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

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GALACTIC-HF

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

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Investigator's Agreement

I have read the attached protocol entitled A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of Omecamtiv Mecarbil on Mortality and Morbidity in Subjects with Chronic Heart Failure with Reduced Ejection Fraction, dated **13 November 2018**, and agree to abide by all provisions set forth therein.

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- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

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

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Signature	
Name of Investigator	Date (DD Month YYYY)

Protocol Synopsis

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

Study Phase: 3

Indication: Heart failure (HF)

Primary Objective:

- to evaluate the effect of treatment with omecamtiv mecarbil (OM) compared with placebo on the time to cardiovascular (CV) death or first HF event, whichever occurs first, in subjects with chronic HF with reduced ejection fraction (HFrEF) receiving standard of care (SoC) therapy
    - An HF event is defined as presentation of the patient 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 Objectives:

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

Safety Objective:

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

Hypotheses:

The primary hypothesis is that when added to SoC, OM is well tolerated and superior to placebo in reducing the risk of CV death or HF events in subjects with chronic HFrEF.

Secondary hypotheses are that OM reduces the individual risks of:

- CV death
- HF hospitalization
- all-cause death

and improves symptoms in subjects with chronic HFrEF compared to placebo.

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.

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

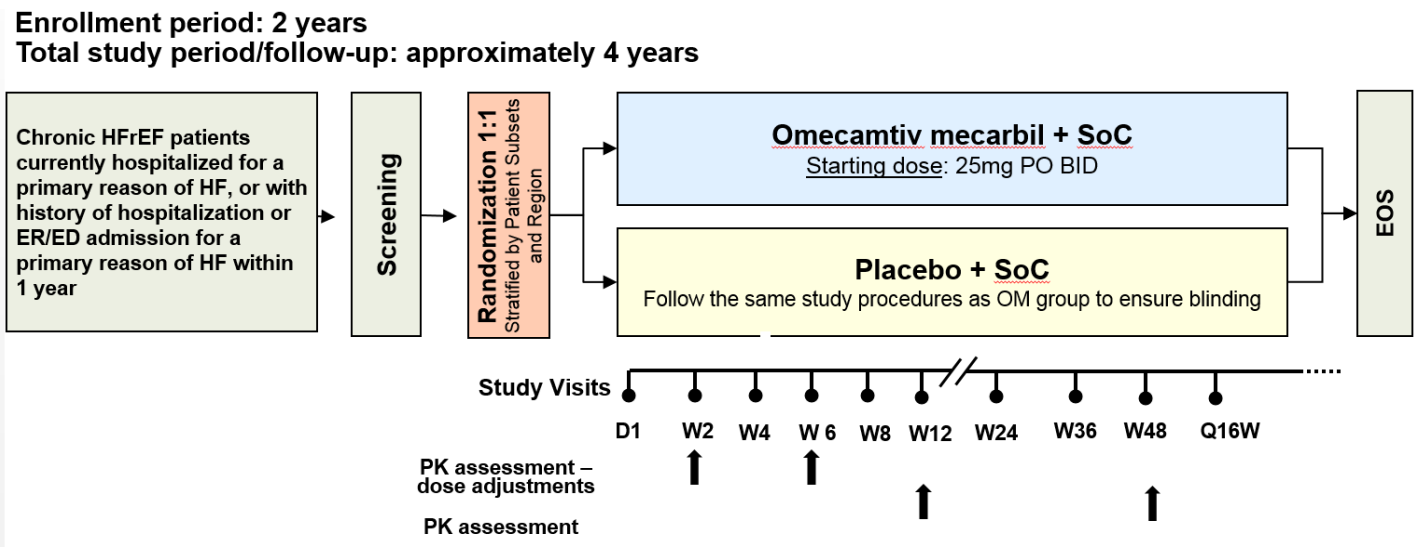
baseline to Week 24 will be assessed using a mixed model fit within each randomization setting containing the baseline TSS value, baseline eGFR, region, visit, treatment, and treatment by visit. An omnibus F-test with 2 numerator degrees of freedom will be used to test the treatment effect of OM versus placebo.

All deaths, HF events, major cardiac ischemic events (myocardial infarction, unstable angina hospitalization, and coronary revascularization), and strokes will be adjudicated by an independent external Clinical Events Committee using standardized definitions (Hicks et al, 2015). For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: Amgen Inc.

Data Element Standards Version/Date:	Version 5, 20 March 2015

Study Design and Treatment Schema



BID = twice a day; ED = emergency department; EOS = end of study; ER = emergency room; HF = heart failure; HfrEF = heart failure with reduced ejection fraction; IP = investigational product; PK = pharmacokinetics; PO = by mouth; Q16W = every 16 weeks; SoC = standard of care

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

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

Abbreviation or Term	Definition/Explanation
TBL	total bilirubin
ULN	upper limit of normal
US	United States

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1. OBJECTIVES

1.1 Primary

- to evaluate the effect of treatment with omecamtiv mecarbil (OM) compared with placebo on the time to cardiovascular (CV) death or first heart failure (HF) event, whichever occurs first, in subjects with chronic HF with reduced ejection fraction (HFrEF) receiving standard of care (SoC) therapy
  - An HF event is defined as presentation of the patient for urgent, unscheduled clinic/office/emergency department (ED) visit, or hospital admission, with a primary diagnosis of HF where the patient exhibits new or worsening symptoms of HF on presentation, has objective evidence of new or worsening HF, and receives initiation or intensification of treatment specifically for HF (Hicks et al, 2015). Changes to oral diuretic therapy do not qualify as initiation or intensification of treatment.

1.2 Secondary

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

1.3 Safety

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

1.4 Exploratory

- to evaluate the effect of OM on the risk for HF events and HF hospitalization in subjects randomized during hospitalization for HF during the first:
  - 30 days after discharge
  - 60 days after discharge
- to evaluate the effect of OM on n-terminal prohormone brain natriuretic peptide (NT-proBNP) changes
- to evaluate the effect of OM on first and recurrent HF events
- to evaluate the effect of OM on recurrent HF hospitalizations
- to evaluate the effect of OM on the composite time of CV death or HF hospitalization, whichever occurs first
- to evaluate the effect of OM on the composite of time to all-cause death or HF hospitalization, whichever occurs first
- to evaluate the effect of OM on resting heart rate

- 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

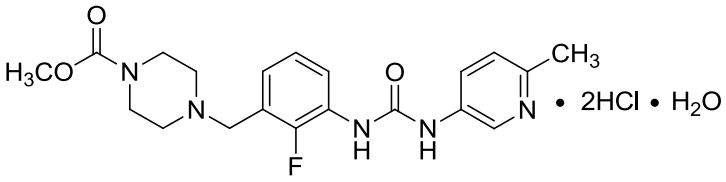
(Yancy et al, 2013; Ponikowski et al, 2016). While several pharmacological and nonpharmacological interventions have been shown to reduce the rate of HF hospitalizations and improve mortality, including angiotensin-converting enzyme inhibitors (ACEis), beta-blockers, aldosterone antagonists, coronary 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

enzymatic domain of the cardiac myosin heavy chain, the force-generating motor protein of the cardiac sarcomere, without increasing cardiac myocyte intracellular calcium (Teerlink et al, 2011; Malik et al, 2011). OM increases the left ventricular systolic ejection time (SET) without changing the velocity of contraction (dP/dt) or increasing the heart rate. Additionally, left ventricular filling pressures, left atrial pressures, and total peripheral vascular resistance decreased, providing evidence that prolongation of SET and increased systolic function can favorably impact the hemodynamics that drive HF symptoms. The salutary effects of OM were achieved without noticeable effect upon myocardial oxygen uptake, blood pressure, or coronary blood flow (Shen et al, 2010; Malik et al, 2011).

2.2.1 Clinical Experience

The clinical development program currently consists of 9 completed phase 1 studies, 4 completed phase 2a studies in subjects with chronic HF, 1 completed phase 2b study in subjects with acute HF, and 1 completed phase 2b study in subjects with chronic HF. The M-F1 formulation was used for 3 phase 1 studies and the phase 2b study in subjects with chronic HF. In addition, 2 studies are ongoing/planned in Japanese subjects using the M-F1 formulation and PK-based dose adjustment strategy; a phase 1b study in healthy subjects (ongoing) and a phase 2b study in subjects with chronic HFrEF.

2.2.2 Studies in Healthy Volunteers

CY 1111, a first-in-human clinical study with OM, was a randomized, double-blind, placebo-controlled, 4-period crossover, dose escalation study designed to evaluate the safety, tolerability, and PK/pharmacodynamic profile of OM administered intravenously to healthy male volunteers (Teerlink et al, 2011). This study included a total of 33 subjects who received infusions of OM at doses ranging from 0.005 mg/kg/hr to 1.0 mg/kg/hr for up to 6 hours. At an infusion rate of 0.5 mg/kg/hr, given for 6 hours, the average maximum observed concentration (C_{max}) was 905 ng/mL. Five subjects received OM infusion of 0.625 mg/kg/hr for 6 hours (average C_{max} = 1203 ng/mL) and tolerated this dose level well. The highest administered dose of 1.0 mg/kg/hr was given to 2 subjects. During the first 3 hours, both subjects tolerated the dosing rate without difficulty; however, both subjects terminated the infusion prematurely, in 1 case at 3 hours and 22 minutes and in the other case, at 4 hours and 12 minutes. The plasma concentrations at 3 hours were 1338 ng/mL and 1333 ng/mL, and estimated plasma

concentrations (based on individual PK modeling) at study drug termination in each subject were 1320 ng/mL and 1550 ng/mL, respectively.

