subjects in each group will be summarized for each dosing group.

- ≤450 msec
- >450 – 480 msec
- >480 – 500 msec
- >500 msec

Statistical analyses of ECG will also be performed per the Cardiac ECG statistical analysis plan.

10.6.6 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to IP by treatment group. Indicators of extent of IP exposure include total IP administration duration (including extended IP exposure due to COVID-19), the total tablet taken count, and total exposure to OM in mg. Placebo exposure will be reported as 0 mg. Total tablet count and total exposure will be calculated for each subject based on data collected on the Drug Accountability eCRF page.

10.6.7 Exposure to Concomitant Medication

The number and proportion of subjects receiving HF therapies of interest will be summarized by preferred term or category for each treatment group using the term from the eCRF or coded by the World Health Organization Drug (WHO DRUG) dictionary for terms requiring coding. Summaries will include baseline concomitant medications and changes in treatment over the study.

10.7 COVID-19 Related Analyses

Additional analyses will be conducted to assess the impact of COVID-19.

10.7.1 Analyses of Efficacy Endpoints

Supportive/sensitivity analyses for the primary endpoint and secondary endpoints as described in Table 1. For the primary endpoint and secondary endpoints derived from the CPET, additional analyses will be conducted using the same ANCOVA model by setting Week 20 CPET assessed after 24 weeks from randomization to missing; setting the Week 20 CPET data from subjects who are infected (positive COVID-19 test with or without symptom) to missing; and setting the Week 20 CPET from subjects with important protocol deviation (per Protocol Amendment 1) due to COVID-19 to missing before repeating the primary analysis.

10.7.2 Identification of Protocol Deviations

A listing of all subjects affected by the COVID-19 related study disruption by unique subject ID and by investigation site, and a description of how the subject's participation was altered will be created.

10.8 Pharmacokinetics and Pharmacokinetic/Pharmacodynamic Analyses

10.8.1 Pharmacokinetic Analyses

Plasma concentrations of OM will be summarized descriptively. Concentration values less than or equal to the lower limit of quantification will be set to zero in the analysis. In the PK data analysis, the lower limit of quantification values (zero) will be excluded.

Actual doses administered and actual sampling times post drug administration will be used in the analysis and nominal times will be used for presenting data in graphs and tables.

In the PK analysis, the following parameter will be summarized:

- Observed concentration prior to the next dose ($C_{predose}$)

Summary statistics of the concentrations of OM will include arithmetic mean, SD and coefficient of variation; median and range; geometric mean and coefficient of variation of geometric mean. The concentrations will be summarized by actual dose at the time of sample collection and overall.

10.8.2 Pharmacokinetic/Pharmacodynamic Analyses

Pharmacodynamic analyses may be performed to explore the relationship between the predose concentration of OM and the primary efficacy endpoint or select secondary endpoints. The predose concentration of OM at Week 20 will be classified into the following categories by quartiles.

- Bin A: $C_{predose} \leq Q1$
- Bin B: $Q1 < C_{predose} \leq Q2$
- Bin C: $Q2 < C_{predose} \leq Q3$
- Bin D: $C_{predose} > Q3$

The following categories of predose concentration of OM at Week 20 will also be evaluated if data permit.

- <200 ng/mL
- ≥200 - ≤750 ng/mL
- >750 ng/mL

The change from baseline in the primary endpoint will be analyzed using the same model for the primary analysis, with term ‘treatment’ replaced by concentration bin (categories defined above and placebo group). Subjects who complete 20 weeks of treatment and provide Week 20 assessment for the primary endpoint will be included in this analysis. The predose concentration of OM from Week 14 will be used if subject Week 20 concentration is not available. Selected secondary endpoints may be analyzed in the same approach using each endpoints’ primary analysis model. The concentration-response relationship will also be estimated using the same model replacing the concentration bin with concentration as a continuous variable.

11. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

12. References

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13. Data Not Covered by This Plan

A subset of subjects will have two structured, qualitative subject interviews, one during the screening period and a second at the end of the follow-up period after the Week 20 CPET is completed. Data collected from the subject interviews are not analyzed under this plan.

