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

AMG 423 (Omecamtiv Mecarbil)

Amgen Protocol Number (AMG 423) 20120227

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Investigator's Agreement

I have read the attached protocol entitled A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of Omecamtiv Mecarbil in Japanese Subjects With Heart Failure With Reduced Ejection Fraction, dated 23 October 2015, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines. The study will be conducted in compliance with the Ministerial Ordinance on Good Clinical Practice for Drugs (Ministry of Health and Welfare Ordinance No. 28, 27 March 1997).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature	
Name of Investigator	Date (DD Month YYYY)

Protocol Synopsis

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

Study Phase: 2

Indication: Heart Failure

Primary Objectives:

- To evaluate pharmacokinetics (PK) of omecamtiv mecarbil in Japanese subjects with heart failure (HF) with reduced ejection fraction
- To evaluate the safety and tolerability of oral omecamtiv mecarbil

Secondary Objectives:

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

Hypotheses: No formal hypothesis testing will be performed. PK parameters following chronic (twice daily [BID] for 16 weeks) dosing will be estimated.

Primary Endpoints:

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

Secondary Endpoint:

- Changes from baseline in SET by echocardiography at week 16

Safety Endpoints:

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

Study Design: This is a double-blind, randomized, placebo-controlled, multicenter, phase 2 study in Japanese HF subjects to evaluate 16 weeks of administration of oral modified- release (MR) omecamtiv mecarbil formulation at 3 dose levels (25 mg BID, 37.5 mg BID, and 50 mg BID), compared with placebo.

Approximately 80 Japanese subjects with chronic stable HF with reduced ejection fraction will be randomized in a 1:1:1:1 manner to receive either placebo (n=20) or omecamtiv mecarbil at a target dose of either 25 mg BID (n=20), 37.5 mg BID (n=20), or 50 mg BID (n=20) on an outpatient basis. Subjects randomized to the 37.5 mg BID and 50 mg BID treatment arms will initiate administration at 25 mg BID and will be up-titrated to 37.5 mg BID or 50 mg BID target dose at the week 4 visit based on steady state $C_{predose}$ result from week 2. Subjects who do not have a week 2 PK value in time for dose adjustment at the week 4 visit will be up-titrated at week 8 based on the steady state $C_{predose}$ result from week 2, if available. Up-titration at week 4 or week 8 visits will occur only if the week 2 $C_{predose}$ is < 200 ng/mL. Subjects with a week 2 $C_{predose}$ ≥ 200 ng/mL (or not available at week 8) will continue at 25 mg BID for the remainder of the study. Subjects randomized to placebo or to 25 mg BID will receive the assigned investigational product (IP) (omecamtiv mecarbil or placebo) throughout the study. PK analysis and dose assignment will be blinded to the study team. To maintain blinding, all subjects will receive new IP supply at week 4 and week 8 visits. An independent Data Monitoring Committee (DMC) will perform a regular formal unblinded review of the accumulating study data. An independent Clinical Events Classification (CEC) Committee will adjudicate deaths, all

hospitalizations, and selected nonfatal cardiovascular (CV) events (including possible myocardial infarction or ischemia).

Sample Size: Approximately 80 Japanese subjects with chronic stable HF

Summary of Subject Eligibility Criteria:

Japanese male and female subjects ≥ 20 and ≤ 85 years of age with chronic stable HF with reduced ejection fraction; treated with optimal pharmacological therapy, including a beta blocker and either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) that is expected to remain stable over the period of participation in the study, unless not tolerated; and left ventricular ejection fraction (LVEF) must be ≤ 40% as determined by central reading of the screening echocardiogram. Enrollment of subjects with atrial fibrillation/flutter is limited to up to approximately 20% of planned enrollment in the study. Randomization will be stratified by presence or absence of atrial fibrillation/flutter at the time of screening via interactive voice response system/interactive Web response system (IVRS/IWRS).

The following are the major exclusion criteria: New York Heart Association (NYHA) class IV; implantation of cardiac resynchronization therapy (CRT) or implantable cardioverter defibrillator (ICD) within 30 days prior to randomization; likely to receive the following within 3 months after randomization, in the investigator's opinion: revascularization, implantation of ICD or CRT, ventricular assist device, continuous or intermittent inotropic therapy, hospice care, or cardiac transplant; severe uncorrected valvular heart disease; hypertrophic obstructive cardiomyopathy, active myocarditis, or constrictive pericarditis, or clinically significant congenital heart disease; major arrhythmia per investigator's judgment; acute myocardial infarction, unstable angina, or persistent angina at rest within 30 days prior to randomization; chronic antiarrhythmic therapy (except amiodarone, digoxin, and beta-blocker therapy), or routinely scheduled outpatient intravenous infusions for HF (eg, inotropes, vasodilators [eg, carperitide], diuretics) or routinely scheduled ultrafiltration; systolic blood pressure (BP) > 160 mm Hg or < 90 mm Hg or diastolic BP > 90 mm Hg, or heart rate (HR) > 110 beats per minute (bpm) or HR < 50 bpm at screening; estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 at screening; past recipient of any major organ transplant or receiving renal replacement therapy by dialysis; total bilirubin (TBL) ≥ 2 times the upper limit of normal (ULN), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 times ULN at screening. Female subjects of childbearing potential cannot be pregnant or planning to become pregnant, or breastfeeding, and must be willing to practice sexual abstinence, or surgical contraceptive methods or use 2 acceptable method(s) of effective birth control during treatment with IP and for an additional 5 days after the end of treatment with IP.

For a full list of eligibility criteria, please refer to Section 4.

Amgen Investigational Product Dosage and Administration: Omecamtiv mecarbil Matrix F1 tablets will be dosed orally at 25 mg BID, 37.5 mg BID, and 50 mg BID.

Procedures:

Subjects are eligible for screening if they have chronic stable HF and reduced ejection fraction. Subjects may also be screened in the hospital setting once they have recovered and are considered clinically stable by the investigator. Subjects must be outpatients at the time of randomization. At the week 4 visit (or at week 8 visit if the week 2 $C_{predose}$ result is not available), subjects randomized to omecamtiv mecarbil 37.5 mg BID or 50 mg BID will be up-titrated if the week 2 $C_{predose}$ is < 200 ng/mL. Subjects will be contacted on day 7 and 6 days after the week 4 and week 8 visits to ensure IP compliance and for safety observation, and will be seen at the study site at weeks 2, 4, 8, 12, and 16, and for the end of study (EOS) visit at week 20.
All visits after Day 1 include a visit window of ± 3 days with the exception of week 2 (-3 days), week 4 (+3 days) and the EOS visit at week 20 (+3 days).

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:

All non-PK endpoints analyses will be performed on the full analysis set (FAS) which includes all randomized subjects who have received at least 1 dose of IP (omecamtiv mecarbil or placebo). PK endpoints analyses will be performed in the subset of FAS where subjects have at least one evaluable omecamtiv mecarbil PK parameter (C_{max}, $C_{predose}$). Generally, subjects will be grouped according to their randomized target dose treatment group assignment. Safety endpoints will be analyzed in the subjects that received at least 1 dose of IP. The safety endpoint of subject incidence of any treatment-emergent adverse event will be summarized descriptively by randomized treatment group. No formal statistical hypothesis will be tested.

In the analyses of primary endpoints, PK parameters will be calculated using non-compartmental methods. Individual PK parameters of omecamtiv mecarbil collected in the omecamtiv mecarbil arm will be summarized with descriptive statistics.

The echocardiographic secondary endpoint will be summarized and analyzed by the stratification factor of presence or absence of atrial fibrillation/flutter at randomization.

Secondary, safety, and exploratory endpoints will be summarized descriptively by randomized treatment group and the titration status. The treatment effect on change from baseline in SET will be summarized descriptively by randomized treatment group and the difference between each omecamtiv mecarbil dose level and placebo will be estimated. The relationship of treatment effect in the SET and its relationship to omecamtiv mecarbil plasma concentrations will be evaluated.