The dose-limiting toxicity of OM in both subjects was consistent with myocardial ischemia or infarction, which included feeling hot, palpitations, chest or throat tightness, dizziness, tachycardia, electrocardiogram (ECG) ST-segment depression, and, in 1 subject, a troponin I elevation in the absence of an increase in creatine kinase-MB (CK-MB) fraction. These findings appeared consistent with preclinical experience in dogs at similar plasma concentrations. Across the dosing levels evaluated in CY 1111, OM infusions demonstrated generally linear PK with dose-proportional increases in C_{max}. Concentration-dependent pharmacodynamic effects on cardiac function as measured by echocardiography were observed. These pharmacodynamic effects included statistically significant placebo corrected increases from baseline in SET, Doppler-derived stroke volume, LVEF, and fractional shortening.

CY 1013 was an open-label, parallel group study in healthy male volunteers designed to understand the potential for certain drug-drug interactions. To define the contribution of the cytochrome P450 isozymes 3A4 and 2D6 to the metabolism of oral OM in humans, 8 subjects who were extensive metabolizers with respect to their CYP2D6 genotype received the potent inhibitor of CYP3A4, ketoconazole, and 9 extensive metabolizers subjects the moderately potent inhibitor, diltiazem, dosed to steady-state to evaluate the PK parameters of a single dose of OM. In addition, 8 subjects who were poor metabolizers with respect to their defined CYP2D6 genotype received oral OM and ketoconazole. In the 24 subjects who completed the study (8 in each group), CYP3A4 inhibition by ketoconazole resulted in approximately 50% and 30% increases in area under the curve (AUC) in extensive metabolizers and poor metabolizer subjects, respectively; but had little impact on C_{max}. Diltiazem had no effect on either the C or AUC of OM in extensive metabolizers subjects. OM was well tolerated in the study with no serious adverse events. These data suggest that CYP3A and CYP2D6 may not be the major enzymes contributing to the metabolism of OM.

Studies CY 1011, CY 1015, and CY 1016 were designed to evaluate the PK parameters of oral preparations of OM, with immediate release (CY 1011 and CY1015) and modified release (CY1016). The studies enrolled a total of 44 males and 20 females. Maximal duration of exposure was 10 days and maximal dose was 30 mg 3 times a day for 7 days. Results from the studies demonstrated very high oral bioavailability for OM approaching 100% under all conditions studied; food appeared to reduce the rate but not

the extent of absorption. OM was well tolerated with no treatment-related serious adverse events in these trials.

2.2.3 Studies in Patients With Heart Failure

Study CY 1121 was a randomized, double-blind, placebo-controlled, crossover study that enrolled 5 sequential cohorts of patients with stable HF (LVEF ≤ 40% [LVEF ≤ 30% in cohort 4]). A total 45 patients (39 males and 6 females) were enrolled and treated with IV study drug infusions ranging from 2 to 72 hours (Cleland et al, 2011).

Three patients experienced serious adverse events (non-ST-elevation myocardial infarction which occurred in the setting of an inadvertent drug overdose [this event was considered related to study drug and reported as a suspected unexpected serious adverse reaction]; septicemia in the setting of a diabetic foot ulcer that was considered unrelated to study drug; and pneumonia that was considered unrelated to study drug) in the study. OM produced increases in echocardiographic indices of cardiac systolic function.

Study CY 1221 was a randomized, double-blind, placebo-controlled study that enrolled HF patients with ischemic cardiomyopathy and angina with LVEF ≤ 35%. A total of 94 subjects were enrolled and treated with 20 hour IV infusions of study drug followed by 7 days of oral dosing; 29 subjects received placebo, 31 received OM at a lower dose regimen, and 34 at a higher dose regimen. The primary safety endpoint was defined as the proportion of subjects stopping an exercise tolerance test during infusion due to unacceptable angina at an exercise stage earlier than baseline. This endpoint was observed in 1 subject receiving placebo and did not occur in any subject receiving OM at either dose regimen. In addition, no consistent differences were observed between placebo and lower or higher dosing regimens of OM with respect to any of the secondary safety endpoints, vital signs, ECGs, or cardiac enzymes.

CY 1021 was an open-label with the objective to evaluate the PK and tolerability of an oral modified release (MR) and an oral immediate release (IR) formulation of OM in patients with stable HF. A total of 35 subjects were enrolled and treated with a dose of 50 mg MR twice a day (BID), 37.5 mg IR 3 times a day, or 100 mg MR BID under fed conditions. A [redacted]-year-old [redacted] patient experienced sudden death in this study after 6 days of dosing with the IR formulation. The patient's history was [redacted] At the time of enrollment into the study, the patient was NYHA

Class III and Canadian Cardiovascular Society Angina Class III. Study site personnel last spoke to the patient on day 6 just prior to the last administered dose. [redacted] had no complaints and reported that [redacted] was taking the study medication as prescribed. Shortly after the last dose on day 6, the patient suddenly lost consciousness and died. Based on day 1 plasma concentrations, the predicted range of day 6 plasma concentrations were approximately 120 to 210 ng/mL.

Of the 122 healthy volunteers and 147 HF subjects who received at least 1 dose of OM in all of the studies described above, 3 subjects (CY 1111, Subject [redacted]; CY 1121, Subject [redacted]; and CY 1121, Subject [redacted]) experienced a clinical syndrome consistent with myocardial ischemia (feeling hot, palpitations, chest or throat tightness, dizziness, tachycardia, ECG ST-segment depression, positive cardiac markers) that occurred at OM plasma concentrations > 1200 ng/mL, although plasma concentrations of OM exceeding 1200 ng/mL have not always been associated with signs of ischemia. In each of these cases, symptoms and signs resolved rapidly with discontinuation of study drug, no new wall motion abnormalities appeared, and overall left ventricular function was unaffected. An additional 6 HF subjects had troponin I levels > upper reference limit at OM plasma concentrations < 1200 ng/mL. Of these 6 subjects, 1 subject (CY 1221, Subject [redacted]) developed troponin elevation only after stenting of the left anterior descending artery, and another subject (CY 1121, Subject [redacted]) had marked hypertension prior to and during drug administration. Two subjects enrolled in an invasive hemodynamic and cardiac function study (CY 1124, Subjects [redacted] and [redacted]) had troponin I levels > upper reference limit after their procedures in the absence of symptoms or ECG changes. While manipulation of catheters in the right and left ventricles has been reported to be associated with increased troponin levels (Kannankeril et al, 2002), a drug association of these troponin elevations cannot be ruled out. The clinical significance of elevated troponins just above the URL in the remaining 2 subjects is unclear.

The phase 2b Study 20100754 (ATOMIC-AHF) was designed to address key questions regarding the relationship between OM plasma concentrations and its safety, tolerability, and efficacy in an intensively monitored, acutely decompensated patient population hospitalized for acute HF. Study 20100754 was a double-blind, randomized, placebo-controlled study of 3 ascending dose cohorts in which IV OM or matching placebo was infused over 48 hours. In each cohort, OM was administered as a loading dose infusion over 4 hours and a maintenance infusion over the remaining 44 hours.

The primary objective of the study was to evaluate the effect of 48 hours of treatment with intravenous OM compared with placebo on dyspnea in subjects hospitalized for acute HF. Secondary objectives included assessment of the safety and tolerability of 3 dose levels of intravenous OM, as well as additional dyspnea assessments, patient global assessment, changes in levels of NT-proBNP, other short-term clinical outcomes, and characterization of the PK of OM and metabolites, including the relationship between OM plasma concentrations and echocardiographic parameters (PK/pharmacodynamic substudy).

A total of 606 subjects comprised the full analysis set (OM, n = 303). In subjects hospitalized due to acute decompensated HF (Study 20100754), OM given as a 48 hour intravenous infusion did not significantly improve dyspnea symptom response defined as minimally, moderately, or markedly better by 7-point Likert scale at 6 hours after investigational product (IP) initiation, and moderately or markedly better at 24 and 48 hours after IP initiation without worsening of HF or death from any cause by 48 hours ($p = 0.331$). A numeric trend toward a reduction in the incidence of death from any cause or worsening of HF or worsening of HF alone within 7 days of IP initiation was observed at higher OM doses compared with placebo. OM did not significantly reduce NT-proBNP levels compared with pooled placebo.

Subject incidence rates for all treatment emergent adverse events were 58% in the pooled OM group and 63% in the pooled placebo group. The most frequently reported treatment-emergent adverse events were cardiac failure (16.5% pooled placebo, 13.5% pooled OM), hypotension (4.6% pooled placebo, 7.9% pooled OM), and hypokalemia (5.9% pooled placebo, 6.6% pooled OM). The incidence of treatment-emergent serious adverse events was similar between the pooled OM and pooled placebo groups (21.8% and 23.1%, respectively). Serious treatment-emergent adverse event preferred terms (PTs) that were reported in > 1% of subjects in the study included cardiac failure (7.4% overall; 6.6%, pooled OM and 8.3%, pooled placebo group), cardiac failure congestive (1.7%; 2.0% and 1.3%), renal failure acute (1.7%; 2.0% and 1.3%), and pneumonia (1.2%; 1.3% and 1.0%). Twenty subjects (11 placebo, 9 OM) died in this study. A modest increase in the upper quartile troponin I change from baseline value was observed in OM groups compared with placebo. No significant association was observed between OM C_{max} or AUC and maximum troponin change from baseline ($p = 0.95$ and 0.83, respectively).