14. Appendices

Appendix A. Analytical Study Week Assignments

Vital signs, KCCQ and NYHA class will be summarized by scheduled study visits in descriptive analyses. Since the actual visits may not exactly coincide with the planned visit day, the actual visit day is mapped to the study visit by non-overlapping consecutive intervals covering the entire time continuum with interval endpoints at half of the distance between scheduled visits. The mapping intervals for all distinct schedules are summarized in Table 3.

Handling multiple records assigned to an analytical study week:

If there is more than one record in a study week interval, the analytical record for that specific study week will be defined as the record closest to the scheduled study day of that specific study week (7 x study week + 1). If two records are equidistant from the scheduled day, then the earlier record will be chosen. If there are multiple records on the same day, the last record will be used. The end of each 2-week interval for actigraphy data, i.e., Week 6-8, Week 12-14 and Week 18-20, will be the day prior to the Week 8, 14 and 20 visit, respectively. The visit window for the end of the interval for actigraphy data follows the same window for KCCQ/NYHA class in Table 3. If subjects miss a visit but actigraphy data are available, then the end of the 2-week interval will be the day prior to the normal visit day.

Table 3 Interval Visit Windows

Scheduled Visit Week (Nominal Day)	Vital signs	KCCQ, NYHA class
Week 2 (15)	(1[a], 21]	
Week 4 (29)	(21, 35]	
Week 6 (43)	(35, 49]	
Week 8 (57)	(49, 77]	(1, 77]
Week 14 (99)	(77, 119]	(77, 119]
Week 20 (141)	>119	>119,

[a] Study Day 1.

Appendix B. Patient-reported Outcome Forms/Instruments

There are 10 summary scores within the KCCQ, which are calculated as follows:

1. Physical Limitation

- Code responses to each of Questions 1a-f as follows:

  Extremely limited = 1
  Quite a bit limited = 2
  Moderately limited = 3
  Slightly limited = 4
  Not at all limited = 5
  Limited for other reasons or did not do = <missing value>

- If at least three of Questions 1a-f are not missing, then compute
  Physical Limitation Score = 100*[(mean of Questions 1a-f actually answered) - 1]/4
  (see footnote at end of this appendix for explanation of meaning of "actually answered")

2. Symptom Stability

- Code the response to Question 2 as follows:

  Much worse = 1
  Slightly worse = 2
  Not changed = 3
  Slightly better = 4
  Much better = 5
  I've had no symptoms over the last 2 weeks = 3

- If Question 2 is not missing, then compute

  Symptom Stability Score = 100*[(Question 2) – 1]/4

3. Symptom Frequency

- Code responses to Questions 3, 5, 7 and 9 as follows:

  <u>Question 3</u>
  Every morning = 1
  3 or more times a week but not every day = 2
  1-2 times a week = 3
  Less than once a week = 4
  Never over the past 2 weeks = 5

  <u>Questions 5 and 7</u>
  All of the time = 1
  Several times a day = 2
  At least once a day = 3
  3 or more times a week but not every day = 4
  1-2 times a week = 5
  Less than once a week = 6
  Never over the past 2 weeks = 7

Question 9
Every night = 1
3 or more times a week but not every day = 2
1-2 times a week = 3
Less than once a week = 4
Never over the past 2 weeks = 5

- If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:

  S3 = [(Question 3) – 1]/4
  S5 = [(Question 5) – 1]/6
  S7 = [(Question 7) – 1]/6
  S9 = [(Question 9) – 1]/4

  Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)

4. Symptom Burden

- Code responses to each of Questions 4, 6 and 8 as follows:

  Extremely bothersome = 1
  Quite a bit bothersome = 2
  Moderately bothersome = 3
  Slightly bothersome = 4
  Not at all bothersome = 5
  I've had no swelling/fatigue/shortness of breath = 5

- If at least one of Questions 4, 6 and 8 is not missing, then compute

  Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

5. Total Symptom Score

= mean of the following available summary scores:
  Symptom Frequency Score
  Symptom Burden Score

6. Self-efficacy

- Code responses to Questions 10 and 11 as follows:

  Question 10
  Not at all sure = 1
  Not very sure = 2
  Somewhat sure = 3
  Mostly sure = 4
  Completely sure = 5

  Question 11
  Do not understand at all = 1
  Do not understand very well = 2
  Somewhat understand = 3
  Mostly understand = 4
  Completely understand = 5