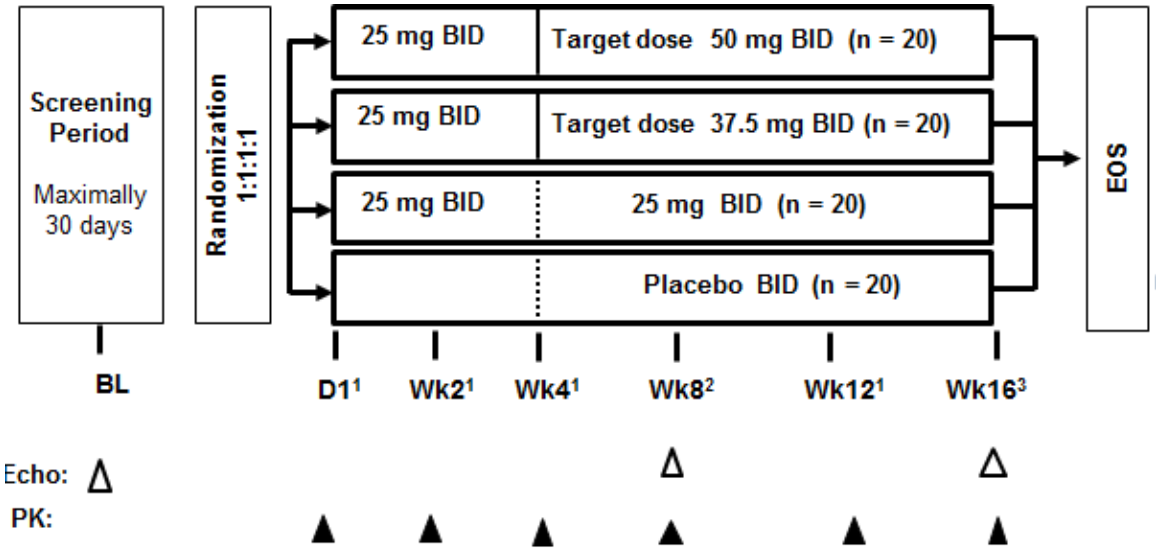
This study will adjudicate deaths, all hospitalizations, and selected nonfatal cardiovascular events by an independent Clinical Events Classification (CEC) Committee. All events occurring after subject randomization until completion of the study at week 20 will be adjudicated.

For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: Amgen, Inc. and Amgen Astellas BioPharma K.K. (AABP)

Data Element Standards Version(s)/Date(s):	5: 20 March 2015

Study Design and Treatment Schema



BL= baseline; PK=pharmacokinetic;BID=twice daily;EOS=end of study;Wk=week

[1]$C_{predose}$ in the morning, at study site

[2]PK samples at predose, at 2 hours ± 30 minutes; 4 hours ± 30 minutes; 6 hours ± 30 minutes; 8 hours ± 30 minutes after IP administration in the morning (0 hours = start of IP). Echocardiogram at week 8 should be performed as close as possible after the collection of PK sample at 2 hours ± 30 minutes following IP administration.

[3]PK samples at predose and at 2 hours ± 30 mins following IP administration. Echocardiogram at week 16 should be performed as close as possible after the collection of PK sample at 2 hours ± 30 minutes following IP administration.

Randomization will be stratified by presence or absence of atrial fibrillation/flutter via IVRS/IWRS.

Blinded titration step at week 4 visit in all arms. Subjects randomized to 37.5 mg BID or 50 mg BID target dose will be up-titrated based on steady state $C_{predose}$ result from week 2. Subjects randomized to 25 mg BID or placebo will receive the assigned IP throughout the study. Up-titration at week 4 or week 8 visits will occur in subjects only if the week 2 $C_{predose}$ is < 200 ng/mL.

Study Glossary

Abbreviation or Term	Definition/Explanation
AABP	Amgen Astellas BioPharma K.K.
ACE	angiotensin-converting enzyme
AE	adverse event
AHF	acute heart failure
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BP	blood pressure
Bpm	beats per minute
BMI	body mass index
BNP	B-type natriuretic peptide
CEC	Clinical Events Classification
Childbearing potential	a female is considered of childbearing potential unless permanently sterilized (she has had a hysterectomy, bilateral oophorectomy, or bilateral salpingectomy or she is postmenopausal). Menopause is defined as: age ≥ 55 years with cessation of menses for 12 or more months; age < 55 years but no spontaneous menses for at least 2 years; age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (spontaneous), AND with postmenopausal gonadotropin levels (luteinizing hormone (LH) and follicle-stimulating hormone levels (FSH) > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved
CI	confidence interval
CK-MB	creatine kinase MB fraction
C_{max}	maximum observed concentration
$C_{predose}$	concentration prior to the investigational product administration
CRT	cardiac resynchronization therapy
CTCAE	Common Terminology Criteria for Adverse Events
Day 1	day investigational product is first administered
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate; eGFR will be calculated by the central laboratory and provided to the investigator.

Abbreviation or Term	Definition/Explanation
EM	extensive metabolizers
End of study	the end of the study is defined as the last day on which the last randomized subject in this study completes the assessments for end-of-study visit (week 20) or terminates the study early
Enrollment	a study subject is given a randomization number
EOS	end of study
eSAE Contingency Report Form	electronic serious adverse event contingency report form (paper-based form)
FSH	follicle-stimulating hormone
HF	heart failure
HR	heart rate; number of cardiac cycles per unit of time
ICD	implantable cardioverter defibrillator
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IP	investigational product (omecamtiv mecarbil or placebo)
IPIM	Investigational Product Instruction Manual
IR	immediate release
IV	Intravenous
IVRS/IWRS	interactive voice response system/interactive Web response system; telecommunication technology that is linked to a central computer in real time as an interface to collect and process information
LH	luteinizing hormone
LVEDD	left ventricular end-diastolic diameter
LVEF	left ventricular ejection fraction
LVESD	left ventricular end-systolic diameter
MR	modified-release
NT-proBNP	n-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
PEP	potential endpoint
PK	pharmacokinetic(s)
PKAS	pharmacokinetic analysis set
PK/PD	pharmacokinetic/pharmacodynamic
PM	poor metabolizers
PR interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG
PT	prothrombin time

Abbreviation or Term	Definition/Explanation
QRS complex	interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT interval	measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG
QTc interval	QT interval corrected for heart rate using accepted methodology
SAE	serious adverse event
SD	standard deviation
SET	systolic ejection time
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (International Conference on Harmonisation Guideline [E6]). Examples of source data include subject identification number, randomization number, and stratification value.
TBL	total bilirubin
ULN	upper limit of normal
URL	upper reference limit

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1. OBJECTIVES

1.1 Primary

The primary objectives of this study are to:

- To evaluate the pharmacokinetics (PK) of omecamtiv mecarbil in Japanese subjects with heart failure (HF) with reduced ejection fraction
- To evaluate the safety and tolerability of oral omecamtiv mecarbil

1.2 Secondary

The secondary objectives of the study are:

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

2. BACKGROUND AND RATIONALE

2.1 Disease

Heart failure is a clinical syndrome marked by impaired cardiac contractility and is the final pathway for a diversity of diseases that afflict the heart (Hilfiker-Kleiner et al, 2006). The rate of cardiovascular mortality or HF hospitalization approaches 25% to 30% at 6 months in patients hospitalized for HF (Konstam et al, 2007; Gheorghiade et al, 2013). In Japan, approximately 1 million people are believed to have HF (Okamoto and Kitabatake, 2003, Okura et al, 2008). Although the prevalence of HF (< 1%) is lower than that in Western industrialized countries, it is expected to rise substantially in the coming decades, mainly due to Japan's rapidly aging population (Japanese Statistics Bureau, 2005; Okura et al, 2008). One-year mortality due to HF is from 4.3% to 9% and 1-year readmissions range from 7.6% to 17.8% (Shiba et al, 2004; Tsutsui et al, 2007; Hamaguchi et al, 2009). While several pharmacological and non-pharmacological interventions have been shown to reduce the rate of HF hospitalizations and improve mortality, including angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, aldosterone antagonists, coronary revascularization, and biventricular pacing (Krum and Teerlink, 2011), mortality and morbidity still remain high as noted above. In addition, these available treatments that are aimed at diverse targets including sodium retention, arterial and venous constriction, neuroendocrine activation, increased heart rate (HR), cardiac dyssynchrony, and arrhythmias often fail to control symptoms or restore quality of life. Another target for treatment of HF is to improve myocardial contractility. HF is a condition most commonly marked by cardiac systolic dysfunction. Over time, in an attempt to preserve cardiac output, a series of compensatory changes can occur characterized by increased sympathetic tone and peripheral vasoconstriction,

as well as the activation of various neurohormonal pathways. Attempts to improve cardiac contractility using adrenergic receptor agonists (ie, dobutamine) or phosphodiesterase inhibitors (ie, milrinone) have met with little success. However, these mechanisms have significant safety liabilities attributable to increased oxygen consumption, intracellular calcium, and arrhythmias (Cuffe et al, 2002; Felker et al, 2003). Cardiac myosin activators like omecamtiv mecarbil are a new mechanistic class designed specifically to increase myocardial contractility without these liabilities.

