STATISTICAL ANALYSIS PLAN

A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of Omecamtiv Mecarbil in Japanese Subjects With Heart Failure With Reduced Ejection Fraction

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Table of Abbreviations

Abbreviation or Term	Definition/Explanation
ACE	angiotensin-converting enzyme
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{12}	area under the concentration-time curve for a 12 hour-dosing interval
AUC_t	area under the concentration-time curve calculated by linear trapezoidal method
ANCOVA	analysis of covariance
BID	twice daily
BMI	body mass index
BNP	brain-type natriuretic peptide
Bpm	beats per minute
C_{2h}	observed plasma concentration 2 hours after morning investigation product administration
CAS	completer analysis set
CDM	clinical data management
CEC	clinical events committee
CHF	chronic heart failure
CI	confidence interval
CK-MB	creatine kinase MB fraction
C_{max}	maximum observed plasma concentration
CPMS	Clinical Pharmacology, Modeling and Simulation
$C_{predose}$	plasma concentration prior to the investigational product administration
CSR	clinical study report
CTCAE	common terminology criteria for adverse events; common toxicity criteria for adverse events
DLRM	dose level review meeting
DMC	data monitoring committee
DQR	data quality review
ECG	electrocardiogram
eCRF	electronic case report form

Abbreviation or Term	Definition/Explanation
eGFR	estimated glomerular filtration rate; eGFR will be calculated by the central laboratory and provided to the investigator
EOI	events of interest
EOS	end of study (for individual subject)
E-R	exposure-response
FAS	full analysis set
HF	heart failure
HR	heart rate
IBG	independent biostatistical group
IP	investigational product
IPD	important protocol deviation
IVRS	interactive voice response system
LLOQ	lower limit of quatification
LVEDD	left ventricular end-diastolic diameter
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVESD	left ventricular end-systolic diameter
LVESV	left ventricular end-systolic volume
LVFS	left ventricular fractional shortening
MedDRA	medical dictionary for regulatory activities
MI	myocardial infarction
MR	modified-release
NYHA	New York heart association
NT-proBNP	n-terminal proBNP (brain natriuretic peptide)
PK/PD	pharmacokinetic/pharmacodynamic
PKAS	pharmacokinetic analysis set
PKS	Pharsight Knowledgebase Server
PR interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart’s electrical cycle as measured by ECG
PT	prothrombin time
QRS complex	interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT interval	measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG
QTcB interval	QT interval corrected for heart rate using Bazett’s formula

Abbreviation or Term	Definition/Explanation
QTcF interval	QT interval corrected for heart rate using Fridericia's formula
RR interval	interval between successive Rs where R is a point corresponding to the peak of the QRS complex as measured by ECG
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SET	systolic ejection time
SV	stroke volume
$t_{1/2}$	terminal half-life
t_{max}	time to C_{max}
ULN	upper limit of normal
URL	upper reference limit

Also refer to the protocol for more abbreviations on clinical terms.

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 (Omecamtiv Mecarbil) Study 20120227, dated 23 October 2015. The scope of this plan includes the final analyses that are planned and will be executed by the Biostatistics department. The pharmacokinetics (PK) analysis will be performed by Department of Clinical Pharmacology, Modeling and Simulation (CPMS).

2. Objectives

2.1 Primary

The primary objectives of this study are (i) to evaluate the pharmacokinetics (PK) of omecamtiv mecarbil in Japanese subjects with heart failure (HF) with reduced ejection fraction and (ii) to evaluate the safety and tolerability of oral omecamtiv mecarbil.

2.2 Secondary

Secondary objective is:

- To measure changes in systolic ejection time (SET) by echocardiography following 16 weeks of treatment.

3. Study Overview

3.1 Study Design

This is a double-blind, randomized, placebo-controlled, multicenter, phase 2 study in Japanese HF subjects to evaluate 16 weeks of administration of oral MR omecamtiv mecarbil formulation at 3 dose levels (25 mg BID, 37.5 mg BID, and 50 mg BID), compared with placebo. Potential subjects will be screened to assess their eligibility to enter the study within 30 days prior to enrollment. Subjects are eligible for screening if they have chronic stable HF and reduced ejection fraction. Subjects may also be screened in the hospital setting once they have recovered and are considered clinically stable by the investigator. Subjects must be outpatients at the time of randomization.