- If at least one of Questions 10 and 11 is not missing, then compute

  Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4

7. Quality of Life

- Code responses to Questions 12, 13 and 14 as follows:

  Question 12
  It has extremely limited my enjoyment of life = 1
  It has limited my enjoyment of life quite a bit = 2
  It has moderately limited my enjoyment of life = 3
  It has slightly limited my enjoyment of life = 4
  It has not limited my enjoyment of life at all = 5

  Question 13
  Not at all satisfied = 1
  Mostly dissatisfied = 2
  Somewhat satisfied = 3
  Mostly satisfied = 4
  Completely satisfied = 5

  Question 14
  I felt that way all of the time = 1
  I felt that way most of the time = 2
  I occasionally felt that way = 3
  I rarely felt that way = 4
  I never felt that way = 5

- If at least one of Questions 12, 13 and 14 is not missing, then compute

  Quality of Life Score = 100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

8. Social Limitation

- Code responses to each of Questions 15a-d as follows:

  Severely limited = 1
  Limited quite a bit = 2
  Moderately limited = 3
  Slightly limited = 4
  Did not limit at all = 5
  Does not apply or did not do for other reasons = <missing value>

- If at least two of Questions 15a-d are not missing, then compute

  Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) – 1]/4

9. Overall Summary Score

= mean of the following available summary scores:
Physical Limitation Score
Total Symptom Score
Quality of Life Score
Social Limitation Score

10. Clinical Summary Score

= mean of the following available summary scores:
Physical Limitation Score
Total Symptom Score

Note: references to **"means of questions actually answered"** imply the following.

- If there are n questions in a scale, and the subject must answer m to score the scale, but the subject answers only n-i, where n-i >= m, calculate the **mean of those questions** as

  (sum of the responses to those n-i questions) / (n-i)

  not

  (sum of the responses to those n-i questions) / n

Appendix C. Average Daily Activity Units over Two-Week Intervals

Actigraphy will be collected during 4 sessions throughout the study for 2-week intervals: Week -2 to Day 1 Randomization, Week 6-8, Week 12-14 and Week 18-20. The daily activity units will be derived using the vector magnitude of total daily counts from the three axes for the days with ≥ 10 hours of wearing during the usual awake time collected on the eCRF page at the end of each wearing period. The start of the awake time will be the time subjects usually woke in the past two weeks from the eCRF page minus 1 hour. The end of the awake time will be the time subjects usually went to bed in the past two weeks from the eCRF page. The minimum number of days with no missing daily activity units needed to calculate the average over the 2-week interval is 7 days. If the number of days in the 2-week interval is more than 14 days, days closer to the end of the interval will be used in the calculation. Average daily activity units for each interval will also be calculated based on the following conditions for sensitivity analysis:

1. ≥10 hours of wearing during the awake time for ≥4 days
2. ≥10 hours of wearing during the awake time for ≥7 days including at least one weekend (Saturday or Sunday)

Appendix D. Sample SAS Codes

The followings are the prototype of the codes that will be used for the final analysis of the study. The final version of the statistical codes to be used will be determined prior to the database lock and will be documented in the specification document for the statistical output of the study.

1. SAS code for the final analysis for the
2. primary endpoint

```
proc mixed data=work;
class <treatment arm> <baseline RER> <AF Y/N> <sex>;
    model chg=<base >  <treatment arm> <baseline RER>  <AF Y/N> <age>
    <sex> <hemoglobin at Week 20>/solution ddfm=kr ;
lsmeans <treatment arm>/pdiff cl;
run;
```

This code assumes that the analysis involves 2 levels in treatment arm (e.g., placebo group is coded as 0 and OM is coded as1).