2.2 Omecamtiv Mecarbil Background

Omecamtiv mecarbil (AMG 423, CK-1827452) is a novel small molecule that increases cardiac contractility by selectively and directly activating the enzymatic domain of cardiac myosin heavy chain, the force-generating motor protein of the cardiac sarcomere, without increasing cardiac myocyte intracellular calcium (Teerlink, 2009; Malik et al, 2011).

2.2.1 Preclinical Information

In vitro experiments demonstrated that omecamtiv mecarbil augments contractility without changing the intracellular calcium transient in isolated cardiac myocytes. It does not inhibit phosphodiesterase type 3. In dog models of systolic HF, infusion of omecamtiv mecarbil significantly augmented left ventricular systolic function and cardiac output by increasing the left ventricular SET without increasing the rate of pressure development (dP/dt) or HR. Additionally, left ventricular filling pressure, left atrial pressure, 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 omecamtiv mecarbil were achieved without noticeable effect upon myocardial oxygen uptake, blood pressure (BP), or coronary blood flow (Shen et al, 2010; Malik et al, 2011).

2.2.2 Clinical Experience

The safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) of oral and intravenous (IV) formulations of omecamtiv mecarbil have been evaluated in 9 completed phase 1 clinical studies in healthy volunteers/end-stage renal disease (ESRD) subjects (Studies CY 1111, CY 1011, CY 1013, CY 1015, CY 1016, CY 1211 [20120255], 20080676, 20090229, and 20090727); and in 4 completed phase 2a studies in chronic HF subjects (Studies CY 1021, CY 1121, CY 1124, and CY 1221); and 1 completed phase 2b study in acute heart failure (AHF) subjects (Study 20100754).

Efficacy was also evaluated in completed Study 20100754. The studies pertinent to this study are summarized below. Refer to the Investigator's Brochure for omecamtiv mecarbil for additional information.

2.2.2.1 Studies in Healthy Volunteers

CY 1111, a first-in-human clinical study with omecamtiv mecarbil, was a randomized, double-blind, placebo-controlled, 4-period crossover, dose escalation study designed to evaluate the safety, tolerability, and PK/PD profile of omecamtiv mecarbil administered IV to healthy male volunteers (Teerlink et al, 2011). This study included a total of 33 subjects who received infusions of omecamtiv mecarbil at doses ranging from 0.005 mg/kg/hr to 1.0 mg/kg/hr for up to 6 hours. The exposures of omecamtiv mecarbil, as measured by area under the curve (AUC) and maximum observed concentration (C_{max}), were approximately dose proportional, with an AUC of 159 (57 standard deviation) ng•hr/mL for treatment administered at an infusion rate of 0.005 mg/hr/kg and 30400 ng•hr/mL when administered at a rate of 1 mg/hr/kg; corresponding C_{max} values for those administration rates were 8.70 (2.20) ng/mL and 1340 ng/mL. The mean clearance ranged from 125 to 207 mL/hr/kg and the mean half life ranged from 17.1 to 23.2 hours and increased slightly with increasing doses. The mean steady state distribution volume was dose independent and ranged from 3.6 to 5.2 L/kg. At the dose of 0.5 mg/kg/hr over 6 hours, the mean (standard deviation [SD]) C_{max} was 905 (183) ng/mL. Across the dosing levels evaluated in CY 1111, omecamtiv mecarbil infusions demonstrated generally linear PK with dose-proportional increases in C_{max}. Concentration-dependent PD effects on cardiac function as measured by echocardiography were observed. These PD effects included statistically significant placebo corrected increases from baseline in SET, Doppler-derived stroke volume, left ventricular ejection fraction (LVEF), and fractional shortening.

CY 1013 was an open-label, parallel group study in healthy male volunteers designed to evaluate the contribution of cytochrome P450 enzymes CYP3A4 and CYP2D6 to the elimination of omecamtiv mecarbil. Healthy volunteer subjects who were either extensive metabolizers (EMs) or poor metabolizers (PMs) with respect to their defined CYP2D6 genotype received oral omecamtiv mecarbil alone and in combination with ketoconazole or diltiazem. Ketoconazole (a potent inhibitor of CYP3A4) caused approximately 51% and 31% increases in the mean AUC of omecamtiv mecarbil in EM and PM subjects, respectively; 1 PM subject had a decrease in omecamtiv mecarbil AUC when given in combination with ketoconazole which contributed to the observed

differences between these 2 groups. In the presence and absence of diltiazem (a moderate inhibitor of CYP3A4), the AUC of omecamtiv mecarbil was similar. CYP3A4 inhibition had little impact on C_{max} and time to C_{max}. When omecamtiv mecarbil was administered alone, the mean AUC was approximately 37% higher in PM subjects (990 ng•hr/mL, n = 8) than in EM subjects (720 ng•hr/mL, n = 8). These results indicate minor involvement of CYP3A4 and CYP2D6 in the metabolism of omecamtiv mecarbil.

Studies CY 1011, CY 1015, and CY 1016 were designed to evaluate the PK parameters of oral preparations of omecamtiv mecarbil. 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 omecamtiv mecarbil approaching 100% under all conditions studied; food appeared to reduce the rate but not the extent of absorption. Omecamtiv mecarbil was well tolerated with no treatment-related serious adverse events in these trials.

In Study 20090727, which compared five modified-release (MR) formulations to the IR formulation, the mean bioavailability of the MR formulations was ~80% with MR-F1, MR-F2 and SCT-F2 and C_{max} was reduced by ~70%. Food had a minimal effect on the PK of the oral MR and immediate release (IR) formulations but reduced inter-subject variability.

Study 20090229 was an open-label, single dose study that evaluated the absorption, metabolism, and excretion of orally- and IV-administered [^{14}C]-omecamtiv mecarbil in 14 healthy volunteers. Approximately 85% of the IV and oral doses of [^{14}C]-omecamtiv mecarbil were recovered in urine and feces. Less than 10% of omecamtiv mecarbil appeared in urine. The major clearance pathway (primarily metabolism) was decarbamylation of omecamtiv mecarbil to M3 followed by further biotransformation. In plasma, omecamtiv mecarbil was the most abundant component, with M3 and M4 (a lactam of M3) the most abundant metabolites at 6.0% and 3.3% of total drug-related AUC, respectively. M3 and M4 were also the major metabolites in urine and feces. Of note, the biological activity of M3 and M4 when assayed against the cardiac sarcomere in vitro was > 10-fold less potent than the parent drug.

2.2.2.2 Studies in Subjects With Heart Failure

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

Three subjects 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. Omecamtiv mecarbil produced increases in echocardiographic indices of cardiac systolic function.

Study CY 1221 was a randomized, double-blind, placebo-controlled study that enrolled HF subjects with ischemic cardiomyopathy and angina with LVEF ≤ 35%. A total of 94 subjects were enrolled and treated with 20 hour infusions of study drug followed by 7 days of oral dosing; 29 subjects received placebo, 31 received omecamtiv mecarbil 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 omecamtiv mecarbil at either dose regimen. In addition, no consistent differences were observed between placebo and lower or higher dosing regimens of omecamtiv mecarbil with respect to any of the secondary safety endpoints, vital signs, electrocardiograms (ECG) or cardiac enzymes.

CY 1021 was an open-label study with the objective to evaluate the PK and tolerability of a MR and an IR oral formulation of omecamtiv mecarbil in subjects with stable HF. A total of 35 subjects were enrolled and treated with a dose of 50 mg MR twice daily (BID), 37.5 mg IR 3 times a day, or 100 mg MR BID under fed conditions. A [redacted]-year-old male subject experienced sudden death in this study after 6 days of dosing with the IR formulation. The subject's history was [redacted] At the time of enrollment into the study, the subject was New York Heart Association (NYHA) Class III and Canadian Cardiovascular Society Angina Class III. Study site personnel last spoke to the subject on Day 6 just prior to the last administered dose. He had no complaints and reported that he was taking the study medication as prescribed. Shortly after the last dose on Day 6, the subject 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 250 healthy volunteers (including 13 ESRD subjects) and the 147 HF subjects in phase 2a studies who received at least 1 dose of omecamtiv mecarbil, 6 healthy volunteers and 8 HF subjects had troponin I above the upper reference limit (URL). There were no subjects with troponin T > URL in the absence of troponin I > URL post baseline. These 14 subjects are included in the Investigator Brochure (Table 6-22 and Appendix B). In 3 of the 14 subjects with troponin I > URL, the troponin I > URL occurred at omecamtiv mecarbil C_{max} plasma concentrations of 1333 ng/mL, 1456 ng/mL, and 1345 ng/mL in healthy volunteer Subject [redacted] (Study CY 1111), HF Subject [redacted] (Study CY 1121), and HF Subject [redacted] (Study CY 1121), respectively. These 3 subjects had similar clinical presentation in terms of their symptoms/signs (tachycardia, chest discomfort, and dizziness), ECG changes, and rise and fall of troponin I, consistent with myocardial infarction. Their symptoms resolved with the discontinuation of omecamtiv mecarbil. In at least 6 of the other 11 subjects with troponin I > URL, a causal relationship with omecamtiv mecarbil could not be excluded.