There was a numerical imbalance in adjudicated myocardial infarctions in OM-treated subjects compared with placebo-treated subjects.

Among the 10 total positively-adjudicated, post-randomization myocardial infarctions in the study (7 OM-treated subjects, 3 placebo treated subjects), 5 occurred in OM-treated subjects in cohort 3. Of these 5 events in cohort 3, 2 occurred several days (day 12 and day 22) after drug had been discontinued (day 2) (half-life of OM is approximately 20 hours), while another occurred only after percutaneous coronary intervention. The remaining 2 subjects with myocardial infarctions had troponin elevations (peak of 0.064 and 0.168 ng/mL); the first of these was asymptomatic and the second was related to a transient episode of exertional angina, which was relieved by nitroglycerin in the setting of a history of chronic exertional angina. The remaining positively-adjudicated, post-randomization myocardial infarctions occurred in cohort 1 subjects (3 placebo, 2 OM).

The phase 2b Study 20110151 (COSMIC–HF) was designed to evaluate an oral MR formulation of OM in subjects with chronic HF with reduced ejection fraction. The study consisted of 2 parts, a dose-escalation phase and a larger and longer expansion phase, which was the first study to use a PK-based titration scheme to identify the target OM dose. The dose(s), formulation and PK-based dose adjustment scheme for the expansion phase were based on results from the dose escalation phase.

The expansion phase of Study 20110151 was designed to evaluate the PK, PD, safety, and tolerability of oral OM in 448 subjects with chronic HF and left ventricular systolic dysfunction. Subjects were randomized 1:1:1 to receive placebo, OM 25 mg BID, or to a PK-based dose adjustment group where 25 mg BID starting dose could be increased to 50 mg BID at Week 8 depending on plasma concentrations of OM after 2 weeks of treatment with the 25 mg dose. Analysis of PK data showed that the PK-based dose adjustment reliably controlled subject exposure to OM . Following 20 weeks of treatment, statistically significant improvements were observed in prespecified secondary endpoint measures of cardiac function in the dose-titration group compared with placebo. Systolic ejection time increased by 25.0 msec ($p<0.001$), stroke volume increased by 3.63 mL ($p=0.022$), and heart rate decreased by 2.97 beats per minute ($p=0.007$). Left ventricular end-systolic and end-diastolic dimensions decreased by 1.79 mm ($p=0.003$) and 1.29 mm ($p=0.013$), respectively, and were associated with statistically significant reductions in left ventricular end-systolic and end-diastolic volumes. There was a 970 pg/mL ($p=0.007$) decrease in NT-proBNP.

Adverse events, including serious adverse events, in subjects receiving OM were comparable with those receiving placebo. The incidence of adjudicated deaths (2.7% in placebo group, 1.4% in OM group), myocardial infarction (1.34% and 0.34%, respectively), and unstable angina (0% and 0.34%, respectively) was similar across groups. Other cardiac adverse events were balanced between placebo and OM groups.

In the OM groups compared with placebo, cardiac troponin assessed per protocol increased by 0.001 ng/mL and 0.006 ng/mL (median change from baseline at Week 20) in the 25 mg twice daily group and dose titration group, respectively. Events of increased troponin (n = 278 across all treatment groups) were independently adjudicated and none were determined to be myocardial ischemia or infarction.

2.2.4 Dose Selection for Phase 3

The OM dosing regimen selected for this phase 3 study (20110203) is oral administration of 25 mg BID at the initiation of treatment. At study visit Week 2 (PK steady-state for initial dose), a predose PK sample will be collected. At Week 4, subjects with Week 2 OM predose plasma concentrations < 200 ng/mL will have their dose increased to 50 mg BID; subjects with Week 2 predose plasma concentrations ≥ 200 and < 300 ng/mL will have their dose increased to 37.5 mg BID, subjects with Week 2 predose plasma concentrations ≥ 300 ng/mL and < 1000 ng/mL will maintain a 25 mg BID dosing regimen, and subjects with plasma concentration ≥ 1000 ng/mL will start administration of placebo BID. Similar to Study 20110151, PK-based dose adjustment in this study will be used to attain effective steady state concentrations for desired PD effect while maintaining OM plasma concentrations < 1000 ng/mL. Please refer to Appendix D for further information on dose adjustment.

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

2.3 Rationale

OM is a promising new oral therapeutic agent for HFrEF patients targeting myocardial contractility. Current recommended pharmacological therapies for chronic HF aim at blocking/controlling the physiological compensatory mechanism. Therapeutic options to directly improve myocardial contractility for these patients are lacking.

The early post-discharge period following a HF hospitalization carries particular high risk for poor clinical outcomes and is known as the "vulnerable phase" (Greene et al, 2015). To help assess effects of OM during this period, the study will enroll some subjects that

are in the hospital transitioning from initial treatment to discharge. The total population in this study allows assessment of OM treatment effect and safety in a more representative population of chronic HFrEF patients.

2.4 Clinical Hypotheses

The primary hypothesis is that when added to SoC, OM is well tolerated and superior to placebo in reducing the risk of CV death or HF events in subjects with chronic HFrEF.

Secondary hypotheses are that OM reduces the individual risks of:

- CV death
- HF hospitalization
- all-cause death

and improves symptoms in subjects with chronic HFrEF compared to placebo.

3. EXPERIMENTAL PLAN

3.1 Study Design

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

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

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

Approximately 1000 sites globally will participate in this study. Sites that do not enroll subjects within 3 months of site initiation may be closed.

3.3 Number of Subjects

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

Approximately 8000 subjects will be randomized.

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.

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)

4.1.2 Exclusion Criteria

201 Currently receiving treatment in another investigational device or drug study, or < 30 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

202 Malignancy within 5 years prior to randomization with the following exceptions: localized basal or squamous cell carcinoma of the skin, cervical intraepithelial neoplasia, stage 1 prostate carcinoma, breast ductal carcinoma in situ.

203 Subject has known sensitivity to any of the products or components to be administered during dosing.

204 Factors expected to interfere with the subject's availability or ability to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge (including ongoing substance abuse).

205 Inability to swallow study medication tablet (eg, swallowing disorders, feeding tubes)

206 Receiving mechanical hemodynamic support (eg, intra-aortic balloon pump counterpulsation), or invasive mechanical ventilation ≤ 7 days prior to randomization

207 Receiving IV inotropes (eg, dobutamine, milrinone, levosimendan) or IV vasopressors (eg, epinephrine, norepinephrine, dopamine, or vasopressin) ≤ 3 days prior to randomization

208 Receiving IV diuretics or IV vasodilators, supplemental oxygen therapy, or non-invasive mechanical ventilation (eg, bilevel positive airway pressure [BiPAP] or continuous positive airway pressure [CPAP] ≤ 12 hours prior to randomization (Note: the use of non-invasive ventilation for sleep disordered breathing is permitted)

209 Acute coronary syndrome (ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, unstable angina), stroke, or transient ischemic attack, major cardiac surgery or cardiac intervention (ie, implantation of cardiac closure devices, cardiac resynchronization therapy, or catheter ablation), percutaneous coronary intervention, or valvuloplasty/other cardiac valve repair or implantation within the 3 months prior to randomization

210 Insertion of other cardiac devices (eg, implantable cardioverter defibrillator, permanent pacemaker, monitoring devices) within 30 days prior to randomization

211 Severe uncorrected valvular heart disease, hypertrophic or infiltrative cardiomyopathy, active myocarditis, constrictive pericarditis, or clinically significant congenital heart disease

212 Untreated severe ventricular arrhythmia (eg, ventricular tachycardia or ventricular fibrillation)

213 Chronic antiarrhythmic therapy, with the exception of amiodarone. Note: for the purposes of this exclusion criterion, digoxin, calcium channel blocker, and beta-blocker therapy are not considered to be chronic antiarrhythmic therapies

214 Symptomatic bradycardia or second or third degree heart block without a pacemaker

215 Routinely scheduled outpatient intravenous infusions for HF (eg, inotropes, vasodilators [eg, nesiritide], diuretics) or routinely scheduled ultrafiltration

216 Systolic blood pressure > 140 mmHg or < 85 mmHg, or diastolic blood pressure > 90 mmHg, or heart rate > 110 beats per minute, or < 50 beats per minute at screening

217 Estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73m^2 or receiving dialysis at screening

218 Hepatic impairment defined by a total bilirubin (TBL) ≥ 2 times the upper limit of normal (ULN), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 times ULN at screening

219 Previously received OM

220 Severe, concomitant non-CV disease that is expected to reduce life expectancy to < 2 years

221 Recipient of any major organ transplant (eg, lung, liver, heart, bone marrow, renal) or anticipated to receive chronic mechanical circulatory support or heart transplantation within 12 months from randomization

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

- A female is considered of childbearing potential unless she has had a hysterectomy, bilateral oophorectomy, or bilateral salpingectomy or she is postmenopausal. Menopause is defined as ≥ 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old; or no spontaneous menses for at least 2 years in a female < 55 years old; or age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy) and with follicle-stimulating hormone (FSH) levels > 40 IU/L, or postmenopausal estradiol levels (< 5 ng/dL), or according to the definition of “postmenopausal range” for the laboratory involved.
- Two acceptable methods of effective birth control include the following 2 options:

  – use of hormonal and barrier combination birth control methods (intrauterine device and barrier method with spermicide, intrauterine device and hormonal birth control method, hormonal birth control method and barrier method with spermicide),

  – 2 barrier methods (each partner must use 1 barrier method except a female condom) with at least 1 of the barrier methods including spermicide (a male and female condom may not be used together due to the risk of tearing)

- Hormonal methods of birth control include oral, intravaginal, transdermal, injectable, or implantable. Barrier methods of birth control include diaphragm with spermicide, cervical cap with spermicide, male or female condom with spermicide, and contraceptive sponge with spermicide. If spermicide is not commercially available in the local country/region a barrier method without spermicide is acceptable.

