Primary Endpoint:

- composite of time to CV death or first HF event, whichever occurs first
  - An HF event is defined as the presentation of the subject for 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.

Secondary Endpoints:

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

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
  - positively adjudicated major cardiac ischemic adverse events are: myocardial infarction, hospitalization for unstable angina, percutaneous coronary intervention/coronary artery bypass graft (Hicks et al, 2015)

Study Design: This is a randomized, placebo-controlled, double-blind, parallel group, multicenter, CV outcomes study in subjects with HFrEF, including subjects with ongoing or history of HF hospitalization. The study is event-driven and will conclude when approximately 1590 CV death events have occurred. 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 strata: US and Canada; Latin America; Western Europe, South Africa, and Australasia; Eastern Europe including Russia; Asia). At randomization, all subjects should be managed with standard of care therapies consistent with regional clinical practice guidelines. Approximately 25% or more of the total planned enrollment will include subjects who are hospitalized for HF at randomization. Enrollment of subjects in atrial fibrillation/flutter at screening is limited to approximately 25%.

Sample Size: Approximately 8000 subjects will be randomized.

Summary of Subject Eligibility Criteria: Subjects must be adults with a history of chronic HF, defined as receiving treatment for HF for a minimum of 30 days before randomization. All subjects should be managed with standard of care therapies consistent with regional clinical practice guidelines according to investigator judgment. Oral SoC therapies for chronic HF (eg, beta blockers, renin-angiotensin-aldosterone system inhibitors) should be present and optimized to the maximally tolerated dose, if not contraindicated. Subjects enrolled during either HF hospitalization or early after HF hospitalization discharge can be reinitiating or titrating oral SoC chronic HF therapies at the time of randomization, per usual clinical practice. For a full list of eligibility criteria, please refer to Section 4.1.1 through Section 4.1.2.

Study Glossary

Abbreviation or Term	Definition/Explanation
ACCF	American College of Cardiology Foundation
ACEi	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARB	angiotensin receptor blocker
ARNi	angiotensin receptor neprilysin inhibitor
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice a day
BiPAP	bilevel positive airway pressure
BNP	B-type natriuretic peptide
CEC	Clinical Events Committee
CK-MB	creatine kinase-MB
C_{max}	maximum observed concentration
CPAP	continuous positive airway pressure
CRF	case report form
CGR-S	Clinician Global Rating Severity
CRT	cardiac resynchronization therapy
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DRE	disease related events
EC	executive committee
ECG	electrocardiogram
eCRF	electronic case report form
ED	emergency department
EDC	electronic data capture
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EOS	end of study
EQ-5D	EuroQOL-5 dimensions questionnaire

Table 2. Schedule of Assessments

Timepoint/Frequency	Screen[a]	Rand D1	W2 ±3d	W4 ±3d	W6 ±3d	W8 ±3d	W12 ±3d	W24 ±7d	W36 ±7d	W48 ±7d	Q16W[b] ±7d	Q48W ±7d	EOS visit[c]
Abbreviated laboratory panel[i]							X	X	X				
NT-proBNP/Troponin I/CK-MB[j]		X	X		X			X		X		X	X
Biomarkers		X			X			X					X
PK samples			X[k]		X[k]		X			X		X	
PATIENT-REPORTED OUTCOMES AND TARGET SYMPTOMS ASSESSMENTS													
KCCQ/PGR-S/CGR-S		X					X	X	X	X		X	
EQ-5D		X					X	X	X	X		X	
NYHA Class	X	X	X	X	X	X	X	X	X	X	X	X	X
ACS signs and symptoms		X	X	X	X	X	X	X	X	X	X	X	X
INVESTIGATIONAL PRODUCT													
IP administration at site		X	X		X								
IP dispensation		X		X		X	X	X	X	X	X	X	
IP tablet count				X		X	X	X	X	X	X	X	X

ACS = acute coronary syndrome; ALP = alkaline phosphatase; ALT = alanine phosphatase; AST = aspartate aminotransferase; BNP = brain natriuretic peptide; CGR-S = Clinician Global Rating Severity; CK-MB = creatine kinase-MB; EOS = end of study; ECG = electrocardiogram; EQ-5D = EuroQOL 5 dimensions questionnaire; FSH = follicle-stimulating hormone; ICF = informed consent form; IP = investigational product; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = n-terminal prohormone brain natriuretic peptide; NYHA = New York Heart Association; PGR-S = Patient Global Rating Severity; PK = pharmacokinetic; Q16W = every 16 weeks; Q48W = every 48 weeks; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase

[a] The screening period can last up to 8 weeks after ICF signature.