Study 20100754, (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure, ATOMIC-AHF) was a phase 2b multicenter, randomized, double-blind, placebo-controlled study to evaluate the effect of 48 hours of IV omecamtiv mecarbil compared with placebo on dyspnea in subjects with left ventricular systolic dysfunction hospitalized for acute HF. The study enrolled 613 subjects into 3 dose escalation cohorts with review of data by an independent external Data Monitoring Committee (DMC) before proceeding to the next cohort.

A total of 303 AHF subjects received at least 1 dose of omecamtiv mecarbil and an equal number received placebo. No statistically significant difference was observed in dyspnea symptom response (primary efficacy endpoint) between omecamtiv mecarbil treatment groups and the pooled placebo group.

Major cardiovascular events were adjudicated by an independent, academic committee in ATOMIC-AHF (Duke Clinical Research Institute Clinical Events Classification (CEC) Committee. Adverse events (58% vs. 63%), serious adverse events (21.8% vs. 23.1%), deaths (2.6% vs. 3.3%), and rehospitalization within 30 days (9.6% vs. 12.2%) were similar between the pooled omecamtiv mecarbil group and the pooled placebo group, respectively. At the 6 month vital status assessment, 38 (12.5%) subjects in the omecamtiv mecarbil groups died compared with 39 (12.9%) subjects in the placebo groups. There were a limited number (10) of positively adjudicated post-randomization myocardial infarctions and a small numeric imbalance was noted in the omecamtiv

mecarbil treated groups (total of 7) compared with 3 in placebo groups (2.3% vs. 1%, respectively). Five of the adjudicated myocardial infarctions in omecamtiv mecarbil-treated subjects occurred in cohort 3, however, 2 occurred more than 7 days after completion of drug infusion and 1 occurred subsequent to a percutaneous coronary intervention. The overall incidence of reported supraventricular tachyarrhythmias (standard MedDRA query [SMQ]) was less (3.6% vs. 6.6%) on omecamtiv mecarbil than on placebo and, within each cohort, rates were lower in the omecamtiv mecarbil group than the placebo group. The overall incidence of ventricular tachyarrhythmias (SMQ) was similar (5.3% omecamtiv mecarbil, 5.9%, placebo). For further details on the clinical experience with omecamtiv mecarbil please consult the Investigator's Brochure.

2.2.2.3 Study in Japanese Subjects

Study 20120255 (CY 1211) was a phase I single center, placebo-controlled, double-blind study comparing the PK of omecamtiv mecarbil between healthy Japanese and Caucasian volunteers. In a 3-period crossover design, 36 subjects (18 Japanese and 18 Caucasians) received 3 separate treatments with at least a 7-day washout between each dosing period. Volunteers received in succession an IV infusion (4 hour) of omecamtiv mecarbil or placebo, multiple 25 mg doses of a MR oral formulation of omecamtiv mecarbil or placebo over 7 days, and a single 50 mg dose of a MR oral formulation of omecamtiv mecarbil or placebo. There were no clinically meaningful differences observed in the PK of omecamtiv mecarbil between Japanese and Caucasian healthy volunteers and all doses of omecamtiv mecarbil in CY 1211 were well tolerated.

2.3 Rationale

Omecamtiv mecarbil is being developed as an adjunctive therapy for subjects with HF with reduced ejection fraction (≤40%) who are already taking a beta-blocker and an ACE inhibitor and/or angiotensin receptor blocker (ARB), unless not tolerated. Targeting myocardial contractility in subjects with systolic dysfunction would appear to be a rational therapeutic approach to preserve cardiac output, to attenuate the compensatory mechanisms including neurohormonal activation, and to prevent or even reverse ventricular remodeling, which ultimately could translate into clinical benefits for HF patients (Hasenfuss and Teerlink, 2011).

Historically, development of heart failure drugs has required careful assessment of the balance of benefit:risk in large phase 3 clinical outcomes studies because there is no well-established validated surrogate endpoint in HF for clinical outcomes. Direct

increase of cardiac function can positively impact clinical outcomes in patients with left ventricular systolic dysfunction as evidenced by the efficacy of cardiac resynchronization therapy (CRT) in HF patients with systolic dysfunction (Moss et al, 2009). Omecamtiv mecarbil is a cardiac myosin activator that has dose-dependent and concentration-dependent effects on cardiac function at plasma concentrations that appear generally well tolerated by subjects with stable chronic systolic HF (Cleland et al, 2011).

The ongoing Study 20110151 (COSMIC-HF) is a global phase 2, randomized, double-blind, placebo-controlled study in subjects with chronic stable HF and systolic dysfunction. This study was designed to compare 3 oral MR formulations in 2 cohorts (escalation phase) of 25 mg BID and 50 mg BID for 7 days to select the most suitable formulation for further study in the dose ranging expansion phase (25 mg BID and 50 mg BID of a single oral MR formulation compared with placebo over 20 weeks of treatment with echocardiographic evaluations). The escalation phase of the study has completed. Following review of PK and safety data from a total of 96 subjects, a single oral MR formulation, MR-F1, was selected for use in the COSMIC-HF expansion phase. Enrollment is complete and the MR-F1 formulation is currently being evaluated at 2 dose levels (25 mg and 50 mg BID) in approximately 450 subjects.

Prior to initiation of subject enrollment into this study (Study 20120227) results from the planned Japanese phase 1 study 20150134, which include PK and safety assessments of repeated 25 mg BID, 37.5 mg BID, and 50 mg BID oral dosing, will be reviewed. It is expected that Study 20150134 will confirm the doses selected are appropriate to be studied in this phase 2 study (Study 20120227).

Study 20120227 will enroll approximately 80 subjects and randomize them to doses of omecamtiv mecarbil (25 mg, 37.5 mg, or 50 mg BID), or placebo. Simulated omecamtiv mecarbil exposures in subjects with low body weight, defined as less than 58 kg based on the median body weight distribution of Japanese subjects with HF, were approximately 25% to 35% higher compared with exposures in non-Japanese HF subjects with a higher body weight, defined as greater than 82 kg based the median body weight of subjects with HF in the ATOMIC-AHF and COSMIC-HF studies (Table 1).

Table 1. Comparison of Omecamtiv Mecarbil Steady State C_{max} and AUC Following BID Dosing of MR-F1 Tablets in Healthy Japanese Subjects

BID Dose (mg)	Simulated Japanese		Simulated Non-Japanese	
	$C_{max,ss}$ (ng/mL)	AUC_{ss} (ng*hr/mL)	$C_{max,ss}$ (ng/mL)	AUC_{ss} (ng*hr/mL)
25	277 [252] (129)	2759 [2501] (1305)	211 [193] (94)	2115 [1918] (962)
37.5	461 [418] (214)	4613 [4171] (2185)	351 [319] (155)	3521 [3201] (1585)
50	614 [557] (286)	6143 [5539] (2929)	469 [427] (209)	4707 [4265] (2130)

Data presented as mean [median] (standard deviation); AUC_{ss}= area under the curve, steady state; C_{max} =maximum plasma concentration; HF=heart failure; BID =twice daily

Though the results of the completed phase 1 Study 20120255 showed that systemic clearance in Japanese and Caucasian subjects was not statistically significantly different, and that the body weight adjusted clearance was essentially identical, this study will include an additional tablet strength of 37.5 mg BID to further explore PK and PD parameters with chronic repeated oral dosing.

2.4 Clinical Hypotheses

No formal hypothesis testing will be performed. PK parameters following chronic dosing (BID for 16 weeks) will be estimated.

3. EXPERIMENTAL PLAN

3.1 Study Design

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

Approximately 80 Japanese subjects with chronic stable HF with reduced ejection fraction will be randomized 1:1:1:1 to receive omecamtiv mecarbil either 25 mg BID dose (n=20), 37.5 mg BID dose (n=20), 50 mg BID dose (n=20) or placebo (n=20) on an outpatient basis. Subjects randomized to 37.5 mg BID target dose and 50 mg BID target dose will initiate administration at 25 mg BID and will be up-titrated to 37.5 mg BID or

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

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

Vital signs, physical examinations, ECGs, Adverse Event/Serious Adverse Event assessments, clinical laboratory evaluations (see Table 3), and collection of concomitant medications will be performed at screening and at specified times per the Schedule of Assessments (Table 2). The overall study design is described in 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 50 centers in Japan will participate in the 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 80 Japanese subjects with chronic stable HF with reduced ejection fraction will be enrolled.