Approximately 80 Japanese subjects with chronic stable HF with reduced ejection fraction will be randomized 1:1:1:1 to receive omecamtiv mecarbil either 25 mg BID dose (n=20), 37.5 mg BID dose (n=20), 50 mg BID dose (n=20) or placebo (n=20) on an outpatient basis. Subjects randomized to 37.5 mg BID target dose and 50 mg BID target dose will initiate administration at 25 mg BID and will be up-titrated to 37.5 mg BID or 50 mg BID respectively at the week 4 visit based on steady state concentration prior to investigational product (IP) administration ($C_{predose}$) result from week 2. Subjects who do not have a week 2 PK value in time for dose adjustment at the week 4 visit will be

up-titrated at week 8 based on the steady state $C_{predose}$ result from week 2, if available. Subjects will be up-titrated to 37.5 mg BID or 50 mg BID at the week 4 or week 8 visits in the titration groups only if the week 2 $C_{predose}$ is < 200 ng/mL. Subjects with a week 2 $C_{predose}$ ≥ 200 ng/mL (or not available at week 8) will continue at 25 mg BID for the remainder of the study. Subjects randomized to placebo or to 25 mg BID will receive the assigned IP throughout the study. IP compliance will also be monitored. PK analysis and dose assignment will be blinded to the study team. To maintain blinding, all subjects will receive new IP supply at the week 4 and week 8 visits. The study includes transthoracic echocardiographic assessments (screening, week 8, and week 16). Enrollment of subjects with atrial fibrillation/flutter at the time of screening will be limited to approximately 20% of planned enrollment. Randomization will be stratified by presence or absence of atrial fibrillation/flutter via the interactive voice response system/interactive Web response system (IVRS/IWRS).

An independent DMC will perform regular formal unblinded review of the accumulating study data. An independent CEC will adjudicate deaths, all hospitalizations, and selected nonfatal cardiovascular (CV) events (including possible MI or ischemia). The end of study (EOS) visit will be performed 4 weeks after the last dose of IP (Week 20 +3 days).

Vital signs, physical examinations, ECGs, Adverse Event/Serious Adverse Event assessments, clinical laboratory evaluations (see Table 3 in protocol), and collection of concomitant medications will be performed at screening and at specified times per the Schedule of Assessments (see Table 2 in protocol). The overall study design is described by a study schema at the end of the protocol synopsis section. Detailed study procedures are provided in Protocol Section 7. The study endpoints are defined in Section 4.1.

3.2 Sample Size

The primary endpoints of this study are the omecamtiv mecarbil PK parameters. PK parameter's mean will be estimated. Assuming the SDs for C_{max} and AUC are in the range of 40 to 90, a sample size of n= 20 subjects in each treatment group, 19 subjects (assuming 5% subjects out of a total n = 20 subjects per treatment arm are excluded from PKAS) will provide a 2-sided 95% confidence interval (CI) with half width of 18 to 41. The SD estimates are from the predicted steady state PK for 25 mg and 50 mg BID doses for Matrix F1 formulation based on simulations performed using PK data following single dose from study 20090727. The table below presents CI half widths given particular SDs in this range for 19 subjects per treatment group.

PK Parameter 95% Confidence Intervals

	Confidence Interval Half Width
Standard Deviation	**N = 19**
40	18.0
50	22.5
60	27.0
70	31.5
80	36.0
90	40.5

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Endpoints

- Concentrations prior to administration ($C_{predose}$) of omecamtiv mecarbil at weeks 2, 4, 12, and 16, and area under the curve (AUC) at week 8

4.1.2 Secondary Endpoint

- Changes from baseline in SET by echocardiography at week 16

4.1.3 Safety Endpoints

Safety endpoints are as follows:

- Subject incidence of adverse events (AEs)
- Changes from baseline in laboratory values and vital signs
- Changes from baseline in ECG

4.1.4 Exploratory Endpoints

Exploratory endpoints are as follows:

- observed values and change from baseline to assessed timepoints of stroke volume, left ventricular end-systolic diameter (LVESD) and left ventricular end-dyastolic diameter (LVEDD)
- observed values and change from baseline to assessed timepoints of HR
- observed values and change from baseline to assessed timepoints of NT-proBNP
- subject incidence of supraventricular tachycardia and ventricular tachycardia arrhythmias requiring treatment from initiation of IP to EOS
- subject incidence of the following clinical outcome endpoints:
    - cardiovascular death or HF hospitalization until EOS
    - all-cause death or HF hospitalization until EOS

- all adjudicated events until EOS; events include, but may not be limited to: cardiovascular death, HF, acute myocardial infarction, myocardial ischemia, unstable angina, and resuscitated sudden death
- new onset atrial fibrillation/flutter
- all-cause death

4.2 Planned Covariates

Covariates include, but are not limited to the following:

Stratification Factor

- atrial fibrillation/flutter per the interactive voice response system (IVRS stratification factor) (presence vs. absence)

Baseline Covariates

- age at study enrollment (< 65 vs. ≥ 65 years)
- sex (male vs. female)
- LVEF (< median vs. ≥ median)
- body mass index (BMI) (< median vs. ≥ median)
- NT-proBNP (< median vs. ≥ median)
- coronary artery disease (CAD) (presence vs. absence)

5. Hypotheses and/or Estimations

No formal hypothesis testing will be performed and all statistical approaches are hypothesis-generating. PK parameters following chronic dosing (BID for 16 weeks) will be estimated and presented along with confidence interval limits.

6. Definitions

6.1 Study Time Points

Randomization Date

The randomization date for each subject is the date the investigator (or designee) confirms in the IVRS that the subject has met all eligibility criteria and is randomized.

Enrollment Date

The enrollment date is the same as the randomization date. The enrollment date is a derived field on the electronic case report form (eCRF) page.

First Dose Date of Investigational Product (IP)

For each subject, the First Dose Date of Investigational Product is defined as the date of the first administration of IP as recorded on the IP administration eCRF page.

Study Day 1

The date of the first investigational product (IP) administration or the date of enrollment for subjects who were not administrated any dose of IP.

Study Day

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

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

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

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

Last Dose Date of Investigational Product

For each subject, the Last Dose Date of Investigational Product is defined as the date of the last administration of investigational product.

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.

6.2 Demographics and Baseline Related Definitions

Age

Age will be calculated as the subject's age in years at enrollment as recorded on the eCRF.

Baseline ECG

For ECG, the baseline value is defined as the mean over all non-missing triplicate averages of 3 (or all available) readings from each set of triplicate taken prior to or on Study Day 1.

Other Baseline Values

For all other variables, the baseline value is defined as the last non-missing value collected prior to or on Study Day 1.

Change from Baseline

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

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

6.3 PK Related Definitions

C_{max}

Observed maximum concentration in Week 8.

C_{2h}

Observed concentration at 2 hours after morning IP administration in Week 16.

t_{max}

Observed time to achieve C_{max}.

$C_{predose}$

Observed concentration at the end of 12-hour treatment interval.

AUC_{8h}

Area under the plasma concentration-time curve estimated for 8 hours in week 8.

$C_{max}/C_{predose}$ ratio

Estimated with C_{max} and $C_{predose}$ observed in week 8.

6.4 Other Study Related Definitions

Analytical Study Week Assignments

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

Actual Treatment Group

A subject's actual treatment group is the randomized treatment group, unless the subject receives the same treatment throughout the study that is different to the randomized treatment group assignment, in which case the actual treatment group is the treatment received. For subjects randomized to omecamtiv mecarbil 37.5 mg BID and 50 mg BID, the actual treatment groups: 25 mg (Not up-titrated to 37.5 mg), 25 mg (Up-titrated to 37.5 mg) and 25 mg (Not up-titrated to 50 mg), 25 mg (Up-titrated to 50 mg) respectively, includes only those subjects who have a minimum IP exposure period of 25 days. Titration status groups may be used in select outputs and these four actual treatment groups should only be compared to each other. The omecamtiv mecarbil

Overall 37.5 mg BID, and Overall 50 mg BID actual treatment groups include all the subjects included in the omecamtiv mecarbil 37.5 mg BID, and 50 mg BID randomized treatment groups respectively.