[b] After study visit Week 48 visits will be conducted every 16 weeks.

[c] After the decision to end the study has been made, subjects will be scheduled for a final study visit.

[d] Only adverse events possibly related to study procedures and serious adverse events are collected during the screening period.

[e] Screening ECG to be performed and read locally for all sites. On study ECG to be performed and read locally, except on sites that have been provided with centralized ECG services equipment.

[f] Chemistry panel for screening includes sodium, potassium, urea, creatinine, total bilirubin, direct bilirubin, CK, AST (SGOT), ALT (SGPT)

[g] Serum pregnancy in females of childbearing potential; FSH only at screening if needed. Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.

[h] Chemistry panel includes sodium, potassium, chloride, calcium, magnesium, phosphorus, urea, creatinine, total bilirubin, direct bilirubin, CK, ALP, LDH, AST (SGOT), ALT (SGPT), and HbA1c.

[i] Abbreviated laboratory panel includes sodium, potassium, urea, creatinine, AST, ALT, total bilirubin, direct bilirubin, and hemoglobin.

[j] Central NT-proBNP, Troponin I, and CK-MB assessments after baseline will be blinded to subjects, investigators, and sponsor (Amgen).

- to evaluate the effect of OM on Kansas City Cardiomyopathy Questionnaire Total Symptoms Score (KCCQ TSS) 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

2. BACKGROUND AND RATIONALE

2.1 Disease

HF is a clinical syndrome marked by impaired cardiac contractility and is a final pathway for many diseases that affect the heart (Hilfiker-Kleiner et al, 2006). HF affects over 26 million people worldwide, with more than 3.5 million people newly diagnosed every year. The prevalence has been shown to increase with age (López-Sendón, 2011), suggesting that as the population ages, the incidence of HF may rise. In the United States (US), more than 5 million people, or almost 2.0% of the population, have HF (Go et al, 2013). In Europe, it has been estimated that at least 15 million people have HF (Dickstein et al, 2008). The annual mortality rate of HFrEF patients in western industrialized countries is typically from 10% to 25% per year; however, depending on the HF severity, this rate can be as low as 5% per year in stable New York Heart Association (NYHA) class I to II HF patients with mild left ventricular systolic dysfunction (LVSD) to as high as 75% per year in patients with NYHA class III to IV and marked LVSD (Mozaffarian et al, 2007; Bhatia et al, 2006; Levy et al, 2006; Solomon et al, 2004). The burden of HF can also be seen in data from recurrent hospital admission. Medicare data and data on commercially insured patients indicate that 12% to 27% of patients hospitalized for HF are readmitted within 30 days after their hospitalization, and all-cause mortality reaches 12% in the same period (Jencks et al, 2009; McIlvennan et al, 2014).

HF is most often caused by coronary artery disease; other common causes include idiopathic hypertension and valvular heart disease (Ambrosy et al, 2014). In an attempt to preserve cardiac output and organ perfusion, the condition progresses through stages with compensatory mechanisms characterized by increased sympathetic tone, peripheral vasoconstriction, and activation of various neurohormonal pathways. These adaptive properties provide short-term relief but can be damaging with long-term or prolonged activation. Patients experience dyspnea, fatigue, and fluid retention and eventually develop pulmonary congestion and peripheral edema. Treatment goals are to improve symptoms, prolong survival, and reduce hospital readmissions

3.4 Replacement of Subjects

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

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

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.