Rationale for the sample size can be found in Section 10.2.

3.4 Replacement of Subjects

Subjects who are withdrawn, removed from treatment or the study, or who voluntarily withdraw prematurely from the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

After signing the informed consent, all eligible subjects should be randomized within 30 days. Treatment duration will be for 16 weeks with the EOS visit at week 20 for a maximal duration of study participation of approximately 24 weeks or 6 months (includes screening, treatment period, and EOS visit).

3.5.2 End of Study

The end of the study is defined as the last day on which the last randomized subject in this study completes the assessments for end-of-study visit (week 20) or terminates the study early.

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).

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 or their legally authorized representative has provided written informed consent prior to initiation of any study-specific activities/procedures

102 Japanese male or female ≥ 20 years and ≤ 85 years of age at the time of written informed consent

103 History of chronic stable HF with reduced ejection fraction, defined as requiring treatment for HF for a minimum of 4 weeks prior to screening

104 Treated for HF with optimal pharmacological therapy. In general, optimal treatment will include a beta-blocker and either an ACE inhibitor or an ARB that is expected to remain stable over the period of participation in the study, unless not tolerated

105 LVEF ≤ 40% by centrally read screening echocardiogram

4.1.2 Exclusion Criteria

201 Implantation of CRT or ICD implantation within 30 days prior to randomization

202 NYHA class IV

203 Likely to receive within 3 months after randomization, in the opinion of the investigator, revascularization, implantation of ICD or CRT, ventricular assist device, continuous or intermittent inotropic therapy, hospice care, or cardiac transplant

204 Severe uncorrected valvular heart disease

205 Hypertrophic obstructive cardiomyopathy, active myocarditis, or constrictive pericarditis, or clinically significant congenital heart disease

206 Acute myocardial infarction, unstable angina, or persistent angina at rest within 30 days prior to randomization

207 Chronic antiarrhythmic therapy, with the exception of amiodarone, digoxin and beta-blocker therapy

208 Routinely scheduled outpatient IV infusions for HF (eg, inotropes, vasodilators [eg, carperitide], diuretics) or routinely scheduled ultrafiltration

209 Systolic BP > 160 mm Hg or < 90 mm Hg, or diastolic BP > 90 mm Hg, or HR > 110 beats per minute (bpm) or HR < 50 bpm at screening

210 Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 by central laboratory during screening

211 Currently taking, or has taken within 14 days prior to randomization, a potent CYP3A4 inhibitor (amprenavir, cobicistat, cyclosporine, clarithromycin, delaviridine, erythromycin, indinavir, itraconazole, nelfinavir, ritonavir, saquinivir, telaprevir, verapamil, voriconazole, grapefruit juice)

212 Currently taking, or has taken within 28 days prior to randomization, a potent CYP3A4 inducer (eg, carbamazepine, dexamethasone, efavirenz, etravirine, nevirapine, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort)

213 Severe, concomitant noncardiovascular disease that is expected to reduce life expectancy to less than 1 year

214 Past recipient of any major organ transplant (eg, lung, liver, heart, bone marrow, renal) or receiving renal replacement therapy by dialysis

215 Malignancy within 1 year prior to randomization with the following exceptions: localized basal or squamous cell carcinoma of the skin or cervical intraepithelial neoplasia

216 Known untreated hypothyroidism or hyperthyroidism, adrenal insufficiency, active vasculitis due to collagen vascular disease

217 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 by central laboratory during screening

218 Any acute or serious co-morbid condition (eg, major infection or hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction, major arrhythmia) that, in the judgment of the investigator, could lead to premature termination of study participation or interfere with the measurement of, or the interpretation of, the efficacy and safety assessments in the study

219 Previously received omecamtiv mecarbil

220 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(s)

221 Recent (within 3 months) history of alcohol or illicit drug abuse based on self-report

222 Female subject is pregnant or breastfeeding or is planning to become pregnant during treatment with IP (omecamtiv mecarbil or placebo) and within 5 days after the end of treatment with IP

223 Female subject of childbearing potential who is not willing to inform her partner of her participation in this clinical study and to use two (2) acceptable methods of effective birth control or practice sexual abstinence or surgical contraceptive methods (vasectomy [male partner] or bilateral tubal ligation/occlusion) during treatment with IP (omecamtiv mecarbil or placebo) and for an additional 5 days after the last dose of IP

- A female is considered of childbearing potential unless permanently sterilized (she has had a hysterectomy, bilateral oophorectomy, or bilateral salpingectomy or she is postmenopausal). Menopause is defined as: age ≥ 55 years with cessation of menses for 12 or more months; age < 55 years but no spontaneous menses for at least 2 years; age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (spontaneous), AND with postmenopausal gonadotropin levels (luteinizing hormone (LH) and follicle-stimulating hormone levels (FSH) > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved.
- acceptable methods of effective birth control include the following combinations:

  intrauterine device and hormonal birth control method, or intrauterine device and barrier method with spermicide, or intrauterine hormonal-releasing system and barrier method with spermicide, or hormonal birth control method and barrier method with spermicide, or two (2) barrier methods (one by each partner) with spermicide (the male partner must use a male condom and the female must use a diaphragm)

  Note: ***spermicides and diaphragm are not approved for use in Japan****. If additional medications are given during treatment which may alter the contraceptive requirements (these additional medications may require a change in the type and/or length of time that contraception is to be utilized or length of time that breastfeeding is to be avoided) the investigator is to discuss these changes with the study subject.*

224 Known sensitivity to any of the products to be administered during dosing

225 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

226 History or evidence of any other clinically significant disorder, 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 (IRB)/Independent Ethics Committee (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 or their legally authorized representative must personally sign and date the informed consent form before commencement of study-specific activities/procedures.

A subject is considered enrolled upon randomization in IVRS/IWRS. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment electronic case report form (eCRF). Randomization will be stratified by presence or absence of atrial fibrillation/flutter via IVRS/IWRS.

All subjects who enter into the screening period for the study (defined as the point at which the subject or legal representative signs the informed consent) will receive a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by 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.

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 will be randomized in a 1:1:1:1 manner to receive either 25 mg BID omecamtiv mecarbil dose (n=20), 37.5 mg BID omecamtiv mecarbil dose (n=20), 50 mg BID omecamtiv mecarbil dose (n=20) or placebo (n=20) on an outpatient basis. Subjects randomized to 37.5 mg BID target dose and 50 mg BID target dose will initiate administration at 25 mg BID and will be up-titrated to the 37.5 mg BID or 50 mg BID target dose at the week 4 visit based on steady state $C_{predose}$ result from week 2.

Subjects who do not have a week 2 PK value in time for dose adjustment at the week 4 visit will be up-titrated at week 8 based on steady state $C_{predose}$ result from week 2, if available. Subjects will be up-titrated at the week 4 or week 8 visit only if the week 2 $C_{predose}$ is < 200 ng/mL. Subjects with a week 2 $C_{predose}$ ≥ 200 ng/mL (or not available at week 8) will continue at 25 mg BID for the remainder of the study. Subjects randomized to placebo or to 25 mg BID will receive the assigned IP throughout the study. To maintain blinding, all subjects will receive new IP supply at week 4 and week 8 visits. There is no other dose adjustment for individual subjects during the study.

Assignment to the treatment arms will be based on a computer-generated randomization schedule prepared by Amgen before the start of the study. A subject may only receive one randomization number and each randomization number will only be assigned to 1 subject.

Once eligibility into the study has been confirmed, a site representative will make the randomization call to the IVRS/IWRS to assign a randomization number to the subject. The randomization call to the IVRS/IWRS is accomplished by entering the pertinent information detailed in the IVRS/IWRS user manual. A confirmation will be sent to the site to verify that the correct information has been entered and to confirm the randomization assigned. A subject will be considered enrolled and randomized into the study when a randomization number is assigned.

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 a 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 appropriate Amgen study contact representative before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

6. TREATMENT PROCEDURES

6.1 Classification of Product(s) and/or Medical Device(s)

The Amgen Investigational Product and/or placebo (IP) used in this study includes: omecamtiv mecarbil and placebo. No investigational medical devices are used in this study.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, destruction, and administration of omecamtiv mecarbil and placebo.

6.2 Investigational Product

6.2.1 Amgen Investigational Product (Omecamtiv Mecarbil)

Omecamtiv mecarbil will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. Omecamtiv mecarbil will be presented as tablets in individually labeled 35ct bottles. Each bottle will have an unique bottle number.

