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

GALACTIC-HF
Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure

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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	23MAY2016	Pre-study version to support discussion
Amendment 1 (v2.0)	07SEPT2016	Original version for approved protocol before study initiated
Amendment 2 (v3.0)	04DEC2019	1. **2.1 Primary Endpoint, p.11** **4.1.1 Primary Endpoint, p.13** **6.1 Study Endpoints, p.15** Clarification of inclusion of presumed CV and presumed sudden deaths in CV death endpoints (exclusion of undetermined/unknown type except in additional analysis) 2. **4.1.3 Safety Endpoint, p.14** **10.6.3 Major Cardiac Ischemic Events, p.38** Additional safety analyses around time to MI to evaluate the MI component of the composite endpoint of major cardiac ischemic adverse events 3. **6.2 Study Time Points, p.17** Added 'blinded' text to first dose date of IP to clarify exclusion of placebo run-in. Also, added 'blinded' text to last dose date of IP for consistency. 4. **6.3 Demographics and Baseline Related Definition, p.20** Added MAGGIC HF risk scores as an additional descriptor of risk for the sampled population 5. **6.3 Demographics and Baseline Related Definition, p.20** Additional texts around baseline eGFR to address potentially missing data cases for the MDRD calculation

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Amendment 2 (v3.0) (Continued)		6. **6.4 Other Study Related Definitions, p.18** Added Randomized Treatment Group definition for completeness 7. **6.4 Other Study Related Definitions, p.21** Updated the 'IP exposure period in Months' definition, to 'Last Dose Date of IP' which is identified in the SAP rather than referencing a form 8. **7.6 Subgroup Analyses, p.23** Additional subgroup analysis on baseline systolic blood pressure < 100 mmHg to provide a clinically relevant threshold beyond the existing data driven sampled population median subgrouping 9. **8 Interim Analyses and Early Stopping Guidelines, p.24** **10.1 General Principles, p.29** Added text around the primary analysis and interim analysis and what is included in each if the study ends early at the second interim due to superiority 10. **10.5.2 Analyses of Secondary Efficacy Endpoints, p.34** Additional analyses around the KCCQ TSS to address an alternative approach to missingness due to deaths, following discontinuation of IP, and due to having a HF event near the KCCQ collection time

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Amendment 2 (v3.0) (Continued)		11. **10.5.3 Analyses of Exploratory Endpoints, p.35** **Appendix B. Time-to-event Endpoint Inclusion and Censoring, p.46** Clarified that time to first events for the primary composite endpoint will also include the component of HF events for urgent or unscheduled clinic/office/ED visit 12. **10.5.3 Analyses of Exploratory Endpoints, p.35** Clarified and provided reference to the Newcombe interval using the minimum risk weight 13. **10.6.8 Exposure to Investigation Product, p.40** Removed summaries for total tablet count due to needed assumptions mapping accountability to exposure 14. **10.6.7 Electrocardiogram (ECG), p.39** Removed QTcB per FDA Guidance for Industry E14 (2017) Clinical Evaluation of QT/QTc Interval Prolongation for Non-Antiarrhythmic Drugs—Questions and Answers (R3) [(accessed on 26 September 2017)]; Available online: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm073161.pdf

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Amendment 2 (v3.0) (Continued)		**15. Appendix A. Analytical Study Week Assignments, p.45** Updated the table intervals to be consistent with the latest protocol **16. Appendix B. Time-to-event Endpoint Inclusion and Censoring, p.46** Clarified the footnote defining the index date by the various endpoints **17. Throughout** Addition of showing results by randomization setting throughout to facilitate risk/benefit evaluation by randomization setting **18. Throughout** 'Sensitivity' analyses was changed to 'Additional' analyses throughout (except for Tipping Point Analysis) to follow language from the ICH E9 (R1) guideline **19. Authors** Updated to current SLS **20. Table of Abbreviations** Updated terms and corrected spelling errors
Amendment 3 (v4.0)	06FEB2020	**1. 7.1 Efficacy Analysis Set, p.22** **7.2 Safety Analysis Set, p.23** **11 Changes From Protocol-Specified Analyses, p.41** Following investigations including a Good Clinical Practice inspection, the sponsor along with the executive committee decided to exclude study site [redacted] from analysis due to data irregularities and lack of source documentation necessary to verify the legitimacy of the irregular findings

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Amendment 3 (v4.0) (Continued)		2. **8 Interim Analyses and Early Stopping Guidelines, p.24** To clarify the trigger for limited unblinding 3. **9.3.2 Handling of Incomplete Dates, p.27** Allow imputation for partial EOS dates due to death where date of death is unknown. Removed text specific to imputing concomitant medication start date to allow for both start and end dates imputation rather than setting to missing.
Amendment 4 (v5.0)	16JUN2020	1. **6.2 Study Time Points, p.19** Updated the LPEPD definition to account for additional scenarios around the use of the long term status forms 2. **10.5 Efficacy Analyses, p.34** **10.5.2 Analyses of Secondary Efficacy Endpoints, p.37** Added a meta-analysis pooled estimate of the KCCQ TSS treatment differences to understand the overall treatment effect. Also, added mixed models for each component of the KCCQ TSS for Symptom Frequency Score and Symptom Burden Score. 3. **10.5 Efficacy Analyses, p.34** **10.5.1 Analyses of Primary Efficacy Endpoint, p.36** **10.7 COVID-19 Related Analyses, p.45** **10.7.1 Investigation Product Discontinuations, p.45** **10.7.2 Analyses of Efficacy Endpoints, p.45** **10.7.3 Identification of Protocol Deviations, p.46**

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Amendment 4 (v5.0) (Continued)		**Appendix B. Time-to-event Endpoint Inclusion and Censoring, p.51** To assess the impact of COVID-19, the following additional analyses are included: • Tipping point analysis modified to censor subjects who prematurely ended the study due to COVID-19 • Cumulative plot of EOIP to evaluate potential rise in EOIP due to COVID-19 • Repeat TTE analyses by shifting the cut-off date earlier in time to contextualize the treatment effect in the pre-, during and post-COVID-19 measures phases • RPSFT models were added to estimate the treatment effects accounting intercurrent events of IP discontinuation due to COVID-19 and overall IP discontinuation • TTE analyses were added that censor subjects at COVID-19 AE start dates • TTE analyses were added that censor subjects at geographic specific COVID-19 impact dates • Listing of subject impacted by COVID-19 per FDA Guidance on Conduct of Clinical Trials of Medicinal Products during COVID-19 Public Health Emergency [(accessed on 27 April 2020)]; Available online: https://www.fda.gov/media/136238/download

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Amendment 4 (v5.0) (Continued)		**4. Appendix A. Analytical Study Week Assignments, p.50** Optimization collection of target therapies was added to provide clarity for the mapping intervals to the study week visits.

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Table of Abbreviations

ACEi	Angiotensin-converting-enzyme inhibitor
ADPC	Analysis Dataset for PK Concentrations
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARB	Angiotensin II receptor blocker
ARNi	Angiotensin receptor-neprilysin inhibitor
AST	Aspartate aminotransferase
BID	Twice a day
CEC	Clinical events committee
CGR-S	Clinician global ration of severity
CK-MB	Creatine (phospho)kinase-MB
CPMS	Clinical Pharmacology Modeling and Simulation
CRT	Cardiac resynchronization therapy
CSR	Clinical study report
CV	Cardiovascular
CV%	Coefficient of variation in percent
DMC	Data monitoring committee
EC	Executive committee
ECG	Electrocardiogram
ECGAS	Electrocardiogram analysis set
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOI	Events of interest
EOIP	**End of investigational product**
EOS	End of study
EQ-5D-5L	EuroQol five dimensions questionnaire five level version
FAS	Full analysis set
GSO-DM	Global Study Operations-Data Management
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
NYHA	New York Heart Association
IBG	Independent biostatistical group
ICD	Implantable cardioverter-defibrillator
IP	Investigational product

IPD	Important protocol deviation
IXRS	Interactive (Web/Voice) Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
LCSSD	Last confirmed survival status date
LLOQ	Lower limit of quantification
LPEPD	Last Non-Fatal Potential Endpoint Collection Date
LVEF	Left ventricular ejection fraction
MAGGIC	Meta-Analysis Global Group in Chronic Heart Failure
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
OM	Omecamtiv mecarbil
PGR-S	Patient global rating of severity
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
PRO	Patient reported outcome
QTcF	Fridericia corrected QT
RPSFT	**Rank preserving structural failure time**
SAS	Safety analysis set
TSS	Total symptom score
URL	Upper reference limit

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for AMG 423 study 20110203 dated 31 August 2016. 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 omecamtiv mecarbil (OM) compared with placebo on the time to cardiovascular (CV) death or first heart failure (HF) event, whichever occurs first, in subjects with chronic HF with reduced ejection fraction (HFrEF) receiving standard of care (SoC) therapy
  - A death is defined as a CV death endpoint if the death is positively adjudicated as a CV death, presumed CV death, or presumed sudden death (Hicks et al. [2015]).
  - A HF event is defined as presentation of the patient for urgent, unscheduled clinic/office/emergency department (ED) 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.