Subject accrual is planned for 24 months. After signing the informed consent, subjects should be randomized within 8 weeks. The expected length of treatment after completion of subject accrual and until the number of required CV death events has been reached is 24 months. Therefore, it is anticipated that follow-up for the first randomized subjects will reach approximately 48 months (4 years), and for the last randomized subjects approximately 24 months (2 years). The actual duration of study for an individual subject may be longer or shorter based upon the amount of time required to reach the specified number of events.

Experiencing a nonfatal primary endpoint does not end study participation for a study subject (see criteria for withdrawal in Section 6.2.1.2 and Section 6.3). Subjects will continue treatment and follow-up procedures until the study ends as described above. All subjects will be followed from randomization through the date of study termination unless the subject has withdrawn consent, irrespective of whether the subject is continuing to receive study treatment.

3.5.2 End of Study

Primary Completion: The primary completion is the date when the last subject is assessed or receives an intervention for the collection of the primary endpoint, 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)

End of Study: The end of study is the same as the primary completion date and is when the last subject has completed the end of study assessments.

A direct relationship has been observed between the plasma concentrations of OM and increases in systolic ejection time, stroke volume, and left ventricular function (Cleland et al, 2011; Teerlink et al, 2011). Excessive exposure to OM may result in signs and symptoms of myocardial ischemia or infarction (eg, increases in heart rate, dizziness, dyspnea, hypotension, chest discomfort or pain, ST-segment depression/elevation on ECG, and/or elevations in troponin I or T). No antidote to OM currently exists. In the event of an overdose, health care providers should be especially vigilant for signs and symptom of myocardial ischemia. Standard medical therapies should be used to treat adverse signs or symptoms that do not promptly resolve with discontinuation of the IP.

6.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

All subjects will have predose PK assessed at Week 2 in order to guide the dose adjustment for subjects randomized to OM. At Week 6, another predose PK will be assessed to reflect the PK results of the previous adjustment. Pharmacokinetics will be assessed on Weeks 12 and 48, and then every 48 weeks throughout the study. See Appendix D for a summary of dose adjustment rules.

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

At Weeks 12, 48, and then every 48 weeks, PK will be assessed and are not part of the PK-based dose adjustment approach (Note: subjects in between visits week 12 and week 24 at the time of local approval of this global amendment number 1 should have a PK assessment conducted during the week 24 visit). Subjects with plasma concentration ≥ 1000 ng/mL at assessments after the Week 8 visit will be requested to stop IP administration, regardless of signs or symptoms. An extra visit will be scheduled and the subject's treatment assignment will be unblinded.

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

Table 2. Schedule of Assessments

Timepoint/Frequency	Screen[a]	Rand D1	W2 ±3d	W4 ±3d	W6 ±3d	W8 ±3d	W12 ±3d	W24 ±7d	W36 ±7d	W48 ±7d	Q16W[b] ±7d	Q48W ±7d	EOS visit[c]
GENERAL PROCEDURES & SAFETY ASSESSMENTS													
Informed consent	X												
Medical/Surgical history	X												
Vital Signs (heart rate, blood pressure)	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events/serious adverse events/potential endpoints/disease-related events[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Instruction on IP administration		X		X		X	X	X	X	X	X	X	
Placebo run-in[o]	X												
Assessment of IP adherence[n]			X		X		X			X		X	
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination/height[m]	X												X
ECG[e]	X	X								X		X	X
Randomization		X											
LOCAL LABORATORY[r]													
Chemistry[f]	X[l]												
Screening BNP or NT-proBNP[q]	X[l]												
Serum pregnancy/FSH[g]	X[l]												
CENTRAL LABORATORY													
Chemistry[h]	X[p]	X								X		X	X
Hematology		X								X		X	X
Screening BNP or NT-proBNP[q]	X[p]												
Serum pregnancy/FSH[g]	X												
Urinalysis		X											X

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Footnotes defined on the last page of the table

Omecamtiv mecarbil plasma concentrations will be measured using an investigational assay. The investigation assay is identified as QMS Omecamtiv Mecarbil Immunoassay which was developed by Thermo Fisher Scientific. The investigational assay will be used in accordance with local regulatory and labeling requirements along with the Instructions for Use provided.