Further details regarding IP storage condition, dispensation, packaging, labeling, accounting procedures, and destruction are outlined in the IPIM.

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

6.2.1.1 Dosage, Administration, and Schedule

Eligible outpatient subjects will be randomized and will initiate administration of IP (omecamtiv mecarbil or placebo). Day 1 is defined as the calendar day when treatment with IP is initiated. The first administration of IP should be on the day of randomization but not later than 5 calendar days after randomization. The time when ingestion of the first dose of IP is completed is defined as Time = 0 hours. Baseline procedures must be completed before initiation of IP and can be performed on the same day.

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) and taken with water as instructed in the IPIM. Administration of each morning and evening dose is to be taken at approximately the same time of day (12 ± 3 hours from the most recent previous dose). If IP cannot be taken or has not been taken within this window, the dose should be recorded as missed and the next dose should be taken at the regular time. Administration of IP will start with the morning dose on day 1 and will end with the morning dose on the day of the subject's week 16 visit. The quantity, date and time, lot number, and bottle number of investigational product is to be recorded on each subject's eCRF.

6.2.1.2 Rules for Withholding Investigational Product due to Myocardial Ischemia or Infarction, Abnormal Blood Pressure or Heart Rate

Omecamtiv mecarbil may result in signs and symptoms of myocardial ischemia or infarction, as described in Section 7.1 of the Investigator's Brochure (eg, increases in HR, dizziness, dyspnea, hypotension, chest discomfort or pain, ST-segment depression on ECG, and/or elevations in troponin I or T). If a subject reports clinical signs or symptoms suggestive of myocardial ischemia or infarction, and/or experiences changes in BP or HR, withholding of IP should be considered. No antidote to omecamtiv mecarbil exists. Standard medical therapies should be used in the presence of signs or symptoms of myocardial ischemia.

The following are mandatory rules for withholding IP:

- The subject experiences clinical signs or symptoms, including ECG changes, consistent with myocardial ischemia or infarction as determined by the investigator
- The subject experiences a symptomatic decrease in systolic BP on 2 successive measurements
- The subject experiences an asymptomatic decrease in systolic BP to < 80 mmHg (measured at 3 successive timepoints over approximately 15 minutes)
- The subject experiences symptoms associated with a HR > 120 bpm, systolic BP > 170 mm Hg, or diastolic BP > 110 mm Hg that are determined by the investigator to warrant termination of the dosing
- The subject experiences sustained systolic BP > 170 mm Hg (measured at 3 successive timepoints over approximately 15 minutes)
- The subject experiences a sustained diastolic BP > 110 mm Hg (measured at 3 successive timepoints over approximately 15 minutes)
- The subject experiences a sustained HR > 120 bpm (measured at 3 successive timepoints over approximately 15 minutes)
- The subject experiences a sustained (measured at 3 successive timepoints over at least 15 minutes) HR increase ≥ 25 bpm from screening or baseline AND HR > 100 bpm

If suspected adverse drug reactions or changes in vital signs, ECGs, or clinical laboratory results are observed during the study and, in the opinion of either the investigator or the Study Medical Monitor, these changes pose a significant health risk, dosing of an individual subject should be stopped and not resumed.

If administration of IP is stopped (up to 5 days after last IP) for any of the reasons above, a blood sample of 5 mL for PK analysis is to be collected as soon as possible .

If a subject experiences clinical signs or symptoms consistent with myocardial ischemia or infarction, the subject should receive immediate medical attention according to the

institution's usual standard of care. Serial cardiac troponin samples (troponin I or T) should be analyzed at the local laboratory. In addition, central laboratory analysis of serial samples for cardiac troponin I and/or creatine kinase MB fraction (CK-MB) as well as serial 12-lead ECGs should be collected. The investigator must notify Amgen immediately of any subject experiencing clinical signs or symptoms of myocardial ischemia or infarction.

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 omecamtiv mecarbil should be permanently discontinued.

6.3 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values during the study (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 investigational product or other protocol-required therapies as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, U.S. Department of Health and Human Services Food and Drug Administration, July 2009.

6.3.1 Criteria for Permanent Discontinuation of Omecamtiv Mecarbil due to Potential Hepatotoxicity

Omecamtiv mecarbil 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:

- TBL > 2x 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 immediately 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 (NASH)
- Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what are noted above, the investigator should determine (based on patient population and/or severity of the hepatotoxicity or event) if Amgen investigational product and other protocol-required therapies should be withheld or permanently discontinued, as deemed appropriate for the safety of the subject, and Amgen medical monitor should be contacted immediately.

6.3.2 Criteria for Conditional Withholding of Omecamtiv Mecarbil due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent withholding of IP outlined above, omecamtiv mecarbil should be withheld if ANY of the following criteria are met, and the subject should be evaluated for DILI:

- 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

Omecamtiv mecarbil should be withheld pending investigation into alternative causes of DILI. If investigational product(s) 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 Omecamtiv Mecarbil After Potential Hepatotoxicity

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 omecamtiv mecarbil should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.3.1) should 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 except for those listed in Section 6.6. All appropriate concomitant medications taken by a subject while on study are to be recorded.

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 investigational product. Any product complaint(s) associated with an investigational product(s) or non-investigational product(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

Other investigational procedures while participating in this study are prohibited. Medications or foods that are known potent inducers or inhibitors of CYP3A4 (see Section 4.1.2 and Appendix D)are prohibited up to the EOS visit, occurring on week 20.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 2. Schedule of Assessments

Timepoint - Day/Week/Month (window)*	Screen	D1	D7	W2 D15 (-3)	W4 D28 (+3)	D34 (+3)	W8 D56 (±3)	D62 (+3)	W12 D84 (±3)	W16 D112 (±3)	W20[a] D140(+3) EOS
General Procedures											
Informed consent	X										
Medical history and demographics	X										
Vital Signs (HR, BP)	X	X[c]		X	X		X[l]		X	X[k]	X
AEs/SAEs/PEPs[b]	X	X		X	X		X		X	X	X
AEs/SAEs and IP compliance verification by phone or other contact			X			X		X			
Concomitant therapy	X	X		X	X		X		X	X	X
Physical examination	X										X
Body height		X									
Body weight		X		X			X		X	X	X
ECG	X	X[c]		X	X		X[d]		X	X[d]	X
Echocardiogram	X						X[l]			X[k]	
Central Laboratory											
PK samples[e]		X[c]		X[c]	X[c]		X[l]		X[c]	X[k]	
Chemistry (including eGFR at screening)	X			X			X		X	X	X
Hematology	X			X			X		X	X	X
Urinalysis		X					X				X
Troponin I, CK-MB [e]		X[c]		X	X		X		X	X	X
NT-proBNP		X[c]			X		X			X	
Samples for Development Therapeutic Monitoring Assay					X				X		
Serum pregnancy, FSH/LH or estradiol[f]	X										X
Digoxin sample (in subjects receiving digoxin)		X		X							
Investigational Product[g]											
IP dispensation and/or administration at site		X		X	X		X		X	X[h]	
IP diary dispensation or collection[i]		X								X	
IP reconciliation (tablet count)				X	X		X		X	X	

Footnotes displayed on the next page of the Table

AE = adverse event; BP = blood pressure; CK-MB = creatine kinase-MB; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; HR = heart rate; IP = investigational product; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PEP = potential endpoint; PK = pharmacokinetic; SAE = serious adverse event.

Please note: vital signs, ECGs, and laboratory samples can be collected at any time during the study visit, unless otherwise specified below.

Visit Windows: For week 2 visit, the visit date could be 3 days prior to the scheduled date of W2; for week 4 visit, the visit date could be 3 days after the scheduled date of W4; for weeks 8, 12, and 16, the visit dates could be 3 days prior to or after the scheduled date of W8, W12, and W16, respectively; for week 20 visit (EOS), the visit date could be up to 3 days after the scheduled date of W20. The Day 34 and 62 telephone calls could be 3 days after the scheduled date of contact.

[a] If early discontinuation, week 20 (EOS) assessments should be performed as close as possible to time of discontinuation

[b] Serious adverse events are collected from signing the informed consent until 30 days after the last dose of IP or EOS, whichever is later, adverse events and PEPs from randomization until EOS, recording of PEPs and hospitalization only during visits to the study site (day 1, weeks 2, 4, 8, 12, 16, 20 [EOS]); if subject is not seen at the study site, AEs/SAEs/PEPs can be collected by phone

[c] Predose in the morning, at study site

[d] Performed as close as possible after the collection of PK sample at 2 hours ± 30 minutes following IP administration.