Investigational Product (IP)

IP includes Omecamtiv Mecarbil 25 mg BID, 37.5 mg BID, and 50 mg BID and Placebo BID.

IP Dose Administered (mg)

From IP administration eCRF, number of tablets administered from each box is # dispensed - # lost or missing - # returned. If any of these numbers is missing, the sum of tablets reported on the IP administration eCRF for the same box will be used. IP dose administered is the sum of all the tablets' dose from all boxes dispensed.

IP Compliance (%)

Total IP dose administered divided by the total planned dose (223 tablets), multiplied by 100.

IP Exposure Period in Days

(Last IP administration date in the IP administration form – date of Study Day 1) + 1.

IP Exposure Period in Weeks

((Last IP administration date in the IP administration form – date of Study Day 1) + 1) / 7.

Study Exposure Period in Days

For each randomized subject, Study Exposure Period = (EOS Date – Randomization Date) + 1.

Study Exposure Period in Weeks

For each randomized subject, Study Exposure Period = ((EOS Date – Randomization Date) + 1) / 7.

Treatment-Emergent Adverse Event (TEAE)

Treatment Emergent adverse events are adverse events occurring between the first dose of IP and EOS. If an AE has an onset date after the date of first dose of IP, or the answer to the eCRF question "Did event start before first dose of investigational product?" is answered "no" then an event will be considered treatment emergent. The algorithm is provided in Appendix B.

7. Analysis Subsets

7.1 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 evaluable omecamtiv mecarbil PK concentration. This analysis set will be used in analyses of all the PK endpoints.

7.2 Full Analysis Set

The full analysis set (FAS) includes all randomized subjects who have received at least one dose of IP (omecamtiv mecarbil or placebo). Efficacy analyses of the secondary and exploratory endpoints will be performed on FAS. All subjects will be analyzed according to their randomized treatment assignment.

7.3 Safety Analysis Set

Safety analyses will be performed on Safety Analysis Set which is defined as the same as the full analysis set. For safety analyses, subjects will in general be analyzed according to their randomized treatment group assignment. If a subject receives the same treatment throughout the study that is different from their randomized treatment group, then the subject will be analyzed by the actual treatment group/schema (note: randomized to 25 mg BID, randomized to 37.5 mg BID but received 25 mg BID, and randomized to 50 mg BID but received 25 mg BID will all be treated as different schemas due to PK levels).

7.4 Completer Analysis Set

The completer analysis set (CAS) includes all subjects in FAS who complete IP administration. This analysis set will be used in sensitivity analysis of the secondary endpoint.

7.5 Subgroup Analyses

The echocardiographic secondary endpoint will be summarized and analyzed by the following subgroups:

IVRS stratification factor

- presence or absence of atrial fibrillation/flutter at randomization.

Baseline Covariates

- age at study enrollment (< 65 vs. ≥ 65 years)
- sex (male vs. female)
- LVEF (< median vs. ≥ median)
- body mass index (BMI) (< median vs. ≥ median)
- NT-proBNP (< median vs. ≥ median)
- Coronary artery disease (CAD) (presence vs. absence)

8. Interim Analysis and Early Stopping Guidelines

No interim analyses are planned for this study.

An external independent DMC will formally review the accumulating data from Amgen's ongoing omecamtiv mecarbil studies to facilitate detection of any increased risk for harm to subjects (eg, unexpected PK concentration due to PK variability). The DMC will review unblinded data approximately every month while subjects are receiving IP.

Based on the totality of evidence, the DMC will make an overall recommendation to the sponsor whether to continue the study according to the protocol or whether to make any changes (eg, including, but not limited to, dose change or stopping enrollment). To protect the status of the blind and to minimize potential operational bias, analyses for the DMC will be provided by the independent biostatistics group which is external to Amgen and supported by designated Amgen staff (eg, Clinical Pharmacology Lead in Protocol Section 10.3), if needed. Details will be 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 the appropriate CPMS representative from Global Biostatistical Sciences.

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 missed visit, or non-evaluability of a data point or an endpoint at a particular point in time. All attempts will be made to capture missing or partial data for this trial prior to the database lock.