  – Note: If additional medications are given during treatment which may alter the contraceptive requirements (these additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized after the last dose of protocol-required therapies) the investigator is to discuss these changes with the study subject.

223 Female subject is pregnant or breastfeeding or is planning to become pregnant or planning to breastfeed during treatment with IP (OM or placebo) or within 5 days after the end of treatment with IP.

224 Planned to be discharged from the hospital to long term care facility (eg, skilled nursing facility) or hospice.

225 History or evidence of any other clinically significant disorder (including cardiac arrhythmia), condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the informed consent form before commencement of study-specific activities/procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (defined as the point at which the subject signs the informed consent form [ICF]) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the IVRS/IWRS. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

Subjects who do not meet all eligibility criteria on the first screening attempt may be rescreened for the study. For each rescreening, a new ICF must be signed and the

rescreening must be reregistered in IVRS/IWRS. Rescreened subjects who are reconsented will repeat all screening procedures (see Section 7.2.1).

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study.

5.1 Randomization/Treatment Assignment

Subjects who meet the eligibility requirements will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups (OM or placebo) in a double-blind manner. 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). Subjects can only be randomized 1 time for this study.

Subjects in the recently and not currently hospitalized for HF setting who meet all eligibility criteria at the end of screening will return to the study site for randomization and day 1 procedures.

Subjects in the currently hospitalized for HF setting who meet all eligibility criteria at the end of screening should be randomized prior to discharge with day 1 procedures occurring during the hospitalization.

The randomization date is to be documented in the subject's medical record and on the enrollment CRF. Randomization numbers will be provided to the site through an IVRS/IWRS.

5.2 Site Personnel Access to Individual Treatment Assignments

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

The investigator is strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

Refer to the Investigational Product Instruction Manual (IPIM) for a description regarding how responsible pharmacists and investigators will access treatment information via the IVR/IWR system, in the event that there is a need to break the blind.

6. TREATMENT PROCEDURES

6.1 Classification of Product

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

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

6.2 Investigational Product

6.2.1 Amgen Investigational Product (OM)

OM will be manufactured and packaged by Amgen Inc. or designee and distributed using Amgen clinical study drug distribution procedures. OM will be presented as tablets. Tablets will be packaged in 14-count blisters. Further details regarding IP storage condition, dispensation, packaging, labeling, and accounting procedures are outlined in the IPIM.

Placebo will be presented in identical containers and stored/packaged the same as OM.

6.2.1.1 Dosage, Administration, and Schedule

IP will be administered orally BID in the morning and evening by the subjects and can be taken under fasted or fed conditions. IP will be swallowed whole (not chewed, crushed, or split) and taken with water as instructed in the IPIM. Each morning and evening administration should be taken at approximately the same time of day. If IP cannot be taken or has not been taken within approximately 12 ± 3 hours from the most recent previous dose, the dose should be missed and the next dose should be taken at the regular time.

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

Subjects randomized to OM will initiate administration at 25 mg BID. At study visit Week 2, a predose blood sample will be collected for all subjects. The results will be blinded to investigators. For subjects randomized to OM, predose PK collected at Week 2 will guide the dose adjustment. A new IP supply will be provided to a subject when PK is assessed for the purpose of dose adjustment regardless of randomized treatment group and outcome of the PK assessment in order to maintain the blind.

Subjects randomized to placebo will receive placebo throughout the study and will be submitted to all protocol procedures in order to maintain the blindness of treatment group allocation and IP dose. Subjects should continue to take IP through the morning of the end of study (EOS) Visit.

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.

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

hospitalization discharge can be reinitiating or titrating oral SoC chronic HF therapies at the time of randomization, per usual clinical practice.

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

Throughout the study, investigators may prescribe or adjust any concomitant medications or treatments deemed necessary to provide adequate supportive care, paying special attention to inhibitors of CYP3A4 discussed in Section 6.6.

All other protocol-required therapies that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

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

6.3 Hepatotoxicity Stopping and Rechallenge Rules

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

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

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

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

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

- AND no other cause for the combination of the above laboratory abnormalities is apparent; important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:
  - hepatobiliary tract disease
  - viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)

- right sided HF, hypotension, or any cause of hypoxia to the liver causing ischemia
- exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- alpha-one antitrypsin deficiency
- alcoholic hepatitis
- autoimmune hepatitis
- Wilson's disease and hemochromatosis
- nonalcoholic Fatty Liver Disease including Steatohepatitis
- nonhepatic causes (eg, rhabdomylosis, hemolysis)

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

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

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

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

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

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

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

The decision to rechallenge the subject must be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

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

6.4 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, paying special attention to inhibitors of CYP3A4, discussed in Section 6.6.

Concomitant therapies are to be collected from screening informed consent date through the EOS visit. The groups of concomitant medications to be recorded will include (but not be limited to):

- Lipid lowering medications
- Analgesics/antipyretics
- Antibiotics
- Antidepressants
- Medication for glycemic control
- Hormone replacement therapy
- Oral corticosteroids
- Cardiovascular medication (eg, HF SoC therapies, antihypertensives, anticoagulants, antiplatelets, antiarrhythmics)

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

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

6.5 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or

performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

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

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

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

Investigational treatments or procedures other than study-provided IP are prohibited. Medications or foods that are known potent inhibitors of CYP3A4 (see examples provided in Table 1) should be avoided, unless deemed necessary by the investigator.

Table 1. Examples of Potent Inhibitors of CYP3A4

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

Throughout the study, investigators may prescribe or adjust any concomitant medications or treatments deemed necessary to provide adequate supportive care.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Screening assessments and study procedures are outlined in this section and in Table 2 (Schedule of Assessments).

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

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).

[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.

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

7.2 General Study Procedures

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

7.2.1 Screening Enrollment

For subjects recently and not currently hospitalized for HF, up to 8 weeks is allowed for screening before the subject must be randomized or screen failed in order to provide flexibility for HF therapy adjustment, visit scheduling, and potential retesting (see Section 7.2.2).

Subjects currently hospitalized for HF are expected to be randomized before discharge. Local laboratory assessments from the current hospitalization can be used to support the subject's eligibility and randomization in order to provide flexibility for randomization before discharge. Central laboratory assessments for screening should be collected after ICF signature for those subjects. If the subject is discharged during screening period and randomized later, subject will be included in the recently and not currently hospitalized for HF randomization setting stratification.

The placebo run-in procedure assesses the subject's ability to swallow an open label placebo tablet successfully (ie, without chewing). The following procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 2):

- confirmation that the ICF has been signed
- demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.
- physical examination
- medical history
- height and weight
- vital signs (blood pressure, heart rate)
- laboratory assessments (chemistry, serum pregnancy [females of childbearing potential only], and FSH [if needed])
- Serious Adverse Event reporting, Adverse Event reporting, Potential Endpoint reporting, Hospitalizations, Disease-related Event reporting (only adverse events possibly related to study procedures and serious adverse events are collected during the screening period from signing of ICF)

- documentation of concomitant therapy
- placebo run-in
- registration in IVRS/IWRS system
- ECG (for cardiac rhythm confirmation)

7.2.2 Retesting

If, in the investigator's judgment, laboratory abnormalities are likely to be transient, blood samples can be retested during screening as long as the subject can be evaluated for eligibility and randomized within the allowed screening period.

7.2.3 Rescreening

Subjects who do not meet all eligibility criteria on the first screening attempt may be rescreened for the study. Rescreen subjects must first be registered as screen failed in IVRS/IWRS and subsequently registered as rescreened. Subjects will maintain the originally assigned subject identification number. For each rescreening, a new informed consent form must be signed. Rescreened subjects who are reconsented will repeat all screening procedures.

7.2.4 Treatment

Subjects in the recently and not currently hospitalized for HF setting who meet all eligibility criteria at the end of screening will return to the study site for randomization and day 1 procedures.

Subjects in the currently hospitalized for HF setting who meet all eligibility criteria at the end of screening should be randomized prior to discharge with day 1 procedures occurring during the hospitalization. Subjects can only be randomized 1 time for this study.

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Table 2). IP is to be administered after completion of vital signs, ECG, and blood draw procedures during each visit that these are required. PRO assessments should be completed first at each visit, where they are required.

- randomization in IVRS/IWRS system
- central laboratory assessments (PK, chemistry, hematology, abbreviated laboratory panel, NT-proBNP, troponin I, biomarkers, and urinalysis))
- vital signs (blood pressure, heart rate)
- weight

- review for adverse events/serious adverse events, potential endpoint reporting (PEP), disease related events (DRE), and acute coronary syndrome (ACS) signs and symptoms
- documentation of concomitant therapy
- ECG
- PROs (should be done before other study procedures)
- NYHA Class/Clinician Global Rating Severity (CGR-S)
- IP administration at site
- IP dispensation
- IP tablet count

If a subject withdraws from the study early, investigators would make every effort to complete and report the observations as thoroughly as possible up to the date of withdrawal. If possible, the end of study procedures should be completed at the time of withdrawal (see Section 7.2.5).