[e] If cardiac troponin is measured locally to evaluate suspected myocardial ischemia or infarction, send samples for troponin I/CK-MB, and PK (up to 5 days after last dose of IP) to the central laboratory

[f] Serum pregnancy testing in females of childbearing potential, FSH/LH or estradiol at screening only, and only if applicable per exclusion criteria.

[g] IP is taken twice daily except on the last day of administration (week 16 visit). Subjects randomized to 37.5 mg BID target dose and 50 mg BID target dose will initiate administration at 25 mg BID. Subjects will be up-titrated to 37.5 mg BID or 50 mg BID target dose at the week 4 visit based on steady state $C_{predose}$ result from week 2. Subjects who do not have a week 2 PK value in time for dose adjustment at the week 4 visit, will be up-titrated at week 8 based on steady state $C_{predose}$ result from week 2, if available. Subjects will be up-titrated at the week 4 or week 8 visits only if the week 2 $C_{predose}$ is < 200 ng/mL. Otherwise, they will continue at 25 mg BID.

[h] Details of IP dispensation and reconciliation are described in the IPIM; dispensation and reconciliation timepoints may differ from the timepoints shown above; IP not dispensed at week 16 visit.

[i] Paper Diary will be dispensed at Day 1 and will be collected at week 16. Subjects will be instructed to enter each administration of IP from Day 1 to week 16 or early termination. The date and time of administration will be noted.

[j] Vital signs and PK samples at predose, at 2 hours ±30 minutes; 4 hours ±30 minutes; 6 hours ±30 minutes; 8 hours ±30 minutes after IP administration in the morning (0 h = start of IP); echocardiogram performed as close as possible after the collection of PK sample at 2 hours ±30 minutes following IP administration.

[k] Vital signs and PK samples at predose and at 2 hours ± 30 mins following IP administration. Echocardiogram should be performed as close as possible after the collection of PK sample at 2 hours ± 30 minutes following IP administration.

7.2 General Study Procedures

7.2.1 Informed Consent

All subjects or their legally authorized representative must personally sign and date the IRB/IEC approved informed consent before any study specific procedures are performed. See Section 11.1 for further details.

7.2.2 Medical History

The subject's relevant medical and surgical history will be obtained prior to enrollment and recorded in the eCRF.

7.2.3 Concomitant Therapy

Prior therapies that were being taken within 30 days prior to screening through the completion of the study should be reported on the eCRF. The therapy name, indication, dose, frequency, route, and start date and stop date should be recorded in the eCRF.

7.2.4 Vital Signs

The following measurements must be performed: systolic/diastolic BP and HR. Subjects should be in a seated or semi-recumbent position for at least 5 minutes before taking vital sign measurements. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign eCRF. Any abnormal measurements may be repeated and reported on the eCRF. All values must be verifiable on the source documents.

7.2.5 Investigational Product Administration Diary

Subjects will be supplied with a diary during the Day 1 visit in which to record the date and time of each administration of IP taken away from the site. Study site staff will review the diary with the subject at each clinic visit for compliance with IP dosing. The study site staff will make a copy of the diary at each visit and transcribe the date and time of each morning and evening dose of IP taken, as directed by the Electronic Case Report Form Completion and Query Resolution Guide. The diary will be retained at the study site as part of the source documentation once the subject has completed his/her study participation.

7.2.6 Adverse Events

Refer to Section 9 for information on the definitions and reporting procedures for adverse events and serious adverse events.

7.2.7 Potential Endpoints

Deaths, hospitalizations and selected nonfatal cardiovascular events will be reported on an ongoing basis to Amgen or designee, as potential endpoints (PEPs). An independent CEC committee will adjudicate deaths, all hospitalizations, and selected nonfatal CV events (including possible MI or ischemia). The adjudicated events will include, but may not be limited to the following: cardiovascular death, HF, acute myocardial infarction, myocardial ischemia, unstable angina, and resuscitated sudden death. Only events occurring after subject randomization until completion of the study will be adjudicated.

7.2.8 Hospitalizations

Information about all hospitalizations up to the EOS (week 20) will be collected.

7.2.9 Physical Examination

The screening physical examination will be a complete physical examination including height and weight. Breast, genital, and rectal examinations are not required at any study visit unless specific evaluation is warranted in accordance with the standard of care. Physical examination findings at screening are to be recorded in the medical and surgical eCRF. The physical examination at the EOS visit at week 20 will consist of an examination to monitor for any changes from the screening physical examination. Any clinically significant change from the baseline physical examination, which represents deterioration, is to be recorded on the Events eCRF.

7.2.10 Physical Measurements

Height and weight should be measured without shoes at Day 1. Weight only will be measured at weeks 2, 8, 12, 16, and at week 20 (EOS).

7.2.11 Electrocardiogram

At each scheduled visit where ECGs are being obtained, three 12-lead ECGs will be collected consecutively approximately 30 seconds to 1 minute apart. Using equipment supplied to each site, all protocol-specified ECGs will be acquired and transmitted to the centralized ECG services provider. The principal investigator or designated physician will review acquired ECGs. One (1) signed, original ECG tracing should be retained with the subject's source documents. At the request of the sponsor, the original ECG should be made available to Amgen.

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine

position, the subject should be in most recumbent position as possible. The ECG must include the following measurements: HR, QRS, QT, QTc, and PR intervals.

The centralized ECG services cardiologists will perform standard interpretations of all tracings. A cardiologist reviewed ECG report will be provided to the study site. Investigators must initial and date the ECG reports upon receipt. If the investigator's interpretation of any protocol-specified or unscheduled ECG differs from that supplied by centralized ECG services provider, it is the responsibility of the investigator to make the final clinical decisions. The investigator's interpretation does not need to be reconciled with that supplied by centralized ECG services cardiologists. Any clinical interventions based on these results need to be documented in the appropriate source documents and eCRF as applicable. It is the responsibility of the investigator to obtain additional ECGs required for the clinical management of the subject, using centralized ECG services equipment or equipment on-site.

Further details regarding ECG collection requirements for this study will be provided in an Investigator ECG Manual distributed to the sites before start of enrollment.

7.2.12 Laboratory Assessments

Central laboratory assessments are to be used to assess subject eligibility (except for the pregnancy test, section 7.2.12.1). All other screening or scheduled study laboratory assessments will also be by central laboratory.

If cardiac biomarkers (troponin I or T) are analyzed locally to evaluate suspected myocardial ischemia or infarction, additional blood samples for troponin I and/or CK-MB analysis by the central laboratory must be collected. The results of the local testing will be maintained in the source documents at the site. Selected local testing results may be entered into the eCRF as instructed by Amgen.

The central laboratory may ship PK samples to Amgen or a specialty laboratory for analysis.

The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all blood and urine samples. The date and time of sample collection will be recorded in the source documents at the site.

Table 3 below outlines the specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted on blood and urine samples.

Table 3. Analyte Listing

Chemistry	Urinalysis	Hematology	Other Labs
Sodium	Specific gravity	Hemoglobin	Pharmacokinetics
Potassium	pH	Hematocrit	Pregnancy test[a]
Chloride	Blood	Mean corpuscular volume	FSH/LH or estradiol[a]
Bicarbonate	Protein	Platelets	NT-proBNP
Total protein	Glucose	White blood cells	Troponin I
Albumin	Bilirubin	Differential	CK-MB
Glucose		• Total neutrophils	PT/INR[b]
Blood urea nitrogen		• Eosinophils	Digoxin[c]
Creatinine		• Basophils	
Total creatine kinase		• Lymphocytes	
TBL		• Monocytes	
Direct bilirubin			
Alkaline phosphatase			
Alanine aminotransferase			
Aspartate aminotransferase			
Magnesium			
Cholesterol			
High-density lipoprotein			
Low-density lipoprotein			
Triglycerides			

CK-MB = creatine kinase-MB; FSH = follicle-stimulating hormone; LH= luteinizing hormone ;NT-proBNP = N-terminal pro-B-type natriuretic peptide; PT/INR = prothrombin time/international normalized ratio; TBL=total bilirubin..

[a] A pregnancy test is required for females of childbearing potential**;** FSH/LH or estradiol only per exclusion in Section 4.1.2.

[b] Performed as given in Appendix A only if DILI follow-up is needed (see Section 6.3.2)

[c] Only in subjects receiving digoxin

7.2.12.1 Pregnancy Test

Qualitative or quantitative human chorionic gonadotropin pregnancy testing will be performed locally or per central laboratory, depending on investigator preference and to facilitate trial operations. Pregnancy testing is required as per Schedule of Assessments (Section 7.1) for all females of childbearing potential as defined in the exclusion criterion (Section 4.1.2).