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

For all time-to-event endpoints, there will be no imputation of the data, except for incomplete dates of the events. For all other endpoints, unless specified otherwise, missing data will not be imputed.

9.3.2 Handling of Incomplete Dates

Adverse event and concomitant medication (collected start date data) with completely or partially missing start dates will be queried. After the issue is queried, if the date is still incomplete with year only or year and month only, the start date will be imputed as described in the table below.

Imputation Rules for Incomplete Dates

	Missing	Imputation	Exception
Start date (AE and concomitant edication)	Day	1	Default to Study Day 1 if an event starts the same year and month as Study Day 1
	Day/Month	1-Jan	Default to Study Day 1 if an event started the same year as Day 1

9.4 Detection of Bias

This study has been designed to minimize potential bias by the use of stratified randomization of subjects into treatment groups and the use of blinding. Other factors that may bias the results of the 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

Important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints will be tabulated in the Clinical Study Report (CSR).

Any unblinding of individual subjects prior to formal unblinding of the study will be documented. The impact of such unblinding on the results observed will be assessed.

For DMC related analyses, details of access to subject level treatment assignments are provided in the protocol, Section 10.3.

Additional sensitivity analyses may be included to assess the impact of potential 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.

9.6 Distributional Characteristics

Distributional assumptions for the primary and secondary endpoints will be assessed. Generally, no other transformations will be applied besides those specified in Section 10. The use of alternative 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 final analysis will be conducted when all subjects have either completed all the scheduled study visits or have early terminated from the study. At that time, the database will be cleaned, processed and a snapshot will be taken; the study will also be unblinded. All endpoints will be analyzed based on this snapshot.

No formal hypothesis will be tested, and all statistical approaches are hypothesis-generating. Descriptive statistics will be presented for all endpoints.

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

Summary statistics for continuous variables will include number of subjects, mean, median, SD, or standard error, lower and upper quartiles, minimum, and maximum. For PK parameters, coefficient of variation (CV) will also be included. For categorical variables, frequency and percentage will be presented. Unless specified otherwise, all confidence intervals for estimates will be 2-sided with a significance level of 0.05.

Subjects will be analyzed based on their randomized or received treatment group assignment as described in Section 7.

Missing data handling is specified in Section 9.3.

For the secondary endpoint SET, sensitivity analyses using the CAS will be conducted to explore the robustness of selected results.

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 treatment group.

Key study dates for the first subject enrolled, last subject enrolled, last subject end of study, and last subject end of investigational product will be presented.

The number of subjects included in and excluded from each analysis set will be summarized.

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.

10.4 Demographic and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized by randomized treatment group and overall for all randomized subjects using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple race.

Demographics include: age, sex, race and region.

Baseline disease characteristics include:

- Physical measurements (height, weight, BMI) and vital signs
- Medical history (HF specific and non-specific, including presence of CAD, HF etiology and LVEF)
- HF related medication history including HF treatment at baseline
- Baseline ECG HR and select electrocardiographic parameters, including SET, SV, LVESD and LVEDD
- Baseline laboratory measurements (HF specific and non-specific, including NT-proBNP and troponin)
- The IVRS stratification factor (presence or absence of atrial fibrillation/flutter).

10.5 Analyses of Primary Endpoints

The primary endpoints are omecamtiv mecarbil PK parameters $C_{predose}$ and AUC, collected in the study (Section 4.1.1).

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 noncompartmental methods using Phoenix WinNonlin (Pharsight Corporation, St. Louis, MO) and will be stored in the validated PKS system. Concentration values less than or

equal to the lower limit of quantification (LLOQ, 1 ng/mL) will be set to zero in the analysis dataset. In the PK data analysis, LLOQ value (zero) will be excluded.

Actual doses administered and actual or nominal sampling times post drug administration will be used in the noncompartmental analysis. Nominal times will be used for presenting data in graphs and tables. All pharmacokinetic parameters and summary statistics will be presented to 3 significant digits.