2.2 Secondary

- to evaluate the effects of OM on time to:
  - CV death
  - heart failure hospitalization
  - all-cause death
- to evaluate the effects of treatment with OM on change in patient-reported outcomes (PROs)

2.3 Safety

- to evaluate the safety of OM as measured by subject incidence of reported adverse events, including serious adverse events of ventricular arrhythmias requiring treatment and positively adjudicated major cardiac ischemic events (fatal and nonfatal myocardial infarction, unstable angina hospitalization, and coronary revascularization) (Hicks et al. [2015])

2.4 Exploratory

- to evaluate the effect of OM on the risk for HF events and HF hospitalizations in subjects randomized during hospitalization for HF during the first:
  - 30 days after discharge
  - 60 days after discharge

- to evaluate the effect of OM on n-terminal prohormone brain natriuretic peptide (NT-proBNP) changes
- to evaluate the effect of OM on first and recurrent HF events
- to evaluate the effect of OM on recurrent HF hospitalizations
- to evaluate the effect of OM on the composite of time to CV death or first HF hospitalization, whichever occurs first
- to evaluate the effect of OM on the composite of time to all-cause death or first HF hospitalization, whichever occurs first
- to evaluate the effect of OM on resting heart rate
- to evaluate the effect of OM on KCCQ changes over time
- to evaluate the effect of treatment with OM on the composite of time to CV death, HF event, myocardial infarction, hospitalization for unstable angina, coronary revascularization, and stroke, whichever occurs first
- to further characterize the pharmacokinetics (PK) of OM

3. Study Overview

3.1 Study Design

This is a randomized, placebo-controlled, double-blind, parallel group, multicenter, CV outcomes study for oral OM in subjects with HFrEF, including subjects with ongoing or history of HF hospitalization. Approximately 8000 eligible subjects will be randomized in a 1:1 ratio to receive either OM or placebo. Randomization will be stratified by randomization setting (currently hospitalized for HF or recently and not currently hospitalized for HF) and region (5 groupings: US and Canada - Latin America - Western Europe, South Africa, and Australasia - Eastern Europe including Russia - Asia). Approximately 25% or more of the total planned enrollment will include subjects who are hospitalized at randomization. Enrollment of subjects with atrial fibrillation will be limited to 20% of each enrollment setting.

The study is event-driven and will conclude when approximately 1590 CV death events have occurred. Amgen along with the study Executive Committee will estimate the date for initiating the end of study procedures based on the anticipated date of occurrence of approximately 1590 CV death events.

Interim analysis for potentially stopping the trial before observing the approximately 1590 CV deaths are planned for when approximately one-third and two-thirds of the planned CV deaths are observed. Futility for the primary endpoint will be assessed at both interim analyses. Efficacy will be assessed only at the second interim analysis.

All deaths, heart failure events, and major cardiac ischemic adverse events (myocardial infarction, unstable angina hospitalization, and coronary revascularization) and strokes

will be adjudicated by an independent external Clinical Events Committee (CEC), using standardized definitions. An external independent Data Monitoring Committee (DMC) will formally review the accumulating data from this trial to ensure there is no avoidable increased risk for harm to subjects. The DMC will also be responsible for conducting the interim analyses and providing recommendations regarding stopping the trial. An Executive Committee (EC) has been formed to advise on trial design and implementation and for assistance in the communication of trial results. Analyses for the DMC will be provided by the Independent Biostatistical Group (IBG), which is external to Amgen. Details for each committee will be provided in committee charters.

3.2 Sample Size

The sample size calculation is based on the CV mortality component of the primary composite endpoint. The control group event rate is assumed to vary by randomization setting. Subjects randomized in a hospital setting are assumed to have greater risk in the first year of 19% followed by the constant yearly outpatient setting rate of 7%. Assuming 25% of subjects will be randomized in the hospital setting, the CV mortality rate in the first year is expected to be 10% overall subjects and 7% for each year thereafter.

A 24 month enrollment period is assumed and the total study duration set to 48 months. The hazard ratio for CV death alone is assumed to be 0.8 after a 3-month treatment lag at the beginning of the trial, where the hazard ratio is assumed to be 1. Additionally assume 10% of subjects discontinue therapy per year and 10% of subjects over the course of the trial will be lost to endpoint determination. The overall type I error is 0.05 for 2-sided testing. After accounting for these factors, a total sample size of approximately 8000 subjects with approximately 1590 subjects experiencing CV death events is required to ensure a power of 90% for testing superiority for CV death (Shih [1995]). Assuming the rates for experiencing either a heart failure event or CV death are double those for CV death alone and the same other assumptions as for CV death alone, the primary composite endpoint is expected to have > 99% power when the primary analysis is triggered.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Endpoint

- composite of time to CV death or first HF event, whichever occurs first
  - A death is defined as a CV death endpoint if the death is positively adjudicated as a CV death, presumed CV death, or presumed sudden death (Hicks et al. [2015]).
  - A HF event is defined as an urgent, unscheduled clinic/office/ED 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.

4.1.2 Secondary Endpoints

- time to CV death
- change in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ TSS) from baseline to Week 24
- time to first heart failure hospitalization
- time to all-cause death

4.1.3 Safety Endpoints

- subject incidence of reported adverse events
- subject incidence of reported serious adverse events of ventricular arrhythmias requiring treatment
- subject incidence of positively adjudicated major cardiac ischemic events
  - adjudicated major cardiac ischemic adverse events are: myocardial infarction, hospitalization for unstable angina, percutaneous coronary intervention/coronary artery bypass graft (Hicks et al. [2015])
- time to first positively adjudicated MI
- time to first positively adjudicated MI or investigator final diagnosis of MI
- time to first positively adjudicated MI or investigator final diagnosis of MI or potential endpoint type of MI

4.1.4 Exploratory Endpoints

- incidence of HF events within the first 30 days and the first 60 days after index hospitalization in subjects randomized during HF hospitalization
- incidence of HF hospitalizations within the first 30 days and the first 60 days after index hospitalization in subjects randomized during HF hospitalization
- change in NT-proBNP from baseline to each assessment
- change in resting heart rate from baseline to each assessment
- time to first HF event

- times to recurrent HF events
- times to recurrent HF hospitalizations
- composite of time to CV death or first HF hospitalization, whichever occurs first
- composite of time to all-cause death or first HF hospitalization, whichever occurs first
- changes in KCCQ scores from baseline to each assessment
- OM concentration at Week 2 and Week 6
- composite of time to CV death, HF event, myocardial infarction, hospitalization for unstable angina, coronary revascularization, and stroke, whichever occurs first

4.2 Planned Covariates

Baseline covariates are eGFR and the stratification factors of randomization setting (currently hospitalized for HF or recently and not currently hospitalized for HF) and region (5 groupings: US and Canada - Latin America - Western Europe, South Africa, and Australasia - Eastern Europe including Russia - Asia). Additional covariates may be explored following subgroup analyses.