7.2.6.11 Safety Data Reporting

Adverse events, serious adverse events, adverse device effects, and disease-related events observed by the investigator or reported by the subject will be collected at all study visits from the signing of the ICF through the EOS visit or 30 days after the last dose of IP, whichever is later (see Section 9 for details).

7.3 Biomarker Development

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

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

Blood Samples

Blood samples are to be collected for biomarker development at the following time points: day 1, Week 6, Week 24, and EOS visit.

7.4 Pharmacogenetic Studies

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

7.5 Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments (Table 2) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods

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

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

9.1.3 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria (unless it meets the definition of a Disease Related Event as defined in Section 9.1.1):

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

A disease related event, as described above, is to be reported as a serious adverse event if

- the subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, or
- if the investigator believes a causal relationship exists between the investigational medicinal product(s)/protocol-required therapies and the event,
- and the event meets at least 1 of the serious criteria above.

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

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

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease Related Events

The investigator is responsible for ensuring that all Disease Related Events observed by the investigator or reported by the subject that occur after the first dose of investigational medicinal product(s)/study treatment/protocol-required therapies through the EOS visit, or 30 days after the last administration of IP, whichever is later, are reported using the Event CRF.

Events assessed by the investigator to be related to the investigational medicinal product(s) **or considered worse than that which would normally be expected for the subject** and determined to be serious, require reporting of the event on the Event CRF as a Serious Adverse Event rather than as a Disease Related Event, and within 24 hours from the acknowledgement of the event.

9.2.2 Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after randomization through end of study/safety follow-up visit, or 30 days after the last administration of IP, whichever is later, are reported using the Event CRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity (and/or toxicity per protocol),
- Assessment of relatedness to OM, and
- Action taken.

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE). Because the criteria for the CTCAE grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to grade 4 “life-threatening” CTCAE grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life-threatening status), it will be left to the investigator’s judgment to also report these abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event’s severity status must be recorded in the subject’s medical record. The grading

scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to the OM. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the IP?

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

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

9.2.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after informed consent through end of study/safety follow-up visit, or 30 days after the last administration of IP, whichever is later, are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event CRF.

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic

Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet /electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSerious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

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

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

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

10.1.1.2 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

10.1.1.3 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)

10.1.1.4 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

10.1.2 Analysis Sets

10.1.2.1 Efficacy Analysis Set

Efficacy analyses will be performed on the full analysis set (FAS), which includes all randomized subjects. Subjects will be analyzed according to their randomized treatment group assignment.

10.1.2.2 Safety Analysis Set

Safety analyses will be performed on the safety analysis set (SAS), which includes all randomized subjects who receive at least 1 dose of IP on study. Unless otherwise specified, for safety analyses, subjects will be grouped according to their randomized treatment group assignment with the following exception: if a subject receives treatment throughout the study that is different than the randomized treatment group assignment, then the subject will be grouped by the actual treatment group.

10.1.3 Covariates and Subgroups

Baseline covariates include, but are not limited to eGFR and the stratification factor of randomization setting and region.

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

- stratification factor of randomization setting (currently hospitalized for HF or recently and not currently hospitalized for HF)
- stratification factor of region (5 strata: 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/flutter at screening (yes, no)
- baseline LVEF (≤ median, > median)
- baseline NT-proBNP by randomization setting excluding subjects in atrial fibrillation/flutter at screening (≤ median and > median)
- baseline resting heart rate (≤ median and > median)
- baseline systolic blood pressure (≤ median and > median)
- 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

composite endpoint and the secondary endpoint time to CV death reach statistical significance. The remainder of the secondary endpoints will be assessed with an overall alpha of 0.001 following the testing diagram if the study is stopped early.

Interim futility and efficacy assessments will be conducted by the Independent Biostatistical Group (IBG) and reviewed by the DMC.

Blinded event rate monitoring during the study will be conducted periodically to assess the study planning assumptions versus the trial aggregate data. This monitoring will be conducted by the sponsor's clinical study team. Appropriate operational actions may be implemented due to results from this monitoring.