3. SAS code for repeated measures mixed model

```
proc mixed data=work;
        class <Subject> <treatment arm> <baseline RER> <AF Y/N> <visit>;
        model <chg> = <base> <treatment arm> <visit> <visit>*<treatment arm>
        <baseline RER> <AF Y/N> <visit>*<base>/ddfm=kenwardroger;
        repeated <visit> / type=un subject=<Subject>;
        lsmeans <visit>*<treatment arm>/cl pdiff;

run;
```

4. The SAS code for multiple imputation under MAR assumption.

```
3.1 primary imputation model:
proc mi data=work seed=&seed out=miout NIMPUTE=50;
    class <baseline RER <1.15>  <baseline RER> <AF Y/N>  <sex> <treatment
    arm> <base NYHA>;
    var <treatment arm>  <baseline RER>  <AF Y/N> <age> <sex> <base
    pVO2> <base hemoglobin> <base eGFR> <base KCCQ total symptom
    score> <baseline NYHA> <base average daily activity unit> <week 20
    hemoglobin>;
    monotone reg (<W20 hemoglobin> =<baseline hemoglobin> <age> <sex>
    <baseline eGFR> );
    monotone reg(W20 pVO2);
run;
```

3.2 multiple imputation for KCCQ and average daily activity unit

```
First missing KCCQ total symptom score and average daily activity unit will be
imputed using MCMC under MAR as below. proc mi data=work1 seed=&seed1
out=miout1 NIMPUTE=50;
    by <baseline RER <1.15>  <baseline RER> <AF Y/N>  <sex> <treatment
    arm> <base NYHA>;
    mcmc  IMPUTE=FULL;
    var <base KCCQ>  <KCCQ Week 8>  <KCCQ Week 14> <KCCQ Week 20>
```

```
    <base daily activity unit> <daily activity unit Week 6-8>  <daily activity unit
    Week 12-14> <daily activity unit Week 18-20>;

 run;
```

The pooled estimates from the 50 imputed datasets are obtained from the following codes.

```
proc mianalyze data=est;
  modeleffects estimate;
  stderr stderr;
run;
```

5. The SAS code for multiple imputation under MNAR assumption using the primary imputation model.

```
proc mi data=work seed=&seed out=miout NIMPUTE=50;
    class <baseline RER <1.15>  <baseline RER> <AF Y/N>  <sex> <trt>
<base NYHA>;
    var <treatment arm>  <baseline RER>  <AF Y/N> <age> <sex> <base
    pVO2> <base hemoglobin> <base eGFR> <base KCCQ total symptom
    score> <baseline NYHA> <base average daily activity unit> <week 20
    hemoglobin>;
    monotone reg (<W20 hemoglobin> =<baseline hemoglobin>, <age>, <sex>,
    <baseline eGFR> );
    monotone reg(W20 pVO2);
    mnar adjust (W20 pVO2/shift=&shift adjustobs=(Trt='1'));
run;
```

tipping point analysis will use the same SAS code. Shift can be set as actual value of decrease of 90% observed mean from the overall mean, , decrease of 70% of mean of the observed mean from overall mean .

6. SAS code for cumulative logit model

```
proc genmod data=work;
        class <Subject> <treatment arm> <baseline RER> <AF Y/N> <visit>;
        model <NYHA> = <treatment arm> <visit> <visit>*<treatment arm>
        <baseline RER> <AF Y/N> /dist=multinomial link=cumlogit
        aggregate=<treatment arm>;
        repeated  subject=<Subject>/type=un;

run;
```

7. The normality assumptions for the ANCOVA analysis will be assessed by residual illustration. The outpred option in the above code stores residuals which are used to test the assumption of normality. Examination of residuals can be done using the following codes.

```
    proc univariate data=outpred normal plot;
        var resid;
        qqplot resid;
    run;
```

8. The SAS code for Kaplan-Meier method is as follows:

```
PROC LIFETEST data=work;
    time <time>*censor(0);
    strata <treatment>;
run;
```

9. SAS code evaluating treatment effect as function of baseline LVEF as continuous variable

```
proc glimmix data=pvo2;
     class <subject> <RANDRER> <RANDAF> < trt01pn> <sex>;
     effect  <spline LVEF>=spline(<base lvef> / naturalcubic
knotmethod=percentilelist(10 50 90)  details);
     model chg=<base> <RANDRER> <RANDAF> <age>_<baseline
hemoglobin> <base weight> <trt01pn> <sex> <spline LVEF> *trt01pn/dist=n
solution ;

      %do value=10 %to 35 %by 1;
              lsmeans trt01pn/diff at lvef=&value e cl;
      %end;
       output out=Out pred=Pred;
       ods output lsmeans=lsm Diffs=diff ;
 run;
```

Signature Manifest

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