5. Hypotheses

The null hypothesis for the primary endpoint is that the hazard ratio for treatment vs placebo (OM/placebo) from a Cox model for the composite of time to CV death or first HF event is 1 and the alternative hypothesis is the hazard ratio is < 1 (favors OM). The null and alternative hypotheses for the secondary time to event endpoints are the same as for the primary endpoint. For the KCCQ TSS, the null hypothesis is that the treatment difference (OM – placebo) of mean change from baseline to Week 24 is 0 for both strata and the alternative is that the treatment difference is > 0 (favors OM) for at least one stratum. The tests will be reported with two sided p-values, but only those favoring OM direction will be considered success. For the F-test for KCCQ TSS, success will be considered if one of the stratum effects favors OM.

6. Definitions

6.1 Study Endpoints

Endpoints Contributing to Primary Analysis

All positively adjudicated endpoints (CV death, heart failure events, major cardiac ischemic events, and stroke) occurring after randomization and prior to or on the analysis cut-off date will be included in the primary analysis.

Heart failure events

Heart failure events included in endpoint analyses will be limited to those positively adjudicated as a heart failure event. The type of heart failure event will be further

classified as hospitalization, urgent emergency room or department visit, or urgent office or practice visit.

Cardiovascular death

A death will contribute as a cardiovascular death endpoint if the death is positively adjudicated as a known CV death, presumed CV death, or presumed sudden death. A death with an undetermined cause without evidence to presume CV death or presume sudden death, termed an unknown cause death, will not be considered as a cardiovascular death except in an additional analysis of time to CV death.

Major cardiac ischemic events

A major cardiac ischemic event is any event positively adjudicated as a myocardial infarction, hospitalization for unstable angina, or a coronary revascularization. A death with one of these event types as a cause of death will contribute an event of that type.

Time to event endpoints

Only events adjudicated as positive are included in the time-to-event analysis. The index date varies by the endpoint. Appendix B summarizes which events are included in analysis and the censor dates for each event type and analysis. The below definitions describe the different calculations for each time-to-event endpoint. Refer to the CEC charter for definitions of each event type.

Time to first event in days

Time-to-first event is defined as the time from the randomization date to the date of the event calculated as:

- For subjects who experienced such event,
    - event = yes (ie, censor = no)
    - time-to-event (days) = adjudicated onset date – randomization date + 1
- For subjects who do not experienced such event,
    - event = no (ie, censor = yes)
    - time-to-event (days) = censor date – randomization date + 1

Time to first HF event/hospitalization after the index hospitalization in days

Time to first HF event/hospitalization after an index hospitalization (the hospitalization at randomization) will be used in exploratory analyses and is only defined for subjects randomized in the hospital setting

- For subjects who experienced such event,
    - event = yes (ie, censor = no)
    - time-to-event (days) = adjudicated onset date – index hospitalization discharge date + 1
- For subjects who do not experienced such event,
    - event = no (ie, censor = yes)
    - time-to-event (days) = censor date – index hospitalization discharge date + 1

Time to first major cardiac ischemic event in days

Time to first major cardiac ischemic event will be used in safety analyses and is only defined for subjects dosed with investigational product (IP)

- For subjects who experienced such event,
    - event = yes (ie, censor = no)
    - time-to-event (days) = adjudicated onset date – first dose date + 1
- For subjects who do not experienced such event,
    - event = no (ie, censor = yes)
    - time-to-event (days) = censor date – first dose date + 1

KCCQ Scores

Algorithms for deriving the scores for the KCCQ instrument at each time point 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 IXRS that the subject has met all eligibility criteria and is randomized and will be captured on the electronic case report form (eCRF).

Enrollment Date

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date in the subject's medical record and in the eCRF.

First Dose Date of Blinded Investigational Product

For each subject, the first dose date of blinded investigational product is defined as the date of the first administration of investigational product (omecamtiv mecarbil or placebo).

Last Dose Date of Blinded Investigational Product

For each subject, the last dose date of blinded investigational product is defined as the date of the last administration of investigational product (omecamtiv mecarbil or placebo). If the date is not available from the administration eCRF, the decision date from the end of IP form will be used.

Study Day 1

Study Day 1 will be the date of the first blinded IP administration. For subjects randomized, but not administered any dose of IP, Study Day 1 will be set to the randomization date.

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 (EOS) Date

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

Study End Date

The study end date is the last end of study date of all randomized subjects.

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, for the purposes of conducting the primary analysis, whether the study concluded according to the prespecified protocol or was terminated. The primary completion is the same as the end of study and is the date when the last subject has completed the study. If the study concludes prior to the time point originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

Vital Status

For mortality endpoints, vital status will be recorded using the following 2 approaches:

- For subjects who died on study, the vital status will be recorded on the EOS eCRF with an EOS reason of death and an EOS date as the date of death.
- For subjects who withdraw early from the study with reasons other than death, an assessment of vital status will be performed during the study closeout, as allowed by local law and regulations, and recorded on an eCRF.

Death recorded from both approaches will be a potential endpoint and adjudicated by the CEC.

Last Confirmed Survival Status Date (LCSSD)

For each subject, the last confirmed survival status date (LCSSD) is the last date on which the subject is either known alive or dead. For subjects who die on study or die after withdrawing early from the study but have death recorded on the Survival and Non-fatal Endpoint Status eCRF, the adjudicated death date will be the LCSSD. For subjects who did not die, the LCSSD will be the later of the EOS date or the last confirmed alive date recorded on the Survival and Non-fatal Endpoint Status eCRF if available. For interim analyses, the LCSSD will be:

- If the subject died: the adjudicated death date
- Otherwise if the subject ended the study: the later of the last alive date on the Survival and Non-fatal Endpoint Status eCRF if the form exists and the EOS date
- Otherwise: the interim analysis data cut-off date.

Last Non-Fatal Potential Endpoint Collection Date (LPEPD)

For each subject, the last non-fatal potential endpoint collection date (LPEPD) is the last date for which the subject non-fatal endpoint status is known. **The LPEPD will be:**

- **If the subject ended IP due to death or completed IP as recorded on the End of IP (EOIP) eCRF: the adjudicated death date for subjects with an adjudicated death date on or prior to the EOS date or else the EOS date**
- **Otherwise: the last date for non-fatal data collection on or prior to EOS date or else the EOS date**

If the LPEPD calculated above is after the EOS date, the LPEPD will be set to the EOS date.

For the interim analyses, the LPEPD will be:

- If the subject ended the study and Survival and Non-fatal Endpoint Status eCRFs available: the last date for non-fatal potential endpoint collection on the Survival and Non-fatal Endpoint Status eCRF
- Otherwise if the subject ended the study and Survival and Non-fatal Endpoint Status eCRFs not available: the adjudicated death date for subjects with an adjudicated death date on or prior to the EOS date and the EOS date for other subjects
- Otherwise: the interim analysis cut-off date.

Analysis Cut-off Date

An analysis cut-off date will be set so that the planned 1590 CV deaths will be achieved with confidence based on available data or the study is decided to be terminated for other reasons. The analysis cut-off date will be used to censor and exclude events occurring close to the termination of the study.

Data Cut-off Date for Interim Analyses

The data cut-off date for each of interim analysis will be determined when each milestone approaches through discussions with the IBG and DMC. This date will be used to censor endpoint data for the formal interim analysis assessments. Events occurring after the interim analysis cut-off date will be excluded but if available those events can be included in additional analyses supporting recommendation making.

Censor Date

Endpoints will be censored differently according to the endpoint and specific analysis being conducted. The details of censoring schema are described in Appendix B.

6.3 Demographics and Baseline Related Definitions

Baseline laboratory parameters, vital signs, KCCQ scores, Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk scores, EQ-5D, PGR-S, CGR-S, NYHA class, and physical measurements

The baseline value for each laboratory parameter, vital sign, KCCQ scores, MAGGIC HF risk scores, EQ-5D, PGR-S, CGR-S, and physical measurement will be 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. The

MAGGIC HF risk score will be calculated using baseline variables as described in Pocock et al. (2013).