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

In the pharmacokinetic analysis, the following parameters will be estimated:

- Observed maximum concentration (C_{max})
- Observed time to achieve C_{max} (t_{max})
- Observed concentration prior to next dose ($C_{predose}$)
- Area under the plasma concentration-time curve (AUC_t) calculated by linear trapezoidal method
- Ratio of C_{max} /$C_{predose}$

Individual concentration-time data will be tabulated and presented graphically. Mean concentration-time profiles for each dose will be provided.

10.6 Analyses of Secondary Endpoint

Echocardiographic parameters and their change from baseline will be summarized by randomized treatment group and scheduled assessment.

Mean differences between treatment groups in SET change from baseline at week 16 will be estimated via repeated-measures model including all observed values, with difference estimates and their 95% confidence intervals presented. The model will include IVRS stratification factor, baseline, treatment group, visit and the interaction of treatment group and visit. Individual subgroup analyses by the IVRS stratification factor and selected baseline covariates as listed in Section 4.2 will be provided. Baseline covariates may also be included in the model one at a time in their original form.

10.7 Analyses of Exploratory Endpoints

Both continuous and categorical exploratory endpoints will be summarized descriptively by cohort, treatment group, and scheduled assessment.

Mean differences between treatment groups in SV, LVESD, LVEDD, and HR change from baseline at scheduled assessments will be estimated via repeated-measures model

including all observed values, with difference estimates and their 95% confidence intervals presented. The model will include IVRS stratification factor, baseline value, treatment group, visit and the interaction of treatment group and visit.

NT-proBNP will be summarized descriptively and analyzed in the same principle as echocardiographic parameters.

For clinical outcome endpoints specified in Section 4.1.4, subject incidence rates for each treatment group will be provided.

For each subject, the first dose date of IP will be used as the starting point for all time-to-event calculation. For each qualifying event, the onset date adjudicated by CEC will be used as event onset date for time-to-event calculation. If not otherwise specified, the adjudicated events that occurred between the first dose date of IP and the end of study date will be included in the analyses of the time-to-event clinical outcome endpoints. Subjects who did not experience a qualifying event will be right censored at the end of study.

Supraventricular tachycardia and ventricular tachycardia arrhythmias will be identified from the corresponding eCRF forms. Subject incidence of supraventricular tachycardia and ventricular tachycardia arrhythmias requiring treatment from initiation of IP to end of study will be summarized for each treatment group.

10.8 Safety Analyses

Adverse events that occur after a subjects's EOS date will be excluded.

10.8.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA), using the current version at the time of final database lock, will be used to code all adverse events (AEs) to a system organ class and a preferred term. All adverse event tables will be summarized by actual treatment group. Treatment-emergent adverse events are events with an onset after the administration of the first dose of investigational product through the end of study as defined in Section 6.3.

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

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.

Summaries of treatment-emergent and serious AEs by preferred term in any treatment arm will be provided in descending order of frequency.

Subject incidence of EOIs (structured MedDRA queries and/or customized queries) will be summarized according to the EOI search strategy categories.

10.8.2 Laboratory Test Results

Laboratory results and their change from baseline will be summarized by actual treatment group and scheduled assessment for a subset of laboratory analytes provided in the protocol, Table 3. These include creatinine, creatine kinase, total bilirubin, direct bilirubin, alkaline phosphatase, alanine aminotransferase, aspartase aminotransferase, NT-proBNP, troponin, CK-MB and digoxin.

Shift tables will be provided by treatment group, which will be based on modified CTCAE 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 “undetected” (< 0.016 ng/mL), “detected” (0.016 – 0.04 ng/mL), and “elevated” (> 0.04 ng/mL) at each scheduled assessment will be summarized overall and by baseline status. Change of troponin status from baseline to the worst post-baseline will be tabulated. These summaries will be repeated by using different thresholds of upper reference limit (URL) in defining status: URL, 2xURL, 3xURL, 4xURL, 5xURL, 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.

CK-MB using different thresholds of URL, will be summarized and presented in the similar way as for troponin.

10.8.3 Vital Signs

Vital signs, including HR (based on measurement of pulse), and their change from baseline will be summarized by actual treatment group and scheduled assessment.

10.8.4 Electrocardiogram (ECG)

For post-baseline assessments where ECG is performed in triplicate, the average of the 3 (or all available) readings will be used for analysis. Observations with the following diagnosis or findings will be excluded from analysis: artificial pacemaker, atrial fibrillation, atrial flutter, left bundle branch block, and right bundle branch block.