10.4.2 Data Monitoring Committee

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

10.4.3 Primary Analysis

The primary analysis will include hypothesis testing for each of the primary and secondary endpoints and include analyses of exploratory endpoints. The primary analysis will occur after the primary completion milestone of observing approximately 1590 CV deaths is achieved. At that point, the database will be cleaned, processed and a snapshot will be taken. The study will also be unblinded. Based on the snapshot, unless specified otherwise, efficacy analyses will be performed on the FAS by randomized treatment group and safety analyses will be performed on the SAS.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Unless otherwise specified, all hypothesis tests will be reported as 2-sided and the full study will have an overall type I error rate of 0.05. Missing data will not be imputed in the primary analysis of the primary and secondary endpoints.

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

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, visit, treatment, and treatment by 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. 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.

10.5.5 Safety Endpoints

10.5.5.1 Adverse Events

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

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

Subject incidence of serious adverse events of ventricular arrhythmias requiring treatment and positively adjudicated major cardiac ischemic adverse events will be tabulated.

10.5.5.2 Laboratory Parameters

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

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

10.5.5.3 Vital Signs

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

10.5.5.4 Electrocardiograms

Selected sites will be provided with centralized ECG services equipment specifically for this study. For these central ECG measurements, summaries over time and/or changes from baseline over time will be provided for all ECG parameters. Subjects' maximum change from baseline in QTcF and QTcB will be categorized and the number and percentage of subjects in each group will be summarized. Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects in each group will be summarized.

The ECG measurements taken at other sites are performed as per SoC for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of these ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials. These locally collected ECG measurements will not be combined with central ECG measurements.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent document is to be prepared in the language(s) of the potential patient population.

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

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

Site Number	Subject ID Number

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes, If yes, please complete all of Section 5:

IP/Drug/Amgen Device		Initial Dose	Latest dose prior to this event, if applicable	Dose	Route	Frequency	Lot # and Seriel #
	AMG 423 *(omecamtiv mecarbil)* ☑ Blinded						Lot # ☐ Unknown Serial # ☐ Unavailable / Unknown
	Dose Start Date **(Day Month Year)**						
	Dose Start Time **(24-hr clock)**						
	Action Taken with Product ☐ Still being Administered ☐ Withheld ☐ Permanently discontinued						

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes, If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

Date Day Month Year	Time (24-hr clock)	Test / Unit										

Investigational Product

Amgen Investigational Product Dosage and Administration: OM or placebo will be administered orally twice a day (BID) in the morning and evening and can be taken under fasted or fed conditions. Subjects randomized to OM will initiate administration at 25 mg BID. At study visit Week 2 (steady-state for initial dose), a blood sample will be collected from all subjects to determine pharmacokinetic (PK) predose level. The results will be blinded to investigators.

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

- Subjects with plasma concentration < 200 ng/mL will start administration of 50 mg BID.
- Subjects with plasma concentration ≥ 200 and < 300 ng/mL will start administration of 37.5 mg BID.
- Subjects with plasma concentration ≥ 300 and < 1000 ng/mL will maintain the administration of 25 mg BID.
- Subjects with plasma concentration ≥ 1000 ng/mL will start administration of placebo BID.
- At study visit Week 6, a predose plasma concentration will be collected from all subjects to confirm plasma concentration achieved while subjects are receiving their targeted dose and assess if potential changes to the dose should be made. The results will be blinded to investigators. For further guidance on procedures regarding PK assessment, please refer to Section 6.2.
- A new investigational product supply will be provided to all subjects at the Week 4 and Week 8 study visits regardless of randomized treatment group and outcome of the PK assessment in order to maintain the blind.

Procedures: Written informed consent must be obtained from all subjects before any screening procedures are performed. The following procedures will occur per the Schedule of Assessments: medical/surgical history, New York Heart Association (NYHA) class, physical examination/height, vital signs, weight, adverse event and concomitant medication assessment, electrocardiogram, PRO assessments, pregnancy testing, urinalysis, blood draw for serum chemistry, hematology, n-terminal prohormone brain natriuretic peptide, troponin I, creatine kinase-MB (CK-MB), biomarkers, and PK samples. For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 2).