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

7.2.5 End of Study Visit

The study is event driven and will conclude when approximately 1590 subjects have experienced an event of CV death. Amgen and executive committee (EC) will determine the termination period based on the anticipated date of occurrence of 1590 CV death events. Investigators will be notified in advance and should schedule the End of Study (EOS) visits for all subjects. The following procedures will be completed during the EOS visit:

- vital signs (blood pressure, heart rate)
- height and weight
- patient reported outcomes (PROs; should be done before other study procedures)
- review for adverse events/serious adverse events/PEPs/DRE/ACS signs and symptoms
- physical examination as per SoC
- ECG
- documentation of concomitant therapy

- central laboratory assessments (chemistry, hematology, urinalysis, NT-proBNP, troponin I, biomarkers)
- IP tablet count

7.2.6 Description of Study Procedures

7.2.6.1 Informed Consent

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

7.2.6.2 Demographic Data

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

7.2.6.3 Medical History

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

7.2.6.4 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure and heart rate. Use of an automated oscillometric device for blood pressure measurement is preferred and recommended. Blood pressure will be recorded in both of the subject's arms unless a concomitant condition favors the use of a particular arm. The arm with the higher systolic reading will be used for eligibility determination. The appropriate size cuff should be used. The subject's pulse should be measured for 30 seconds and the number multiplied by 2 to obtain heart rate. Blood pressure measurement can be repeated if the previous reading is outside of the eligibility range. The repeat blood pressure measure should be taken at least 2 minutes following the previous measure.

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

Record all measurements on the vital signs CRF.

7.2.6.5 Physical Examination

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

7.2.6.6 Height and Weight

Height in centimeters should be measured without shoes. Weight in kilograms should be measured without shoes.

7.2.6.7 Electrocardiogram

Subject must be in a supine position in a rested and calm state for at last 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position as possible. The ECG must be performed prior to blood draws or other invasive procedure. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals, and assessment of cardiac rhythm.

ECGs must be conducted as follows:

Screening ECG

- 1 local ECG (all sites)

On study ECGs (day 1, week 48, every 48 weeks [Q48W])

- Centralized ECG services: ECG in triplicate run consecutively
- No centralized ECG services: 1 local ECG

The principal investigator or designated site physician will review all ECGs (regardless of using a centralized service or not centralized service). Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original noncentralized ECG will be made available to Amgen.

Further detail about the equipment provided and its use for this study will be provided in an Investigator ECG Manual distributed to the sites before start of enrollment.

7.2.6.8 Concomitant Therapy

For the following concomitant medications categories (see Section 6.4), investigators must document whether therapy was being taken at any time point during the study: lipid lowering medications, analgesics / antipyretics, antibiotics, antidepressants,

hormone replacement therapy, oral corticosteroids, CV medication (eg, HF SoC therapies, antihypertensives, anticoagulants, antiplatelets, and antiarrhythmics).

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

Initiation of nonpharmacological treatments for HF (eg, implantable cardioverter defibrillator, cardiac resynchronization therapy [CRT]) and coronary revascularization will be recorded on the CRF.

7.2.6.9 Patient-reported Outcomes

Subjects will be asked to complete the KCCQ, Patient Global Rating Severity (PGR-S), and EQ-5D questionnaires in a quiet place prior to the medical consultation and prior to undergoing any tests and procedures to avoid biasing their response to the questionnaires. Site staff will be asked to check the questionnaires for completeness before the subject leaves the clinic or hospital.

7.2.6.10 Laboratory Assessments

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

Table 3. Analyte Listing

Chemistry		Urinalysis	Hematology	Other Labs
Sodium	Creatinine	Specific gravity	Hemoglobin	OM plasma concentration (PK)
Potassium		pH	Hematocrit	Pregnancy test[a]
Chloride	Total bilirubin	Blood	RBC	FSH[a]
Calcium	Direct bilirubin	Protein	RDW	NT-proBNP
Magnesium	CK	Glucose	MCV	Troponin I
Phosphorus	ALP	Bilirubin	MCH	HbA1c
	LDH		MCHC	CK-MB
Urea	AST (SGOT)		WBC	
	ALT (SGPT)		Platelets	

OM = omecamtiv mecarbil; PK = pharmacokinetic; RBC = red blood cell; FSH = follicle-stimulating hormone; RDW = red cell distributions width; NT-proBNP = N-terminal pro-B-type natriuretic peptide; CK = creatine kinase; MCV = mean corpuscular volume; ALP = alkaline phosphatase; MCH = mean corpuscular hemoglobin; HbA1c = Glycated hemoglobin; LDH = lactic acid dehydrogenase; MCHC = mean corpuscular hemoglobin concentration; CK-MB = creatine kinase-MB; AST = aspartate aminotransferase; WBC = white blood cell; ALT = alanine aminotransferase

[a] A pregnancy test is required for females of childbearing potential; FSH only per exclusion.

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

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,

discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving IP and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from IP or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 2) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treatment physicians, from the review of medical records) and collection of data, including endpoints and adverse events. Subjects who have discontinued investigational product and/or protocol required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the change to the Schedule of Assessments (Table 2) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

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

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

Preferably the subject should withdraw consent in writing and, if the subject or the subject's representative refuses or is physically unavailable, the site should document

and sign the reason for the subject's failure to withdraw consent in writing. The informed consent for the study should note that although a subject is free to leave the study and stop taking study medication, the investigators hope the patient will remain for follow-up status evaluations.

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

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

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

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

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

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

- subject request
- safety concern (eg, due to an adverse event, pregnancy)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)
- OM plasma concentration ≥ 1000 ng/mL when assessed after Week 8

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease Related Events

Events that are not submitted for adjudication as potential endpoints, but that are anticipated to occur in the study population due to the underlying disease, may be reported a**s** Disease Related Events. In this study, subjects will have HFrEF with an LVEF of ≤ 35%. It is expected that the study subjects will experience events related to chronic HFrEF. Examples of events related to HF include:

- fluid overload signs and symptoms (eg, edema, pulmonary congestion, dyspnea, orthopnea, hepatic congestion) not requiring urgent, unscheduled clinic/office/ED visit, or hospital admission
- renal function impairment (eg, cardiorenal syndrome, acute renal failure) not requiring urgent, unscheduled clinic/office/ED visit, or hospital admission

If the event is considered worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the IP and disease worsening, the event should not be considered a Disease Related Event and must be reported as an Adverse Event or Serious Adverse Event.

If a Disease Related Event is considered **as an adverse event and is** serious, the event should be reported within 24 hours of the acknowledgement of the event.

9.1.2 Adverse Events

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

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

Only adverse events considered related to study procedures and serious adverse events are reported after signing of the informed consent until randomization.

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.

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.

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

- 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

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.

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.

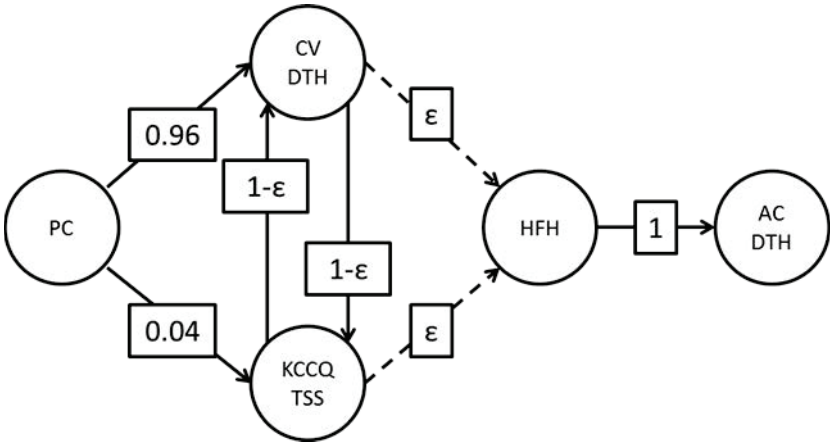
10.5.2 Multiplicity Adjustments

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

direction of the statistically significant effect favors omecamtiv mecarbil. Exploratory endpoints will be assessed using a nominal alpha level of 0.05 and not have multiplicity adjustments.

Figure 2. Multiplicity Testing Propagation Approach



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

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

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

10.5.3 Primary Efficacy Endpoint

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

Kaplan-Meier estimates of cumulative incidence of the composite endpoint will be computed.

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

10.5.4 Secondary Efficacy Endpoints

The secondary endpoints of time to CV death, time to first HF hospitalization, and time to all-cause death will be assessed using a Cox model stratified by randomization setting and region and include terms for baseline eGFR and treatment.

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.

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.

- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

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

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

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

Subjects may be eligible for continued treatment with Amgen IP(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply

Amgen IP(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

12.2 Study Documentation and Archive

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

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

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

Elements to include:

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

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

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

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

Amgen is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data;

and adherence to local regulations on the conduct of clinical research. The Amgen representative is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

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

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

Data capture for this study is planned to be electronic:

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

12.4 Investigator Responsibilities for Data Collection

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

12.5 Language

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

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

12.6 Publication Policy

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

Authorship of any publications resulting from this study will be determined on the basis of the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (International Committee of Medical Journal Editors, 2013, updated 2014), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial

Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

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

13. REFERENCES

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

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

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

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

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

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

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.2.2.