PR, RR, QRS, QT, QTcB and QTcF intervals and their change from baseline will be summarized by actual treatment group and scheduled assessment.

Subjects will be categorized into the following groups per their maximum change from baseline in QTcB and 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 QTcB and QTcF. Unscheduled assessments will be included in the determination of the maximum post baseline value. The number and percentage of subjects in each group will be summarized.

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

10.8.5 Exposure to Investigational Product

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

Exposure definitions are provided in Section 6.4.

10.8.6 Exposure to Concomitant Medication

Concomitant medications will be coded by the World Health Organization Drug (WHO DRUG) dictionary. The number and proportion of subjects receiving oral medications of interest will be summarized by medication category, preferred term and regimen dose, unit and frequency at baseline and EOS for each treatment group.

11. Changes From Protocol-specified Analyses

During the initial development of this document, it was realized that there are protocol-specified analyses that cannot be implemented/performed and the protocol is not required to be amended. HF treatment at baseline will not be included as a baseline covariate. HF treatment, including BB, ACEi or ARB, is one of the expansion phase inclusion criteria and therefore the study is not expected to support subgroup analysis of no HF treatment at baseline. These changes will also be documented in the Clinical Study Report.

The definition of the PKAS was clarified to require one evaluable PK concentration rather than PK parameter as stated in the protocol.

12. Literature Citations / References

13. Data Not Covered by This Plan

This SAP does not address the analysis for the secondary objective

- to explore the potential relationship between omecamtiv mecarbil exposure and changes from baseline in SET

14. Appendices

Appendix A. Analytical Study Week Assignments

Selected endpoints will be summarized by scheduled study visits in descriptive analyses. Since the actual visits may not exactly coincide with their scheduled visit day, the actual visit day is mapped to the study visit by non-overlapping consecutive intervals covering the entire time continuum. The mapping intervals for all distinct schedules are summarized in the following table, for non-PK endpoints:

	Actual Visit Day (Study Day)							
Scheduled visit	VS*, CC, ECG	WT, CH, HE	PE	NT	ECHO	UR	DG	NYHA
BL/Day 1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1
Day 15 (Week 2)	> 1 – ≤ 21	> 1 – ≤ 35					> 1	
Day 28 (Week 4)	> 21 – ≤ 42			> 1 – ≤ 42				
Day 56 (Week 8)	> 42 – ≤ 70	> 35 – ≤ 70		> 42 – ≤ 84	> 1 – ≤ 84	> 1 – ≤ 98		
Day 84 (Week 12)	> 70 – ≤ 98	> 70 – ≤ 98						
Day 112 (Week 16)	> 98 – ≤ 126	> 98 – ≤ 126		> 84	> 84			
Day 140 (Week 20)	> 126	> 126	> 1			> 98		

VS: vital signs; WT: body weight; CC: cardiac troponin and CK-MB; PE: physical examination; NT: NT-proBNP; ECHO: electrocardiography; CH: chemistry; HE: hematology; UR: urinalysis; DG: Digoxin.
*Vital signs on week 8 and 16 are to be measured multiple times for E-R analysis purpose, and the value before morning dose will be used for non-PKPD analysis.

Handling multiple records assigned to an analytical study day/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 × 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.

Exceptions to these rules are:

- vital signs, the latest one prior to first IP administration on that day will be used in the non-PKPD analysis;
- cardiac troponin, CK-MB, and creatine kinase, where the worst non-missing value within the interval will be used in the analysis.

Appendix B. Treatment Emergent Adverse Event Algorithm

Dates	eCRF Flag of "Did event start before first dose of investigational product?"	Treatment Emergent?
AE onset date > 1st IP date	No	Yes
AE onset date < 1st IP date	Yes	No
AE onset date > 1st IP date	Yes	Yes
AE onset date < 1st IP date	No	Yes
AE onset date = 1st IP date	No	Yes
AE onset date = 1st IP date	Yes	No
Cannot determine even after date imputation specified in section *9.3.2*	Yes	No
Cannot determine even after date imputation specified in section *9.3.2*	No	Yes