Baseline estimated glomerular filtration rate (eGFR)

The baseline eGFR will be calculated from demographic information and baseline serum creatinine by the MDRD formula (Levey et al. [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. Otherwise, the average value of the baseline eGFR from other subjects with the same age, sex, and race will be used to fill in the missing data. If no subject has the same age, sex, and race, then age group will be used.

Randomization setting and region

The stratification variables of randomization setting (currently hospitalized for HF or recently and not currently hospitalized for HF) and region (5 groupings: US and Canada - Latin America - Western Europe, South Africa, and Australasia - Eastern Europe including Russia - Asia) will be those recorded at randomization in IXRS.

Updated versions of these variables obtained on the eCRF for randomization setting or investigator details data for region will be used for the subgroup analyses.

Baseline electrocardiogram (ECG) parameters

The baseline value for each ECG parameter will be the mean over all central non-missing triplicate averages of 3 (or all available) readings from each set of triplicate taken prior to or on Study Day 1.

Change from Baseline

The arithmetic difference between a post-baseline value and the baseline value for a given variable at a given time point is defined as:

Change from baseline = (post-baseline value at given time point – baseline value).

Percent Change from Baseline

The percent change from baseline for a given variable at a given time point is defined as:

100 × [(post-baseline value at given time point – 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.

Randomized Treatment Group

A subject's randomized treatment group is the assignment at randomization to either AMG 423 + SoC or Placebo + SoC.

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.

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. The dose group will be the last dose received on or prior to Week 12 (on or prior to Study Day 91). Note that for subjects who discontinue IP prior to this date, the dose group will be the last dose received.

IP Exposure Period in Months

For subjects dosed with IP:

[(Last Dose Date of IP – date of Study Day 1) + 1]/ 365.25 * 12.

Study Exposure Period in Months

For each randomized subject:

Study Exposure Period = (EOS Date – Randomization Date + 1)/ 365.25 * 12.

Treatment-emergent Adverse Event

For the purpose of reporting, an investigator reported event starting on or after first dose of investigational product as determined by the flag indicating if the event started prior to the first dose on the Events eCRF and up to and including 30 days after the end of investigational product will be labeled as a treatment-emergent adverse event. This classification does not depend on event type collected on the Events eCRF or adjudication result for those events with a type of potential endpoint.

7. Analysis Subsets

7.1 Efficacy Analysis Set

Efficacy analyses will be performed on the full analysis set (FAS), which includes all randomized subjects excluding subjects in [redacted] study site [redacted] 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 1 dose of IP on study excluding subjects in [redacted] study site [redacted] 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 PK analysis set (PKAS) includes all randomized subjects who have received at least one dose of omecamtiv mecarbil 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 Electrocardiogram Analysis Set

The electrocardiogram analysis set (ECGAS) will include all subjects in the SAS with at least one central ECG measurement.

7.5 Interim Analyses Sets

Interim analyses will be performed by the IBG and results reviewed by the Data Monitoring Committee (DMC) when approximately one-third and two-thirds of the planned CV deaths have been observed. For the interim analyses, interim versions of the FAS will be created that include all subjects randomized up to the data cut-off date for the interim analyses.

7.6 Subgroup Analyses

Subgroup analyses will be conducted for the primary composite endpoint and the secondary endpoint of time to cardiovascular death. Prespecified subgroups for the analysis include, but are not limited to:

- randomization setting (currently hospitalized for HF or recently and not currently hospitalized for HF)
- region (5 groupings: US and Canada - Latin America - Western Europe, South Africa, and Australasia - Eastern Europe including Russia - Asia)
- age (< 65 years, ≥ 65 years)
- sex (male, female)
- baseline weight (quartiles)
- race (black or African American, white, Asian, other)
- ethnicity (Hispanic or Latino, not Hispanic or Latino)
- baseline NYHA Class (II, III/IV)
- diabetes mellitus at baseline (yes, no)
- primary cause of HF (ischemic, nonischemic)
- medical history of myocardial infarction (yes, no)
- presence of atrial fibrillation (yes, no)
- baseline LVEF (≤ median, > median)
- baseline NT-proBNP by randomization setting excluding atrial fibrillation/flutter subjects (≤ median, > median)
- baseline resting heart rate (≤ median, > median)
- baseline systolic blood pressure (≤ median, > median)
- baseline systolic blood pressure < 100 mmHg
- baseline eGFR (≤ 60 mL/min/1.73m^2, > 60 mL/min/1.73m^2)
- baseline use of ACEi
- baseline use of ARB
- baseline use of aldosterone inhibitor
- baseline use of ARNi
- baseline presence of CRT
- baseline presence of ICD

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 Data Monitoring Group 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 Amgen in accordance with the DMC charter.

In addition to DMC data review meetings, independent interim analyses for futility will occur when approximately one-third and two-thirds of the planned total cardiovascular death endpoints are observed. The interim analysis will be conducted by the IBG and assessed by the DMC. The timing of these interim analyses will be determined in discussions with the DMC. Further, the boundary at the first interim will be on the harm side so the first futility assessment provides some guidance on earlier termination of the study if there are signs of harm. Superiority will be assessed at the second interim as well. This superiority assessment is performed to check if there is strong favorable benefit-risk profile and consistency between the composite endpoint and its component of time to CV death.

The futility bounds will be determined based on the observed information fraction at the time of the interim analysis using a beta spending function. Only the primary composite endpoint will be formally assessed for futility. The spending function to determine the bounds will be a nonbinding gamma (Hwang, Shih, and De Cani [1990]) with parameter -4 and beta of 0.01:

$$f(t; \text{beta}, \text{gamma}) = \text{beta} * (1-\exp(-\text{gamma} * t))/(1 - \exp(-\text{gamma}))$$

At the planned information fractions of one-third and two-thirds, this spending function will have early termination for futility guidance bounds of approximately hazard ratio z-score > 0.78 for the first interim analysis and z > -0.68 for the second interim. A positive direction z-value is indicative of favoring placebo.

If the study is terminated for superiority at the second interim analysis, the following endpoints and components will be assessed using the interim analysis data:

- composite of time to CV death or first HF event, whichever occurs first
- time to CV death
- change in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ TSS) from baseline to Week 24
- time to first heart failure hospitalization
- time to all-cause death

- time to first HF event
- composite of time to CV death or first HF hospitalization, whichever occurs first
- composite of time to all-cause death or first HF hospitalization, whichever occurs first
- composite of time to CV death, HF event, myocardial infarction, hospitalization for unstable angina, coronary revascularization, and stroke, whichever occurs first

The primary composite endpoint and the secondary endpoint time to cardiovascular death will be assessed using the Haybittle -Peto approach with an overall one-sided alpha of 0.0005 (two-sided 0.001). The guidance for the superiority assessment is both endpoints achieve statistical significance at an overall one-sided alpha of 0.0005 for stopping early due to superiority. The same multiplicity adjustment alpha propagation approach for the primary analysis will be used for the interim analysis. The DMC will also review safety data to assess risk relative to benefit in making recommendations. If the study is terminated early for superiority, the interim analysis hypothesis test results will be used as the primary hypothesis test results. The same data cut-off will be used to assess the remainder of the secondary endpoints (change in KCCQ TSS from baseline to Week 24, time to first HF hospitalization, and time to all-cause death) using the same overall one-sided alpha of 0.0005 following the testing diagram (Figure 1). Safety analyses will use all available data when the study is terminated. Exploratory endpoints not associated with primary and secondary components will not be assessed using the interim analysis data.

The futility and superiority stopping guidance for the interim analysis is considered nonbinding. Details for procedures following a recommendation from the DMC to terminate the study are contained in the DMC charter. If the DMC recommends to terminate the study at the second interim analysis, blinding restrictions will be removed for limited staff to support the interim analysis. Removal of access restrictions will be documented and those members unblinded will be prohibited from being involved in the study conduct and monitoring during the study close-out period.

Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be stored in the Amgen official document management system at the conclusion of the study. Further details are provided in 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

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

An Analysis Dataset for PK Concentrations (ADPC) will be provided to CPMS from Biostatistics.

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 the database lock.

The frequency and pattern of missing data for non-time-to-event efficacy endpoints will be assessed through descriptive summaries of the measurements over time.

For all time-to-event endpoints (for examples, primary and secondary endpoints), there will be no imputation of the data except for incomplete dates of the events.

9.3.2 Handling of Incomplete Dates

Missing and partially missing dates will be queried. Partial/missing onset dates adjudicated by the CEC for time-to-event endpoints 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
- If the event is death, set the date to be the maximum of the above date, EOS date, and last confirmed alive date

Adverse event (AE) and concomitant medication with completely or partially missing dates will be queried. If the date is still incomplete with year only or year and month only after the query, the start date will be imputed as described in Table 1.

Partial EOS dates due to death will be imputed by using the adjudicated death date (or imputed adjudicated death for partial date). If the death is pending adjudication then use the AE date (or imputed AE date for partial date).

Table 1. Incomplete Adverse Event and Concomitant Medication Dates Imputation

	Missing	Imputation	Exception
AE and concomitant medication	Day	1	Default to Study Day 1 if an event occurred the same year and month as Study Day 1
	Day / Month	1-Jan	Default to Study Day 1 if an event occurred the same year as Study Day 1

9.4 Detection of Bias

It is not expected that any study conduct procedures or statistical analyses 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
- DMC related analyses
- Informative censoring

Major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints will be tabulated in the Clinical Study Report (CSR). Additional analysis may be conducted excluding subjects with major protocol deviations or censoring subjects at the time of the deviations.

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.

For DMC related analyses, details of access to subject level treatment assignments are provided in the protocol, Section 10.3. Analyses for the DMC will be provided by the IBG, which is external to Amgen. Details on the DMC are provided in the DMC charter. Any additional unblinding beyond protocol specified will be documented in the CSR. No impact from the DMC review of unblinded data is expected since all of DMC members and the IBG supporting DMC are independent to the Amgen study team and the study's Executive Committee.

Reasons for study withdrawal will be summarized in the CSR. If there is a differential study withdrawal rate (lost to follow-up or full consent withdrawn) between treatment groups, then the impact on primary and secondary endpoints will be explored.

Additional sensitivity analyses may be included to assess the impact of the biases on the primary and secondary endpoints. 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 clinical 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.

PK plasma concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard practice.

9.6 Distributional Characteristics

The time to event analyses will use a Cox proportional hazards model. The proportionality assumption and function form of the continuous covariate of baseline eGFR will be assessed graphically. 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 risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.3 or later.

10. Statistical Methods of Analysis

10.1 General Principles

The study will conclude when approximately 1590 subjects have experienced a key secondary endpoint event of cardiovascular death. At that time, 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 by actual treatment group.

If the study is terminated early due to superiority, the data cut used for the interim will be used for hypothesis testing for the primary and secondary efficacy analyses. The primary analysis will occur at the final analysis and include estimation for time-to-event endpoints up to the analysis cut-off date using the final analysis data and other efficacy and safety endpoints using the final data. Additional analyses utilizing the final analysis data with data cuts of the interim analysis cut-off date and termination decision date data cut will be conducted for the primary and secondary endpoints. If the analysis cut-off date aligns with one of these additional data cut-off dates, that additional data cut-off will not be performed The alpha for testing all primary and secondary endpoints when terminating early for superiority will be that of the second interim analysis. Exploratory endpoints will report nominal p-values regardless of when the study completes.

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. Missing data will not be imputed in the primary analysis of the primary and secondary endpoints except for in additional analyses of the KCCQ TSS accounting for event driven missingness.

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

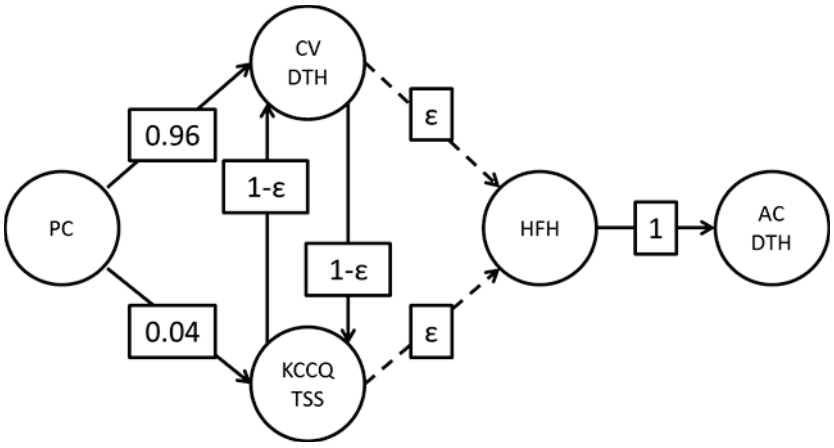
Continuous variables will be summarized using descriptive statistics, including the number of observations (n), mean, standard deviation or standard error, median, the first quartile and third quartile, minimum, and maximum. Categorical variables will be summarized using the number and percent of subjects. Events occurring prior to randomization will be excluded from incidence summaries.

Multiplicity Adjustment

In order to preserve an overall type I error rate of 0.05 for the primary and secondary endpoints, the following multiplicity adjustment will be performed:

A total alpha of 0.001 (one-sided 0.0005) will be used for assessing superiority at the second interim analysis. If the study continues, a total alpha of 0.05 will be used for testing at the primary analysis triggered based on observing approximately 1590 CV deaths. Within an analysis, the total alpha will apply to all primary and secondary endpoint hypothesis tests. The primary endpoint will be tested first with the total alpha. If the primary endpoint reaches statistical significance, a Bonferroni split will be used where 0.96α is allocated to testing the time to CV death and 0.04α is allocated to testing change baseline in the KCCQ TSS. Alpha from a statistically significant result for these two endpoints after the split will propagate to the other endpoint (Bretz et al. [2009]) with a small alpha (0.0001 × fraction of the α used in the statistically significant test) propagating to testing time to first heart failure hospitalization. If statistical significance is achieved for both the time to CV death and change from baseline in the KCCQ TSS, time to first heart failure hospitalization will be tested at the full alpha. If time to first heart failure hospitalization is statistically significant, time to all-cause death will be tested with the same alpha as time to first heart failure hospitalization. Figure 1 illustrates the multiplicity testing propagation approach. Alpha will only propagate if the direction of the statistically significant effect favors omecamtiv mecarbil. Exploratory endpoints will be assessed using a nominal alpha level of 0.05 and not have multiplicity adjustments.

Figure 1. Multiplicity Testing Propagation Approach



PC = primary composite endpoint; CV DTH = time to CV death; KCCQ TSS = Kansas City Cardiomyopathy Questionnaire Total Symptom Score; HFH = time to first heart failure hospitalization; AC DTH = time to all-cause death.

Each circle represents a hypothesis test. The values in boxes on the arrows indicate the fraction of α propagated in the direction of the arrow to the next hypothesis test(s). ε = 0.0001, a small value to complete the graph while prioritizing the CV death and KCCQ TSS endpoints over the time to first heart failure hospitalization and all-cause death endpoints. Dashed arrows used to emphasize this prioritization.

No multiplicity adjustment will be made for exploratory, additional, or sensitivity analyses.

10.2 Subject Accountability

The number and percent of subjects who were randomized, received investigational product, completed investigational product, discontinued investigational product and reasons for discontinuing, completed study, and discontinued study and reasons for discontinuing will be summarized by randomized treatment group and randomization setting.

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol. Subject incidence of IPDs and eligibility deviations will be summarized by treatment group and randomization setting for all randomized subjects.