Statistical Considerations: The primary analysis will include hypothesis testing for each of the primary and secondary endpoints and include analyses of exploratory endpoints. The primary analysis will occur after approximately 1590 CV deaths have occurred. Unless specified otherwise, efficacy analyses will be performed on the full analysis set, which includes all randomized subjects, by randomized treatment group. The safety analyses will be performed on the safety analysis set, which includes all randomized and dosed subjects. 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. To preserve the overall type I error rate at 0.05, a sequentially rejective multiple test procedure will be used.

An interim analysis for superiority is planned when approximately two-thirds of the planned 1590 CV deaths are observed and will use a 2-sided alpha of 0.001 and the same multiplicity adjustments as for the planned primary analysis. Interim analyses for futility based on the primary composite endpoint are planned when approximately one-third and two-thirds of the planned 1590 CV deaths are observed.

The primary analysis of the primary composite endpoint will use a likelihood ratio test from a Cox model including baseline estimated glomerular filtration rate (eGFR) and the treatment group and stratified by randomization setting and region. The secondary endpoints of time to CV death, time to first heart failure hospitalization, and time to all-cause death will be assessed using the same Cox model setup as the primary composite endpoint. Change in the KCCQ TSS from

Abbreviation or Term	Definition/Explanation
FAS	full analysis set
GCP	Good Clinical Practice
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
IBG	Independent Biostatistical Group
ICD	implanted cardiac defibrillator
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IP	investigational product
IPIM	Investigational Product Instruction Manual
IR	immediate release
IRB	institutional review board
IVRS	interactive voice response system
IWRS	interactive web response system
KCCQ TSS	Kansas City Cardiomyopathy Questionnaire Total Symptom Score
LDH	lactate dehydrogenase
LVEF	left ventricle ejection fraction
LVSD	left ventricular systolic dysfunction
MR	modified release
MRA	mineralocorticoid receptor antagonist
NT-proBNP	n-terminal-prohormone brain natriuretic peptide
NYHA	New York Heart Association
OM	omecamtiv mecarbil
PK	Pharmacokinetic
PGR-S	Patient Global Rating Severity
PO	by mouth
PRO	patient-reported outcome
Q48W	every 48 weeks
SAS	safety analysis set
SET	systolic ejection time
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SoC	standard of care

[k] All subjects. Blood sample must be collected before the administration of IP.
[l] Local laboratory assessment at screening are accepted only for subjects randomized during hospitalization.
[m] Height to be measured during screening only.
[n] Investigator to discuss with subject IP administration and adherence during the previous 7 days, as per Section 6.2.1.1.
[o] To assess subject's ability to swallow the whole tablet successfully (open label placebo) per instruction (ie, without chewing).
[p] Central laboratory assessment at screening applies to all subjects regardless of randomization setting (currently hospitalized for HF and recently and not currently hospitalized for HF).
[q] Subjects on therapy with sacubitril/valsartan should have NT-proBNP assessed during screening phase.
[r] Local laboratory assessments for screening can be used to support eligibility of hospitalized subjects, in order to provide flexibility for randomization before discharge.

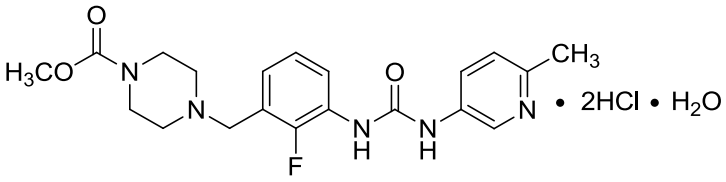
(Yancy et al, 2013; Ponikowski et al, 2016). While several pharmacological and nonpharmacological interventions have been shown to reduce the rate of HF hospitalizations and improve mortality, including angiotensin-converting enzyme inhibitors (ACEis), beta-blockers, aldosterone antagonists, coronary revascularization, and biventricular pacing (Jessup and Brozena, 2003; Krum and Teerlink, 2011), mortality and morbidity still remain high as noted above. In addition, these available treatments, acting on the compensatory mechanisms (eg, sodium retention, arterial and venous constriction, neuroendocrine activation, and increased heart rate) often fail to control symptoms or restore quality of life.