Additional Clinical Assessments and Observation

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

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

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

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

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

Appendix B. Sample Serious Adverse Event Report Form

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the initial adverse event term: _____
and start date and start time: Day _____ Month _____ Year _____ Start time (24-hr clock) _____

<<For completion by Amgen prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

3. ADVERSE EVENT

Provide the date the Investigator became aware of this Information: Day_____ Month_____ Year_____

Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Start Time 24-hr clock	Date Ended Day Month Year	Stop Time 24-hr clock	Check only if event occurred before first dose of IP/drug under study No ✓	 Yes ✓	Is event serious? ☐ Yes ☐ No	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP/drug under study or an Amgen device used to administer the IP/drug under study? AMG 423 (omecamtiv mecarbil) No✓	 Yes✓	Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
							☐ Yes ☐ No					
							☐ Yes ☐ No					
							☐ Yes ☐ No					

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes, If yes, please complete all of Section 4:

Date Admitted Day Month Year	Time Admitted (24-hr clock)	Date Discharged Day Month Year	Time Discharged (24-hr clock)

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										

	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.*		

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm / dd / yyyy_____ ☐ Unknown

Estimated date of delivery mm_____ / dd_____/ yyyy_____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm / dd / yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm / dd / yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

Effective Date: March 27, 2011

Page 1 of 1

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

Effective Date: 03 April 2012, version 2.

Page **1** of **1**

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

Effective Date: 03 April 2012, version 2.

Page **1** of **1**

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

Study Visit	Week 2 Plasma Concentration (ng/mL)	Current Dose BID	New Dose BID
Week 4	< 200	25 mg	50 mg
	≥ 200 - < 300		37.5 mg
	≥ 300 - < 1000		no change
	≥ 1000		placebo
Study Visit	**Week 6 Plasma Concentration (ng/mL)**	**Current Dose BID**	**New Dose BID**
Week 8	< 750	Any	no change
	≥ 750 - < 1000	25 mg	no change
		37.5 mg	25 mg
		50 mg	37.5 mg
	≥ 1000	25 mg	placebo
		37.5 mg	25 mg
		50 mg	
Study Visit	**Any Plasma Concentration (ng/mL)**	**Current Dose**	**New Dose**
Week 12	≥ 1000	Any	Withdraw IP
Week 48			
Q 48 weeks			
Unscheduled			

BID = twice a day; IP = investigational product; Q 48 = every 48

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

Adapted from Yancy et al, 2016. ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure and Ponikowski et al, 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.

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

ACCF = American College of Cardiology Foundation; ACE = angiotensin-converting enzyme; AHA = American Heart Association; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor neprilysin inhibitor; CR = controlled release MRA = mineralocorticoid receptor antagonist; NA = not applicable

Amendment 1

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

Amgen Protocol Number (AMG 423) 20110203

EudraCT Number 2016-002299-28

GALACTIC-HF

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

Amendment Date: 7 September 2017

Rationale:

This protocol is being amended to:

- Move pharmacokinetic (PK) and associated assessments from week 24 to week 12
- Add electrocardiograms (ECGs) at screening and update guidance language for ECGs
- Clarify that there can be limited enrollment of subjects in atrial flutter at screening
- Clarify language around hospitalization in terms of inclusion criteria
- Update inclusion criteria #104 to provide guidance for qualifying left ventricle ejection fraction (LVEF)
- Add exception to exclusion criteria #206 to indicate that noninvasive ventilation is permitted for specific indications
- Update exclusion criteria #209 to include cardiac intervention and other cardiac valve repair
- Update exclusion criteria #211 to include infiltrative cardiomyopathy
- Update exclusion criteria #221 to indicate that subjects anticipated to receive cardiac support or heart transplantation are not eligible
- Clarifications of windows for randomization, day 1, and IP administration
- Administrative and editorial edits, and edits made for clarification of protocol

Description of Changes:

Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Global	**Replace:** 31 August 2016	**With:** **07 September 2017**	Administrative change.
Global		**Change:** Editorial changes (including typographical, grammatical, and formatting) have been made throughout the document.	Editorial
Title Page		**Add:** **Amendment 1 07 September 2017**	Administrative change
Investigator's Agreement	**Replace:** 31 Aug 2016	**With:** **07 September 2017**	Administrative change
Study Glossary		**Add:** **eCRF electronic case report form** **EF ejection fraction** **Q48W every 48 weeks**	Editorial
Section: Protocol Synopsis, Study Design	**Replace:** Enrollment of subjects with atrial fibrillation will be limited to 20% of each enrollment setting.	**With:** Enrollment of subjects **in** atrial fibrillation**/flutter at screening is** limited to **approximately** 25%.	Clarify limited enrollment includes subjects in atrial flutter

Table 1. Summary of Amendment Changes

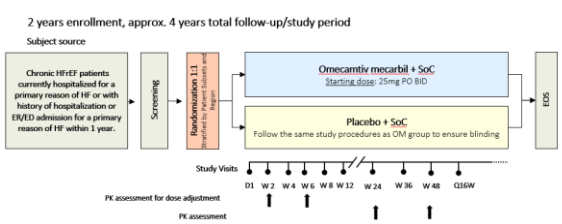
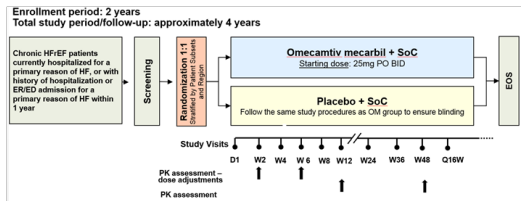
Section	Text in Protocol	Amended Text	Rationale for Change
Section: Protocol Synopsis, Summary of Subject Eligibility Criteria	**Replace:** For a full list of eligibility criteria, please refer to Section 4.1 through Section 4.1.2.	**With:** For a full list of eligibility criteria, please refer to Section **4.1.1** through Section 4.1.2.	Editorial change to include accurate Section numbers for eligibility criteria
Protocol Synopsis: Study Design and Treatment Schema	**Replace:** 	**With:** 	Updated to reflect PK assessment at week 12 instead of week 24.
Section: 3.1 Study Design, Paragraph 1	**Replace:** Enrollment of subjects with atrial fibrillation will be limited to 20% of each enrollment setting.	**With:** Enrollment of subjects **in** atrial fibrillation**/flutter at screening is** limited to **approximately** 2**5**%.	Clarify limited enrollment includes subjects in atrial flutter at screening
Section: 3.2 Number of Sites	**Replace:** Approximately 800 sites globally will participate in this study.	**With:** Approximately **10**00 sites globally will participate in this study.	Updated number of sites that will participate in this study

Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 4.1.1 Inclusion Criteria, Criterion 104	**Replace:** LVEF ≤ 35%, per subject's most recent medical record, not in the setting of acute decompensation	**With:** 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.**	Clarify the acceptable date of the most recent LVEF assessment. Clarify the instances which the assessment of the LVEF are not acceptable for eligibility
Section: 4.1.1 Inclusion Criteria, Criterion 107	**Replace:** Current hospitalization with primary reason of HF or prior HF hospitalization, or urgent HF admission to emergency department (ED)within 1 year prior to screening	**With:** Current**ly 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**	Clarification of medical history requirements for subjects not currently hospitalized for HF during randomization.

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Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 4.1.1 Inclusion Criteria, Criterion 108	**Replace:** 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 with atrial fibrillation, the cut off levels are: BNP ≥ 375 pg/mL or NT-proBNP ≥ 1200 pg/mL)	**With:** 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)	Clarify limited enrollment includes subjects in atrial flutter at screening
Section: 4.1.2 Exclusion Criteria, Criterion 204	**Replace:** Subject not likely to be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge.	**With:** **Factors expected to interfere with the subject's availability or ability** to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge **(including ongoing substance abuse)**.	Clarification that substance abuse should be considered an exclusion criterion for eligibility

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Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 4.1.2 Exclusion Criteria, Criterion 206	**Replace:** Receiving mechanical hemodynamic support (eg, intra-aortic balloon pump counterpulsation), or mechanical ventilation (including non-invasive mechanical ventilation, ie, bilevel positive airway pressure [BiPAP] or continuous positive airway pressure [CPAP] devices) ≤ 7 days prior to randomization	**With:** Receiving mechanical hemodynamic support (eg, intra-aortic balloon pump counterpulsation), or **invasive** mechanical ventilation ≤ 7 days prior to randomization	Moved non-invasive ventilation indication to criterion 208.
Section: 4.1.2 Exclusion Criteria, Criterion 208	**Replace:** Receiving IV diuretics or IV vasodilators, or supplemental oxygen therapy ≤ 12 hours prior to randomization	**With:** Receiving IV diuretics or IV vasodilators, supplemental oxygen therapy**, or non-invasive mechanical ventilation (eg, bilevel positive airway pressure [BiPAP] or continuous positive airway pressure [CPAP]** ≤ 12 hours prior to randomization **(Note: the use of non-invasive ventilation for sleep disordered breathing is permitted)**	Clarification about a non-invasive ventilation indication which is an exception to the exclusion criteria