10.4 Demographic and Baseline Characteristics

Demographic (ie, age, age group [< 65, >= 65 and >= 75], sex, race, region, and ethnicity), stratification variables, and baseline disease characteristics (heart failure history, characteristics, etiology, and device usage) will be summarized by treatment group, randomization setting, and overall using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple races as well as by combination of races. Other related medical history will be summarized using appropriate descriptive statistics. Descriptive statistics of regimens will be produced to describe the baseline heart failure standard of care therapies by treatment group, randomization setting, and overall.

10.5 Efficacy Analyses

A table summarizing the primary and secondary efficacy endpoints and planned analysis methods is below:

Table 2. Endpoint Summary Table

Endpoints	Primary Summary and Analysis Method	Additional Analyses (sensitivity)	**COVID-19 Related Analyses**
Primary Endpoint			
Composite of time to CV death or first HF event, whichever occurs first	• Cox model stratified by randomization setting and region and containing terms for baseline eGFR and treatment group	• Stratified logrank test • Repeat of Cox model excluding events after the min(LPEPD, EOS date, analysis cut-off date) • Tipping point analysis (sensitivity)	• **Repeat of Cox model by shifting the cut-off date earlier in time** • **RPSFT models for any and COVID-19 related IP discontinuations** • **Repeat of Cox model censoring subjects at the time of the COVID-19 AE start date** • **Repeat of Cox model censoring subjects at the geographic specific COVID-19 impact dates**
Secondary Endpoints			
Time to CV death	• Cox model stratified by randomization setting and region and containing terms for baseline eGFR and treatment group	• Repeat of Cox model including all undetermined cause deaths as CV deaths and all events up to the LCSSD	• **Repeat of Cox model by shifting the cut-off date earlier in time** • **RPSFT models for any and COVID-19 related IP discontinuations** • **Repeat of Cox model censoring subjects at the time of the COVID-19 AE start date** • **Repeat of Cox model censoring subjects at the geographic specific COVID-19 impact dates**

Table 2. Endpoint Summary Table

Endpoints	Primary Summary and Analysis Method	Additional Analyses (sensitivity)	**COVID-19 Related Analyses**
Secondary Endpoints (Continued)			
Time to first heart failure hospitalization	• Cox model stratified by randomization setting and region and containing terms for baseline eGFR and treatment group		• **Repeat of Cox model by shifting the cut-off date earlier in time** • **RPSFT models for any and COVID-19 related IP discontinuations** • **Repeat of Cox model censoring subjects at the time of the COVID-19 AE start date** • **Repeat of Cox model censoring subjects at the geographic specific COVID-19 impact dates**
Time to all-cause death	• Cox model stratified by randomization setting and region and containing terms for baseline eGFR and treatment group	• Repeat of Cox model including all events up to the LCSSD	• **Repeat of Cox model by shifting the cut-off date earlier in time** • **RPSFT models for any and COVID-19 related IP discontinuations** • **Repeat of Cox model censoring subjects at the time of the COVID-19 AE start date** • **Repeat of Cox model censoring subjects at the geographic specific COVID-19 impact dates**

Table 2. Endpoint Summary Table

Endpoints	Primary Summary and Analysis Method	Additional Analyses (sensitivity)	**COVID-19 Related Analyses**
Secondary Endpoints (Continued)			
Change in KCCQ TSS from baseline to Week 24	• Mixed model containing the baseline value, region, baseline eGFR, scheduled visit, treatment, and interaction of treatment with scheduled visit fit within each randomization setting. Only planned visits at Week 12 and 24 will be included. • **Random effects meta-analysis approach for the overall treatment effect** • Regression model with treatment, baseline eGFR, baseline KCCQ TSS, and stratification factors using fractional hot deck imputation with cells by treatment, discontinuation of IP, randomization setting, region, baseline value, Week 12 KCCQ TSS, and recency of a heart failure event.	• Repeat regression model for the domain of subjects known to be alive at the planned Week 24	

Table 2. Endpoint Summary Table

Endpoints	Primary Summary and Analysis Method	Additional Analyses (sensitivity)	**COVID-19 Related Analyses**
Exploratory Endpoint			
• **Composite of time to CV death or first HF hospitalization, whichever occurs first**			• **Repeat of Cox model by shifting the cut-off date earlier in time** • **RPSFT models for any and COVID-19 related IP discontinuations** • **Repeat of Cox model censoring subjects at the time of the COVID-19 AE start date** • **Repeat of Cox model censoring subjects at the geographic specific COVID-19 impact dates**

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10.5.1 Analyses of Primary Efficacy Endpoint

The primary endpoint is the composite of time to CV death or first HF event, whichever occurs first. The composite endpoint will be assessed using a Cox model stratified by randomization setting and region. The Cox model will include terms for baseline eGFR and the treatment group. The treatment effect will be tested using a likelihood ratio test and 95% confidence intervals for the model parameters will be computed. Intervals and parameters will be exponentiated to display on the hazard ratio scale.

Kaplan-Meier estimates of cumulative incidence of the composite endpoint will be computed by randomization setting and overall. Associated 95% pointwise confidence intervals will be estimated using the log transformation.

The Cox model will be fit for subgroups of each stratification factor and the other prespecified subgroups.

The following analyses will be conducted:

- Stratified logrank test (no use of baseline eGFR)
- Repeat of the Cox model including events only up to the minimum of the LPEPD, EOS date, and analysis cut-off date
- Tipping point analysis (sensitivity) where subjects who discontinued the study early (not ending the study due to death or **COVID-19**) have five randomly drawn exponentially distributed time-to-event variables multiply imputed with specified hazard ratios. The hazard ratio for imputing where the p-value crosses alpha will be determined.

The assumptions of the Cox model will be investigated graphically. In particular, the Schoenfeld residuals for each covariate will be examined.

Additional analysis with different transformations or additional terms (for example, spline or polynomial expansions) for baseline eGFR may be conducted after reviewing the plots.

The interaction of baseline eGFR and treatment group will be assessed by adding the interaction term to the Cox model and reporting the associated coefficient and 95% confidence interval. Interactions between the treatment group and subgroups will be assessed by 95% confidence intervals for the ratio in treatment group hazard ratios from the subgroup models computed using Wald methods (exponentiated difference in beta coefficients).

Positively adjudicated endpoints and the components (heart failure events and CV deaths) as first event in the primary composite endpoint and regardless of being the first event in the primary composite endpoint will be tabulated. Events including those obtained after the analysis cut-off date will also be tabulated as an additional analysis.

10.5.2 Analyses of Secondary Efficacy Endpoints

Analyses for time to CV death, time to first heart failure hospitalization, and time to all-cause death will use the same model as for the primary composite endpoint. Overall Kaplan-Meier estimation will occur using the same approach as for the primary composite endpoint. For time to CV death and time to all-cause death, an additional analysis including all events up to the LCSSD (including any after the analysis cut-off date) and including all undetermined cause deaths as CV deaths will be conducted using the same Cox model. Graphical methods for assessing the models will be repeated for the secondary time to event endpoints.