Reduced left ventricle ejection fraction (LVEF) is a central factor in HF, yet there are no safe medical therapies to directly improve cardiac function at the level of the cardiac sarcomere in HF patients. The compensatory mechanisms cited above are deployed in attempt to preserve cardiac output and organ perfusion in a scenario of impaired myocardial contractility. Attempts to improve cardiac contractility through chronic stimulation of the adrenergic receptor pathway (eg, dobutamine or ibopamine) or phosphodiesterase inhibitors (ie, milrinone) in chronic HF patients have not been successful (Tacon et al, 2012). Both agents have significant safety liabilities due to their mechanism of action. The increase of intracellular calcium can improve contractility but at the expense of increased tissue oxygen consumption and arrhythmias. The addition of long-term oral milrinone to SoC in severe chronic HFrEF patients has shown increased mortality and morbidity (Packer et al, 1991). Oral ibopamine, a dopaminergic receptor agonist (DA-1 and DA-2) also did not demonstrate clinical benefits when added to SoC in HFrEF outpatients (Hampton et al, 1997).

2.2 Amgen Investigational Product Background

The molecular formula of OM is C20H24FN5O3·2HCl·H2O and the chemical structure is provided in Figure 1.

Figure 1. Chemical Structure of Omecamtiv Mecarbil



OM (AMG 423, CK-1827452) is a novel small molecule classified as a cardiac myosin activator that increases cardiac contractility by selectively and directly activating the

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS).

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

101 Subject has provided informed consent

102 Male or female, ≥ 18 to ≤ 85 years of age at signing of informed consent

103 History of chronic HF (defined as requiring treatment for HF for a minimum of 30 days before randomization)

104 LVEF ≤ 35%, per subject's most recent medical record, within 12 months prior to screening. The most recent qualifying LVEF must be at least 30 days after any of the following, if applicable: 1) an event likely to *decrease* EF (eg, myocardial infarction, sepsis); 2) an intervention likely to *increase* EF (eg, cardiac resynchronization therapy, coronary revascularization); or 3) the first ever presentation for HF.

105 NYHA class II to IV at most recent screening assessment

106 Managed with HF SoC therapies consistent with regional clinical practice guidelines according to investigator judgment of subject's clinical status

Oral SoC therapies for chronic HF (eg, beta blockers, renin-angiotensin-aldosterone system inhibitors) should be present, if not contraindicated. Subjects enrolled during either HF hospitalization or early after HF hospitalization discharge can be reinitiating or titrating oral SoC chronic HF therapies at the same time of randomization with the goal of achieving optimized therapy on study.

107 Currently hospitalized with primary reason of HF OR one of the following events within 1 year to screening: 1) hospitalization with primary reason of HF; 2) urgent visit to ED with primary reason of HF

108 B-type natriuretic peptide (BNP) level ≥ 125 pg/mL or an NT-proBNP level ≥ 400 pg/mL at most recent screening assessment (subjects receiving angiotensin receptor-neprilysin inhibitor [ARNi] must use NT-proBNP assessment; for subjects in atrial fibrillation/flutter at screening, the cut off levels are: BNP ≥ 375 pg/mL or NT-proBNP ≥ 1200 pg/mL)

If IP cannot be taken or has not been taken within approximately 12 ± 3 hours from the most recent previous dose, the dose should be missed and the next dose should be taken at the regular time.

If a subject experiences clinical signs or symptoms consistent with acute myocardial ischemia or infarction, the subject should receive immediate medical attention according to the institution's usual SoC, and the IP administration should be withheld. Serial cardiac ischemic markers and ECGs should be analyzed locally. Results from local laboratory assessment of Troponins (I or T), CK-MB, and BNP or NT-proBNP should be recorded in the CRF. A central laboratory PK sample, Troponin I, CK-MB, and NT-proBNP should be collected in all subjects experiencing such events as close as possible to the event and the time last IP was taken. The results of the PK assessment, when present, will routinely remain blinded to the sponsor and investigators. The Data Monitoring Committee (DMC), however, will receive unblinded PK data. Amgen should be notified of suspected acute myocardial ischemia or infarction within 24 hours of knowledge of the event.