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Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 4.1.2 Exclusion Criteria, Criterion 209		**Add:** Acute coronary syndrome (ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, unstable angina), stroke, or transient ischemic attack, major cardiac surgery **or cardiac intervention (ie, implantation of cardiac closure devices, cardiac resynchronization therapy, or catheter ablation)**, percutaneous coronary intervention, or valvuloplasty**/other cardiac valve repair or implantation** within the 3 months prior to randomization	Inclusion of the initiation of cardiac resynchronization therapy to the 3-month window from procedure to randomization.
Section: 4.1.2 Exclusion Criteria, Criterion 210	**Replace:** Implantable cardioverter defibrillator or initiation of cardiac resynchronization therapy (CRT) (with/without implantable cardioverter defibrillator) within 30 days prior to randomization	**With:** **Insertion of other cardiac devices (eg, i**mplantable cardioverter defibrillator**, permanent pacemaker, monitoring devices)** within 30 days prior to randomization	Clarification of cardiac devices referred in this criterion. Deletion of "initiation of cardiac resynchronization therapy" from this criterion.
Section: 4.1.2, Exclusion Criteria, Criterion 211	**Replace:** Severe uncorrected valvular heart disease, or hypertrophic obstructive cardiomyopathy, active myocarditis, constrictive pericarditis, or clinically significant congenital heart disease	**With:** Severe uncorrected valvular heart disease, hypertrophic **or infiltrative** cardiomyopathy, active myocarditis, constrictive pericarditis, or clinically significant congenital heart disease	Addition of infiltrative cardiomyopathy as an exclusion criteria

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Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 4.1.2 Exclusion Criteria, Criterion 221		**Add:** Recipient of any major organ transplant (eg, lung, liver, heart, bone marrow, renal) **or anticipated to receive chronic mechanical circulatory support or heart transplantation within 12 months from randomization**	Clarification about eligibility of subjects listed for heart transplantation or mechanical circulatory support.
Section: 5.1 Randomization/Treatment Assignment, Paragraphs 2, 3 and 4	**Replace:** Subjects in the recently and not currently hospitalized for HF setting who meet all eligibility criteria at the end of screening will return to the study site for day 1. Subjects in the currently hospitalized for HF setting who meet all eligibility criteria at the end of screening will be randomized with day 1 occurring during the admission.	**With:** Subjects in the recently and not currently hospitalized for HF setting who meet all eligibility criteria at the end of screening will return to the study site for **randomization and** day 1 **procedures**. Subjects in the currently hospitalized for HF setting who meet all eligibility criteria at the end of screening **should** be randomized **prior to discharge** with day 1 **procedures** occurring during the **hospitalization**.	Updated to add randomization for clarification
Section: 6.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation, Paragraph 1	**Replace:** Pharmacokinetics will be assessed on Week 24 and Week 48, and every 48 weeks throughout the study. See Appendix D for a summary of dose adjustment rules.	**With:** Pharmacokinetics will be assessed on Week**s 12** and 48, and **then** every 48 weeks throughout the study. See Appendix D for a summary of dose adjustment rules.	Changed PK from week 24 to week 12.

Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 6.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation, Paragraph 3	**Replace:** At Week 24, Week 48, and every 48 weeks, PK will be assessed and are not part of the PK based dose adjustment approach.	**With:** At Week**s 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)**.	To provide guidance for PK assessment for those subjects that are in between visits at the time of this protocol amendment.
Section: 6.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation, Paragraph 6	**Replace:** 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 last IP administration time recorded.	**With:** 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**.	Clarification of language
Section: 6.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation, Paragraph 8		**Add:** **Subjects reinitiating IP after withholding for reasons other than cardiac ischemic events will restart on the same IP dose as established before the event.**	To provide guidance for subjects who restart IP for AEs other than cardiac ischemic events.

Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 6.3.1 Criteria for Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity, Paragraph 1	**Replace:** OM should be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:	**With:** OM **must** be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:	Editorial change to clarify IP discontinuation.
Section: 6.3.2 Criteria for Conditional Withholding of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity, Paragraph 2	**Replace:** Amgen IP and other protocol-required therapies, as appropriate should be withheld pending investigation into alternative causes of DILI.	**With:** Amgen IP and other protocol-required therapies, as appropriate **must** be withheld pending investigation into alternative causes of DILI.	Editorial change to clarify IP discontinuation.
Section: 6.3.3 Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity	**Replace:** The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, investigator, and Amgen. If signs or symptoms recur with rechallenge, then OM should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.3.1) should never be rechallenged.	**With:** The decision to rechallenge the subject **must** be discussed and agreed upon unanimously by the subject, investigator, and Amgen. If signs or symptoms recur with rechallenge, then OM **must** be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.3.1) **must** never be rechallenged.	Editorial change to clarify conditions that must be met before rechallenge.

Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 6.4 Concomitant Therapy, Paragraph 3	**Replace:** If a subject is not taking beta blockers, ACEi/ARB/ARNi, or MRA, investigators should record the reason why any of those agents are not prescribed.	**Add:** If a subject is not taking beta blockers, ACEi/ARB/ARNi, or MRA, **or taking doses below those recommended by local guidelines,** investigators should record the reason **in the electronic case report form (eCRF)**.	Clarification
Section: 7.1 Schedule of Assessments, Table 2, Assessment of IP Adherence Row		**Delete:** "~~X~~"under week 24 **Add:** "**X**" under week 12 ± 3d	Assessments changed from week 24 to week 12.
Section: 7.1 Schedule of Assessments, Table 2, ECG Row		**Add:** "**X**" in the column "Screen"	Add screening ECG
Section: 7.1 Schedule of Assessments, Table 2, Serum pregnancy/FSH row (footnote)		**Delete:** X[i]	Editorial change, not correct footnote
Section: 7.1 Schedule of Assessments, Table 2, Abbreviated Laboratory Panel Row		**Add:** "**X**" in the column W12 ± 3d "**X**" in the column W36 ± 7d	Added assessments for abbreviated laboratory panel to weeks 12 and 36.
Section: 7.1 Schedule of Assessments, Table 2, PK Samples Row		**Delete:** "~~X~~[k]" in the column W2 ± 3d **Add:** "**X**" in the column W12±3d	Assessments changed from week 24 to week 12.

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Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 7.1 Schedule of Assessments, Table 2, KKCQ/PGR-S/CGR-S and EQ-5D Rows		**Delete:** "~~X~~" in the column W8 ± 3d **Add:** "**X**" in the column W36 ± 7d	Assessments changed from week 8 to week 36.
Section: 7.1 Schedule of Assessments, Table 2 footnote e	**Replace:** ECG to be read locally, except on sites that have been provided with centralized ECG services equipment.	**With:** **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.	Addition of screening ECG and clarification of language about locally read ECGs.
Section: 7.1 Schedule of Assessments, Table 2 footnote j	**Replace:** NT-proBNP, Troponin I, and CK-MB results will be blinded to subjects, investigators, and sponsor (Amgen).	**With:** **Central** NT-proBNP, Troponin I, and CK-MB **assessments after baseline** will be blinded to subjects, investigators, and sponsor (Amgen).	Editorial change to clarify that central assessments of these parameters will be done kept blinded to all players after day 1.
Section: 7.1 Schedule of Assessments, Table 2 footnote m	**Replace:** Height to be measured at study visit D1 only.	**With:** Height to be measured **during screening** only.	Updated to indicate that height only measured at screening, not day 1.
Section: 7.1 Schedule of Assessments, Table 2 footnote n	**Replace:** Date and time of IP administration during the previous 48 hours.	**With:** **Investigator to discuss with subject** IP administration **and adherence during the previous 7 days, as per Section 6.2.1.1.**	Editorial changes for clarity and addition of link for reference.
Section: 7.1 Schedule of Assessments, Table 2 footnote o	**Replace:** (eg, without chewing)	**With:** (**ie**, without chewing)	Editorial change

Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 7.2.1 Screening Enrollment, Paragraph 2		**Add:** Subjects currently hospitalized for HF are expected to be randomized before discharge. Local laboratory assessments **from the current hospitalization** can be used to support **the** subject's eligibility and randomization in order to provide flexibility for randomization before discharge. Central laboratory assessments for screening should be collected **after ICF signature** for those subjects. If the subject is discharged during screening period and randomized later, subject will be included in the recently and not currently hospitalized for HF randomization setting stratification. **The placebo run-in procedure assesses the subject's ability to swallow an open label placebo tablet successfully (ie, without chewing).**	To clarify language regarding laboratory assessments/randomization window, and to define the purpose of the placebo run-in.
Section: 7.2.1 Screening Enrollment, Paragraph 2 Bullet 6		**Delete:** • vital signs (~~sitting~~ blood pressure, heart rate)	Editorial change to make consistent with the rest of the protocol.
Section: 7.2.1 Screening Enrollment, Paragraph 2 Bullets 10, 11, and 12		**Add:** • **placebo run-in** • registration in IVRS/IWRS system • **ECG (for cardiac rhythm confirmation)**	Updated to add ECG at screening to align with updated Schedule of Assessments, and to include placebo run-in at screening.

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Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 7.2.4 Treatment, Paragraphs 1 and 2	**Replace:** Subjects in the recently and not currently hospitalized for HF setting who meet all eligibility criteria at the end of screening will be randomized and will return to the study site for day 1. Subjects in the currently hospitalized for HF setting who meet all eligibility criteria at the end of screening will be randomized with day 1 occurring during the ongoing. Subjects can only be randomized 1 time for this study.	**With:** Subjects in the recently and not currently hospitalized for HF setting who meet all eligibility criteria at the end of screening will return to the study site for **randomization and** day 1 **procedures**. Subjects in the currently hospitalized for HF setting who meet all eligibility criteria at the end of screening **should** be randomized **prior to discharge** with day 1 **procedures** occurring during **the hospitalization**. Subjects can only be randomized 1 time for this study.	Updated to add randomization for clarification.