Change in KCCQ TSS from baseline to Week 24 will be assessed using a mixed model fit within each randomization setting containing the baseline TSS value, region, baseline eGFR, scheduled visit, treatment group, and the interaction of treatment group with scheduled visit. Only the planned visits at Week 12 and Week 24 will be included. An unstructured covariance matrix will be used within each randomization setting to correlated observations over time within a subject. Treatment group means and differences in means for each visit will be estimated marginalizing over the baseline TSS value, baseline eGFR, and region using the pooled mean over all subjects in the FAS within each randomization setting. Associated 95% confidence intervals for change from baseline will be reported for each visit within each randomization setting. An omnibus F-test with two numerator degrees of freedom will be used to test the treatment effect of OM versus placebo. The test will use the marginalized mean differences to placebo within each randomization setting at Week 24. **An overall pooled estimate for the KCCQ TSS treatment difference to placebo will also be calculated using a likelihood based approach of Hardy and Thompson (1996). Similarly, for each component of the KCCQ TSS, Symptom Frequency Score and Symptom Burden Score, the change in score from baseline to Week 24 will also be assessed using the mixed model.**

As an additional analysis, a cell based fractional hot deck imputation method will be used to impute to missing Week 24 KCCQ TSS values. Cells will be based on baseline value in quartiles, randomized treatment, discontinuation of IP prior to the Week 24 visit, randomization setting, region, directionality of change from baseline to Week 12, and occurrence a HF event in the month before or after the Week 24 visit. Fully efficient fractional imputation (FEFI) method as described in Kim and Fuller (2013) will be used to impute the missing data in each cell. Subjects with a death prior to Week 24 will be included in cells with subjects having a HF event. The imputation-adjusted jackknife replicate weights will be computed for variance estimation. Imputation will occur sequentially in steps as described in Mukhopadhyay (2016). Values not imputed after using the full cell specification will be attempted to be imputed by removing from the cell creation one at a time in order of region, directionality of Week 12, and the baseline value. Values not imputed after this sequential step will be attempted to be imputed by removing from the cell creation combinations of those variables in increasing order and adding recency of HF event and discontinuation of IP at the end of the increasing sequence of removals. Estimates of the mean differences between treatment groups and associated 95% confidence intervals of KCCQ TSS values from baseline and

Week 24 will be provided by randomization setting and computed from a regression model with Week 24 KCCQ TSS as the response and treatment, baseline eGFR, baseline KCCQ TSS, and region in the model. A separate domain estimate for the domain of subjects alive at week 24 of the mean differences between treatment groups and associated 95% confidence intervals will also be provided by randomization setting.

10.5.3 Analyses of Exploratory Endpoints

HF events and hospitalizations during the first 30 and 60 days after index hospitalization

Counts and proportions of subjects in the FAS randomized in the hospital setting and discharged from the hospital with an event in ≤ 30 days and ≤ 60 days will be reported. Kaplan-Meier estimates and associated 95% confidence intervals will also be reported. Separate calculations will be done for HF events and for HF hospitalizations.

Change in NT-proBNP from baseline to each assessment

Summary statistics for change from baseline in NT-proBNP at each scheduled visit by treatment group and randomization setting will be reported. Mean differences between treatment groups and associated 95% confidence intervals will be provided.

Time to first events

Analyses for each time to event endpoint will use the same model as for the primary composite endpoint. Overall Kaplan-Meier estimation will occur using the same approach as for the primary composite endpoint. The component of the HF events of urgent or unscheduled clinic/office/ED visit will additionally be estimated using the same approach.

Times to recurrent HF events and HF hospitalizations

Times to recurrent HF events and recurrent HF hospitalizations will be assessed separately by:

- A semiparametric joint frailty model of recurrent HF events/hospitalizations and CV death as a terminal event as described in Liu, Wolfe, and Huang (2004). The two component models (recurrent HF events/hospitalization model and CV death) will have baseline functions stratified by randomization setting and region and contain terms treatment group and a common mean 1 gamma distributed frailty random variable to handle correlation between the two processes.
- A negative binomial regression where HF events/hospitalizations and CV death are considered as events. If an event/hospitalization occurs on the same day as a CV death, only one event will contribute to the count. The model will include terms for the stratification factors and treatment group.

- Mean cumulative rate function estimates as described in Ghosh and Lin (2000), where all-cause death is considered a terminating event. Estimation will be by treatment group and randomization setting. These estimates will estimate the expected number of events/hospitalizations where a subject who dies cannot have additional events/hospitalizations.

For each approach, point estimates and associated 95% confidence intervals will be computed.

Changes in KCCQ scores from baseline to each assessment

Summary statistics for change from baseline in each KCCQ score at each scheduled visit by treatment group and randomization setting will be reported. The empirical cumulative distribution function for changes in KCCQ TSS from baseline to Week 24 will be estimated and plotted by treatment group, randomization setting, and by categories defined by the baseline PGR-S (moderate or greater vs less than moderate). Empirical cumulative distribution functions for changes in KCCQ TSS from baseline to Week 24 using the fractionally imputed data will also be provided by treatment group and randomization setting. The proportion of subjects within each treatment group achieving an increase from baseline of 5, 8, 10, 12, and 15 points or more in the KCCQ TSS will be reported overall, by randomization setting, and by baseline PGR-S. The risk difference for each threshold will be estimated using the minimum risk weights of Mehrotra and Railkar (2000) and Newcombe interval as described in Yan and Su (2010). Summary statistics for the individual questions included in the KCCQ TSS score by treatment group and randomization setting will be reported. Mean differences between treatment groups and associated 95% confidence intervals will be provided.

Changes in resting heart rate from baseline to each assessment

Summary statistics for change from baseline in resting heart rate as measured by ECG at each scheduled visits and by treatment group and randomization setting will be reported for subjects in the ECGAS. Mean differences between treatment groups and associated 95% confidence intervals will be provided by randomization setting.

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 and randomization setting.

Subject incidence of AEs will be summarized for all treatment-emergent AEs, serious AEs, AEs leading to withdrawal of investigational product, fatal AEs and AEs of interest (EOI).

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.

Subject incidence of all treatment-emergent AEs, serious AEs, AEs leading to withdrawal of investigational product and fatal AEs will be tabulated by system organ class and preferred term in descending order of frequency. Subject incidence of adverse events of interest (structured MedDRA queries and/or customized queries) will also be summarized according to their categories. Subject incidence of all post treatment serious adverse events up to the max of the end of study or 30 days after last dose of IP will be summarized by treatment group and randomization setting.

10.6.2 Laboratory Test Results

Laboratory results and their change from baseline will be summarized by treatment group and randomization setting 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, alanine aminotransferase, aspartase aminotransferase, NT-proBNP, troponin, and CK-MB.

Shift tables will be provided by treatment group and randomization setting, which will be based on modified (using only the numerical thresholds) 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 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.

Number and percentage of subjects with shifts in CK-MB using the same respective thresholds of the URL as for troponin will be summarized.

10.6.3 Major Cardiac Ischemic Events

Subject incidence of positively adjudicated major cardiac ischemic events will be tabulated by treatment group and randomization setting for any event and each event type. Kaplan-Meier estimates for time to first major cardiac ischemic event will be computed along with 95% confidence intervals. Time to first MI (positively adjudicated, positively adjudicated MI or investigator final diagnosis of MI, and positively adjudicated MI or investigator final diagnosis of MI or potential endpoint type of MI) will be analyzed using the same model as the primary composite endpoint. Subject incidence including events obtained after the analysis cut-off date will also be tabulated as an additional analysis.

10.6.4 Serious Adverse Events of Ventricular Arrhythmias Requiring Treatment

Subject incidence of serious adverse events of ventricular arrhythmias requiring new or alteration of treatment will be tabulated by treatment group and randomization setting.

10.6.5 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 and randomization setting.

10.6.6 Strokes

Subject incidence of positively adjudicated strokes will be tabulated by treatment group and randomization setting.

10.6.7 Electrocardiogram (ECG)

Where multiple 12-lead ECG measurements are taken at the same assessment time point (they are planned to be recorded in triplicate 30 seconds apart) the mean value will be calculated and used in the analysis. The baseline ECG is defined as the mean of all pre-dose assessments; the mean of values in a triplicate should be calculated before taking the mean of the triplicate averages.

Predose unscheduled ECG measurements taken up to 5 minutes after the last assessment of a triplicate will be included in the average for a time point. Where an ECG is missing within a triplicate, all available data will be averaged for that time point.

PR, RR, QRS, QT, and 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

10.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group and randomization setting. Indicators of extent of IP exposure include total IP administration duration.

10.6.9 Exposure to Concomitant Medication

The number and proportion of subjects receiving heart failure 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 including supportive analyses for the primary composite endpoint, secondary endpoints, and exploratory endpoint as described in Table 2.