Restarting IP after a cardiac ischemic event may be considered after appropriate management of the case, and assessment of the likely cause of the event and the potential relatedness of the event to IP. The decision to reinitiate the subject after a cardiac ischemic event should be discussed and agreed upon unanimously by the subject, investigator, and Amgen. Subjects experiencing acute cardiac ischemic events suspected to be related to IP should not be rechallenged. When restarting, subjects initiate OM 25 mg BID or placebo BID, according to initial group allocation. A new predose PK assessment will be conducted after 2 weeks from IP reinitiation, and dose adjustment will occur at the next IP dispensation visit. The adjustment follows the same procedures as for study visit Week 4, limiting the maximum dose to what was assigned before the event.

Subjects reinitiating IP after withholding for reasons other than cardiac ischemic events will restart on the same IP dose as established before the event.

6.2.1.3 Other Protocol-required Therapies

At randomization, recently and not currently hospitalized for HF or currently hospitalized for HF subjects should be optimally managed consistent with HF SoC therapies defined by regional clinical practice guidelines. Oral SoC therapies for chronic HF (eg, beta blockers, renin-angiotensin-aldosterone system inhibitors) should be present, if not contraindicated. Subjects enrolled during either HF hospitalization or early after HF

produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

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

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

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

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

9.2.2.3 Reporting a Safety Endpoint as a Study Endpoint

All potential endpoints (death, HF events, major cardiac ischemic event, and stroke) must be recorded on the Event CRF within 24 hours of knowledge of the event. Information regarding dates of onset and resolution, severity, action taken, investigator assessment of relatedness, and assessment of seriousness must be collected.

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapies report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur after the last dose of protocol-required therapies through 5 days after the end of treatment with IP.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C).

If a lactation case occurs while the female subject is taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur after the last dose of protocol-required therapies through 5 days after the end of treatment with IP.

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C).

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

- composite of time to CV death or first HF event, whichever occurs first
- An 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.

- baseline presence of CRT
- baseline presence of implanted cardiac defibrillator (ICD)

10.2 Sample Size Considerations

The sample size calculation is based on the CV death 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 death 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 HF 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 greater than 99% power when the primary analysis is triggered.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators or subjects prior to the study being formally unblinded except as specified (eg, Section 5.2 and Section 9.2.2.2).

10.4 Planned Analyses

10.4.1 Interim Analyses

Futility for the primary endpoint will be assessed when approximately one-third and two-thirds of the overall required CV deaths are observed. Efficacy will be assessed when approximately two-thirds of the overall required CV deaths are observed. An alpha of 0.001 (Haybittle-Peto approach; Haybittle, 1971; Peto et al, 1976) will be used for assessing superiority. The DMC can recommend stopping the trial if the primary

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.

All deaths, HF events, major cardiac ischemic adverse events (myocardial infarction, unstable angina hospitalization, and coronary revascularization), and strokes will be adjudicated by an independent external CEC, using standardized definitions. The CEC is external to Amgen and primarily comprises both academic clinical physicians (to include cardiologists) and medical reviewers trained on the clinical trial protocol, the CEC charter, and CEC processes. The chairman of the CEC is responsible for overseeing the operations in conformance with the CEC charter and for supervising the flow of data between the sponsor/data management and the CEC. Committee members are qualified in the appropriate subspecialty and free of conflict of interest. The CEC is blinded to treatment allocation and reviews events according to prespecified criteria defined in the CEC charter.

10.5.2 Multiplicity Adjustments

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 2 endpoints after the split will propagate to the other endpoint (Bretz et al, 2009) with a small alpha (0.0001 x 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 2 illustrates the multiplicity testing propagation approach. Alpha will only propagate if the

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

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

11.2 Institutional Review Board/Independent Ethics Committee

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

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

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

11.3 Subject Confidentiality

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

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

	Site Number	Subject ID Number	

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date Day Month Year	Time (24-hr clock)	Additional Tests	Results	Units

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee –	Title	Date
_____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*		