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Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 7.2.6.7 Electrocardiogram, Paragraphs 1 and 2	**Replace:** Subject must be in a supine position in a rested and calm state for at last 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position as possible. Sites who have been provided with centralized ECG services equipment specifically for this study ECGs should be performed in a standardized method, ≥ 3 baseline ECGs collected ≥ 30 minutes apart, with each baseline ECG in triplicate run consecutively (ie, total ≥ 9 ECGs), and run consecutively, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.	**With:** Subject must be in a supine position in a rested and calm state for at last 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position as possible. **The ECG must be performed prior to blood draws or other invasive procedure. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals, and assessment of cardiac rhythm.** **ECGs must be conducted as follows:** **Screening ECG** • **1 local ECG (all sites)** **On study ECGs (day 1, week 48, every 48 weeks [Q48W])** • **Centralized ECG services: ECG in triplicate run consecutively** • **No centralized ECG services: 1 local ECG**	Updated to add guidance for screening ECGs and on study ECGs.

Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 7.2.6.8 Concomitant Therapy, Paragraph 2	**Replace:** The dosage of beta blockers, ACEi/ARB/ARNi, diuretics, and MRAs will be recorded. If a subject is not taking beta blockers, ACEi/ARB/ARNi, or MRA, investigators should record the reason why any of those agents are not prescribed.	**With:** The dosage of beta blockers, ACEi/ARB/ARNi, diuretics, and MRAs will be recorded. If a subject is not taking beta blockers, ACEi/ARB/ARNi, or MRA, **or taking doses below those recommended by local guidelines,** investigators should record the reason **in the eCRF**.	Clarification
Section: 8.1 Subject's Decision to Withdraw		**Add:** **For subjects who have withdrawn consent for further follow-up, investigators will review public records as permitted by applicable law to determine vital status of the subject at the end of the study or before.**	Clarification

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Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 9.1.1, Disease Related Events	**Replace:** Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. In this study, subjects will have HFrEF with an LVEF of ≤ 35%. It is expected that the study subjects will experience events related to chronic HFrEF. Examples of events related to HF include: • fluid overload signs and symptoms (eg, edema, pulmonary congestion, dyspnea, orthopnea, hepatic congestion) • renal function impairment (eg, cardiorenal syndrome, acute renal failure) • Such events do not meet the definition of an Adverse Event unless assessed to be more severe than expected for the subject's condition.	**With:** **Events that are not submitted for adjudication as potential endpoints, but that are** anticipated to occur in the study population due to the underlying disease**, may be reported at Disease Related Events**. In this study, subjects will have HFrEF with an LVEF of ≤ 35%. It is expected that the study subjects will experience events related to chronic HFrEF. Examples of events related to HF include: • fluid overload signs and symptoms (eg, edema, pulmonary congestion, dyspnea, orthopnea, hepatic congestion) **not requiring urgent, unscheduled clinic/office/ED visit, or hospital admission** • renal function impairment (eg, cardiorenal syndrome, acute renal failure) **not requiring urgent, unscheduled clinic/office/ED visit, or hospital admission**	Clarification on Disease Related Events definition.

Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 9.1.1, Disease Related Events (Continued)	Disease Related Events and/or Disease Related Outcomes that do not qualify as Serious Adverse Events: • An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a Disease Related Event. • Death due to the disease under study is to be recorded on the Event CRF. If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the IP/study treatment protocol required therapies and disease worsening, this must be reported as an Adverse Event or Serious Adverse Event.	If the **event** is **considered** worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the IP and disease worsening, **the event should not be considered a Disease Related Event and** must be reported as an Adverse Event or Serious Adverse Event. **If a Disease Related Event is considered serious, the event should be reported within 24 hours of the acknowledgement of the event.**	
Section: 9.2.1 Reporting Procedures for Disease Related Events		**Add:** Events assessed by the investigator to be related to the investigational medicinal product(s) 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.**	Clarification of serious adverse event reporting.

Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 9.2.2.3 Reporting a Safety Endpoint as a Study Endpoint	**Replace:** Safety events (eg, mortality and morbidity) that are efficacy endpoints (death and HF events) are reported on an Event CRF. Death and HF events will be recorded in the 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 will be collected. The Clinical Events Committee (CEC) will adjudicate all events of death, HF, myocardial infarction, hospitalization for unstable angina, coronary revascularization, and stroke events using prespecified criteria (Hicks et al. 2015). Investigators will be informed if a reported potential endpoint is negatively adjudicated (does not meet the definitions of an endpoint) and may be prompted for additional information for adverse event reporting. A negatively adjudicated safety endpoint will be reviewed by Amgen. Action taken could include no action, or reporting on the Event CRF as a disease-related event, adverse event, or serious adverse event.	**With:** **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.	Clarification that all serious adverse events should be reported to Amgen within 24 hours of acknowledgement.

Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 9.2.2.3 Reporting a Safety Endpoint as a Study Endpoint (Continued)	Death events that are associated with drug exposure or toxicity (eg, angioedema, blood dyscrasias, rhabdomyolysis, hepatic injury, anaphylaxis, and Stevens-Johnson Syndrome), and all major cardiac ischemic events (safety endpoints) must also be communicated to Amgen within 24 hours of knowledge of the event for adverse event evaluation		
Section: 10.1.3 Covariates and Subgroups, Paragraph 2, Bullet 12		**Add:** • presence of atrial fibrillation**/flutter at screening** (yes, no)	Updated this prespecified subgroup to clarify that atrial fibrillation should be present at screening, and that this can include atrial flutter.
Section: 10.1.3 Covariates and Subgroups, Paragraph 2, Bullet 14	**Replace:** • baseline NT-proBNP by randomization setting excluding atrial fibrillation/flutter subjects (≤ median and > median)	**With:** • baseline NT-proBNP by randomization setting excluding **subjects in** atrial fibrillation/flutter **at screening** (≤ median and > median)	Updated this prespecified subgroup to clarify that baseline NT-proBNP by randomization excludes subjects in atrial fibrillation/flutter at screening.
Section: Appendix D, Study Visit Column	**Replace:** Week 24	**With:** Week **12**	Assessments changed from week 24 to week 12.

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Amendment 2

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

Amgen Protocol Number (Omecamtiv Mecarbil [AMG 423]) 20110203

EudraCT number 2016-002299-28

NCT Number NCT02929329

Amendment Date: 13 November 2018

Rationale:

This protocol is being amended to:

- Align with the language in the informed consent form, which states omecamtiv mecarbil plasma concentrations will be measured using an investigational device
- Update language surrounding disease related events (DREs) to align with text in other sections of the protocol
- Remove self-evident corrections language as Amgen is retiring the use of self-evident corrections
- Make editorial, typographical, and formatting changes throughout the document

Description of Changes

Section: Global

Change: Updated version date from 07 September 2017 to **13 November 2018**.

Section: Global

Change: Made editorial (formatting, typographical, and grammatical) corrections throughout the protocol.

Section: Title Page

Add:

NCT Number NCT02929329

Section: Title Page

Add:

Date:	31 August 2016
Amendment 1 Date:	07 September 2017
Amendment 2 Date:	**13 November 2018**

Section: 7.2.6.10 Laboratory Assessments, Paragraph 2

Add:

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.

Section: 9.1.1 Disease Related Events

Replace:

Events that are not submitted for adjudication as potential endpoints, but that are anticipated to occur in the study population due to the underlying disease, may be reported at Disease Related Events. In this study, subjects will have HFrEF with an LVEF of ≤ 35%. It is expected that the study subjects will experience events related to chronic HFrEF. Examples of events related to HF include:

- fluid overload signs and symptoms (eg, edema, pulmonary congestion, dyspnea, orthopnea, hepatic congestion) not requiring urgent, unscheduled clinic/office/ED visit, or hospital admission
- renal function impairment (eg, cardiorenal syndrome, acute renal failure) not requiring urgent, unscheduled clinic/office/ED visit, or hospital admission

If the event is considered worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the IP and disease worsening, the event should not be considered a Disease Related Event and must be reported as an Adverse Event or Serious Adverse Event.

If a Disease Related Event is considered serious, the event should be reported within 24 hours of the acknowledgement of the event.

With:

Events that are not submitted for adjudication as potential endpoints, but that are anticipated to occur in the study population due to the underlying disease, may be reported a**s** Disease Related Events. In this study, subjects will have HFrEF with an LVEF of ≤ 35%. It is expected that the study subjects will experience events related to chronic HFrEF. Examples of events related to HF include:

- fluid overload signs and symptoms (eg, edema, pulmonary congestion, dyspnea, orthopnea, hepatic congestion) not requiring urgent, unscheduled clinic/office/ED visit, or hospital admission
- renal function impairment (eg, cardiorenal syndrome, acute renal failure) not requiring urgent, unscheduled clinic/office/ED visit, or hospital admission

If the event is considered worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the IP and disease worsening, the event should not be considered a Disease Related Event and must be reported as an Adverse Event or Serious Adverse Event.

If a Disease Related Event is considered **as an adverse event and is** serious, the event should be reported within 24 hours of the acknowledgement of the event.

Section: 9.2.1 Reporting Procedures for Disease Related Events, Paragrah 2

Add:

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.

Section: 12.3 Study Monitoring and Data Collection, Paragrah 6

Delete:

~~Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit Week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.~~