10.7.1 Investigational Product Discontinuations

To assess changes to IP exposure due to COVID-19, a cumulative plot of EOIP with discontinuation reasons by calendar time starting from the end of 2019 will be created. Additionally, for each analysis cut-off date the same Cox model will be repeated for the primary composite endpoint, secondary time to event endpoints, and exploratory composite endpoint of time to first HF hospitalization or CV death. The HR treatment effect and pointwise 95% confidence intervals by analysis cut-off dates will be graphically displayed.

The hypothetical of no IP discontinuation due to COVID-19 and overall treatment effect will be assessed separately using a rank preserving structural failure time (RPSFT) models accounting for treatment switching to off treatment from intercurrent events as described in Robins and Tsiatis (1991). HR estimates and associated 95% confidence intervals will be computed for the primary composite endpoint, secondary time to event endpoints, and exploratory composite endpoint of time to first HF hospitalization or CV death.

10.7.2 Analyses of Efficacy Endpoints

The same Cox model will be repeated for the primary and secondary time-to-event endpoints as well as time to first HF hospitalization or CV death for the following censoring approaches:

- **at the time of the COVID-19 start date for subjects with a COVID-19 AE reported**
- **at the beginning of COVID-19 impact based on geographic locations of the study site**

10.7.3 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 Pharmacokinetic

All data for PK analyses will be extracted from a secure folder and mapped via a clinical connector into the Pharsight Knowledgebase Server (PKS) system (Pharsight Corporation, St. Louis, MO).

Omecamtiv mecarbil plasma concentration-time data will be analyzed by summary statistics. Concentration values less than or equal the lower limit of quantification

(LLOQ, 1 ng/mL) will be set to zero in the ADPC dataset. In the PK data analysis, the LLOQ 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 pharmacokinetic analysis, the following parameter will be summarized:

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

Summary statistics of the PK parameter will include arithmetic mean, standard deviation and CV%; median and range; geometric mean and CV% of geometric mean. The pharmacokinetic parameter will be summarized by dose level and sampling time.

Individual concentration-time data will be tabulated.

11. Changes From Protocol-specified Analyses

The protocol indicates all randomized subjects are used for analyses. SAP version 4 supersedes this by excluding study site [redacted] from analyses. Data from this site will be retained for potential sensitivity analyses.

12. Literature Citations / References

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13. Data Not Covered by This Plan

EQ-5D-5L index calculations are country specific and the calculations and analyses will be described in another analysis plan. NYHA class, CGR-S, and additional analyses to support the KCCQ TSS are not analyzed under this plan.

14. Appendices

Appendix A. Analytical Study Week Assignments

Laboratory parameters, ECGs, PROs, vital signs, **and optimization collection of targeted therapies** 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 the following table.

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.

Scheduled Visit Week[a]	Vital signs, **Optimization collection of targeted** therapies, Weight, NYHA class	ECG, Chemistry and Hematology Excluding labs from abbreviated panel	Chemistry and hematology including in the abbreviated laboratory panel	KCCQ, PGR-S, CGR-S, EQ-5D	NT-proBNP, Troponin I, CK-MB
Week 2	(1, 21]				(1, 28]
Week 4	(21, 35]				
Week 6	(35, 49]				(28, 105]
Week 8	(49, 70]				
Week 12	(70, 126]		(1, 126]	(1, 126]	
Week 24	(126, 210]		(126, 210]	(126, 210]	(105, 252]
Week 36	(210, 294]		(210, 294]	(210, 294]	
Week 48	(294, 392]	(1, 504]	(294, 504]	(294, 504]	(252, 504]
Q16W	((n – 8)*7, (n+8)*7]				
Q48W		((q-24)*7, (q+24)*7]	((q-24)*7, (q+24)*7]	((q-24)*7, (q+24)*7]	((q-24)*7, (q+24)*7]

n = 48 + (16 × y), for y = 1, 2, 3
q = 48 + (48 × z), for z = 1, 2, 3
[a] Actual visit day is mapped to the scheduled study visit by the provided intervals in days

Appendix B. Time-to-event Endpoint Inclusion and Censoring

All time-to-event endpoints in this study can be categorized as in the table below. The event inclusion and censoring approach will vary depending on the category of an endpoint.

Category	Endpoint
Composite	• Time to CV death or HF event, whichever is first • Time to CV death or HF hospitalization, whichever is first • Time to all-cause death or HF hospitalization, whichever is first • Time to first major cardiac ischemic event • Time to CV death, HF event, myocardial infarction, hospitalization for unstable angina, coronary revascularization, or stroke, whichever is first
Non-mortality	• Times to first and recurrent HF events (includes those with the discharge date as the starting point) • Times to first and recurrent HF hospitalizations (includes those with the discharge date as the starting point) • Time to first HF urgent or unscheduled clinic/office/ED visit
Mortality	• Time to cardiovascular death • Time to all-cause death

Endpoint analyses will include all positively adjudicated events from index date[a] up to the dates in the following table by type:

Category	Primary Analysis	Additional Analyses	**COVID-19 Related Analyses[e]**
Composite[b]	Mortality component: min(LCSSD, analysis cut-off date) Non-mortality component: min(LPEPD, EOS date, analysis cut-off date)	Mortality component: min(LPEPD, EOS date, analysis cut-off date) Non-mortality component: min(LPEPD, EOS date, analysis cut-off date)	**Mortality component: min(LCSSD, analysis cut-off date, COVID-19 AE start date)** **Non-mortality component: min(LPEPD, EOS date, analysis cut-off date, COVID-19 AE start date)** **Mortality component: min(LCSSD, analysis cut-off date, geographic specific COVID-19 censoring)** **Non-mortality**

Footnotes defined on next page of the table

Category	Primary Analysis	Additional Analyses	**COVID-19 Related Analyses[e]**
			component: min(LPEPD, EOS date, analysis cut-off date, geographic specific COVID-19 censoring)
Non-mortality[c]	min(LPEPD, EOS date, analysis cut-off date)	None	**min(LPEPD, EOS date, analysis cut-off date, COVID-19 AE start date)**
			min(LPEPD, EOS date, analysis cut-off date, geographic specific COVID-19 censoring)
Mortality[d]	min(LCSSD, analysis cut-off date)	LCSSD	**min(LCSSD, analysis cut-off date, COVID-19 AE start date)**
			min(LCSSD, analysis cut-off date, geographic specific COVID-19 censoring)

[a] The index date varies by the endpoint. For time-to-first event, time to first HF event/hospitalization after the index hospitalization, and time to first major cardiac ischemic event the index date is randomization date, index hospitalization, and first dose date, respectively.
[b] Only the primary endpoint of composite of time to CV death or first HF event, whichever occurs first will have a planned additional analysis among the composite endpoints.
[c] For recurrent event analyses using the mortality events, mortality events will only be included up to the same date as the non-mortality events.
[d] For the time to cardiovascular death additional analysis, all undetermined deaths will also be included (ie, the endpoint will be time to cardiovascular or undetermined/unknown cause of death)
[e] **Only applies to the additional analyses censoring subjects at the time of the COVID-19 AE start date in the Cox model and geographic specific COVID-19 impact date**

For subjects without events and for recurrent event endpoints, subjects will be censored using the following table by type:

Category	Primary Analysis	Additional Analyses	**COVID-19 Related Analyses**
Composite	min(LPEPD, EOS date, analysis cut-off date)	min(LPEPD, EOS date, analysis cut-off date)	**Min(LPEPD, EOS date, analysis cut-off date, COVID-19 AE start date)** **Min(LPEPD, EOS date, analysis cut-off date, geographic specific COVID-19 censoring)**
Non-mortality	min(LPEPD, EOS date, analysis cut-off date)	None	**min(LPEPD, EOS date, analysis cut-off date, COVID-19 AE start date)** **min(LPEPD, EOS date, analysis cut-off date, geographic specific COVID-19 censoring)**
Mortality	min(LCSSD, analysis cut-off date)	LCSSD	**min(LCSSD, analysis cut-off date, COVID-19 AE start date)** **min(LCSSD, analysis cut-off date, geographic specific COVID-19 censoring)**

Appendix C. 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