7.2.12.2 Troponin

Troponin I (also referred to as troponin in this protocol) will be measured by central laboratory in this study. The central laboratory troponin samples may be batched for

analysis and may be assayed several weeks or months after collection. Therefore, the results of the central laboratory troponin analysis will not be routinely provided to the investigator.

At any time during a subject's study participation when local troponin I or T are drawn to evaluate suspected myocardial ischemia or infarction, additional samples for cardiac troponin and/or CK-MB analysis by the central laboratory must be collected. A sample for PK analysis should be collected as well unless it has been more than 5 days since the last administration of IP.

The cardiac troponin assay selected for Study 20120227 is the Siemens ADVIA Centaur Ultra Troponin I, an assay designated as "guideline acceptable" per the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation (ESC/ACCF/AHA/WHF) Expert Consensus Document on the Universal Definition of Myocardial Infarction (Apple FS, 2009; Thygesen et al, 2012).

7.2.12.3 Pharmacokinetics of Omecamtiv Mecarbil

Blood samples for measurement of omecamtiv mecarbil will be drawn before and after administration of investigational product at the timepoints shown in the Schedule of Assessments (Section 7.1). Approximately 5 mL of blood will be collected at each time point.

In addition to the PK samples listed in the Schedule of Assessment, Section 7.1, at any time during a subject's study participation when local troponin I or T are drawn to evaluate suspected myocardial ischemia or infarction, additional blood samples for cardiac troponin I and/or CK-MB analysis by the central laboratory and, if within 5 days of the last dose of IP, a sample for PK analysis must be collected.

Samples will be processed and frozen per the central laboratory manual. The site will be expected to complete a shipping log or requisition that will include subject identification information and the time and date of collection for each sample shipped. Missing samples must be clearly documented on the shipping log or requisition. Please refer to the central laboratory manual for instructions on sample collection, processing, and shipping of PK samples.

Omecamtiv mecarbil will not be measured in screening samples and samples from subjects not receiving active investigational treatment (omecamtiv mecarbil).

7.2.12.4 Digoxin

Blood samples for measurement of digoxin levels (only in subjects taking digoxin) will be drawn on Day 1 and week 2 visits as shown in the Schedule of Assessments (Section 7.1). Date, time, and dose of digoxin taken within 3 days prior to the blood sampling collection and the date and time of blood sampling must be recorded in the Laboratory Requisition Form. Approximately 2.5 mL of blood will be collected at each time point.

7.2.12.5 Omecamtiv Mecarbil Therapeutic Monitoring Assay

Blood samples of 5 mL each will be collected from all subjects at the time points outlined in Table 2 to validate the omecamtiv mecarbil drug monitoring (TDM) assay. The omecamtiv mecarbil TDM assay is a fast-turn-around assay intended to aid omecamtiv mecarbil dose titration in subjects receiving treatment.

7.2.12.6 Pharmacogenomic Studies

If the subject consents to the optional pharmacogenomic portion of this study, DNA analyses may be performed. These optional pharmacogenomic 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 HF and/or to identify subjects who may have positive or negative response to omecamtiv mecarbil. No additional samples will be collected for this part of the study. For subjects who consent to these analyses, DNA may be extracted from samples already collected.

7.2.13 Echocardiograms

Assessments for subjects enrolled into the study includes echocardiograms at the timepoints detailed in the Schedule of Assessments (Section 7.1). Where possible, staff involved in the treatment and evaluation of the study subject should not view study echocardiograms. Further, the sonographer should abstain from commenting on any observations in the echocardiograms that may be potentially unblinding. The echocardiograms will be sent to the central echocardiography laboratory for analysis. Please refer to the echocardiography instruction manual for detailed information on acquiring, storing, and transmitting the echocardiograms.

7.3 Screening and Enrollment

7.3.1 Screening

The following procedures are to be completed during the screening period as outlined in the Schedule of Assessments (Table 2):

- Written Informed Consent (to be completed prior to any screening procedures)
- Demographic data including sex, age at time of enrollment, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally demographic data will be used to study the impact of biomarker variability and pharmacokinetics of the protocol-required therapies.
- Vital signs (HR, BP)
- Serious adverse event assessment (from signing of informed consent)
- Concomitant therapy
- Physical examination as per standard of care
- Medical/surgical history
- ECG (centrally read)
- Blood samples for chemistry, hematology, and, for women of childbearing potential, serum pregnancy testing, and, if necessary to determine childbearing potential, FSH and LH, or estradiol by central laboratory (note that eGFR will be calculated by the central laboratory and provided to the investigator for eligibility)
- Echocardiogram (centrally read)

If eligibility is confirmed, subjects should be randomized within 30 days of signing the informed consent form.

7.3.2 Rescreening

Subjects who in the opinion of the investigator, require major medication changes (eg, uptitration of BP medications, uptitration of diabetes medications) can be put on the new medication schedule and rescreened after at least 4 weeks. Subjects who screen fail due to a transient laboratory abnormality can be considered for rescreening at least 4 weeks after prior screen fail. Rescreening requires signing of a new informed consent. Rescreened subjects who are reconsented will repeat all screening procedures. Rescreened subjects will maintain the originally assigned subject identification number. Subjects who fail any of the eligibility criteria during screening or rescreening need to be recorded as screen failed in IVRS/IWRS before they can be reconsented and reregistered in IVRS/IWRS for rescreening. Please note that the clinical trial agreement may limit the number of paid rescreens.

7.4 Treatment Period

Adverse events, serious adverse events , PEPs, and concomitant medications, will be reported until EOS at week 20. If a subject is not seen at the study site, adverse events/serious adverse events/PEPs should be collected by phone. For details on reporting of adverse events and serious adverse events, please refer to Section 9.

The following procedures will be completed during the study at the times designated in the Schedule of Assessments (Table 2).

- Vital signs (HR, BP)
- Adverse events/serious adverse events/PEPs, if applicable
- Concomitant therapy
- Body height, at Day 1 visit only
- Body weight, at Day 1, weeks 2, 8, 12, and 16
- ECG (centrally read), at Day 1, weeks 2, 8, 12, and 16
- Echocardiogram, at weeks 8 and 16 (centrally read)
- Blood samples for chemistry and hematology, at weeks 2, 8,12, and 16
- Blood samples for digoxin levels (only in subjects taking digoxin), at Day 1 and week 2
- PK sample collection, at Day 1, weeks 2, 4, 8, 12, and 16
- Urine sample for urinalysis, at Day 1 and week 8
- Blood samples for troponin I, CK-MB, at Day 1 and weeks 2, 8, 12, and 16
- NT-proBNP, at Day 1, and weeks 4, 8, and 16
- Therapeutic Monitoring Assay sample collection at weeks 4 and 12
- IP dosing on site, at Day 1, weeks 2, 4, 8, 12, and 16
- IP dispensation, at Day 1, week 4 and week 8
- IP reconciliation (tablet count) at weeks 2, 4, 8, 12, and 16
- Diary dispensation, Day 1
- Return diary, week 16

7.4.1 Telephone Contact Days 7, 34, and 62

- AEs/SAEs and IP compliance will be verified by phone or other contact

7.5 Safety Follow-up Visit/End of Study Visit

The following procedures will be completed at the week 20 EOS visit as designated in the Schedule of Assessments (Table 2).

- Vital signs
- Adverse events/serious adverse events/PEPs, if applicable

- Concomitant therapy
- Physical examination
- Body weight
- ECG (centrally read)
- Blood samples for chemistry and hematology
- Blood samples for cardiac troponin I, CK-MB
- Urine sample for urinalysis
- Serum pregnancy

7.6 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 or other cardiovascular conditions, the dose response and/or prediction of response to omecamtiv mecarbil, and characterize aspects of the molecule (eg, mechanism of action/target). 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, in accordance with applicable law and subject informed consent.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results 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 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) and collection of data, including endpoints and adverse events. 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 a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study. At a minimum, if possible, the procedures listed under the final study visit should be performed.

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(s) 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, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, protocol-specified criteria [see TREATMENT PROCEDURES], pregnancy)
- death
- lost to follow-up
- decision by Sponsor (other than subject request, safety concern, lost to follow-up)

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 Adverse Events

9.1.1 Definition of 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.

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.

9.1.2 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- 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

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 drug-induced liver injury reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Reporting of Adverse Events

9.2.1 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 the Safety

Follow-up Visit/End of Study (EOS) are reported using the applicable case report form (eg, Event eCRF), including events that are reported to the CEC for adjudication.

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 investigational product
- Action taken

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) grading scale. The grading scale used in this study is described in Appendix A. If the severity of an adverse event changes from the date of onset to the date of resolution, record a single event for each level of severity on the Event eCRF.

The investigator must assess whether the adverse event is possibly related to IP (omecamtiv mecarbil or placebo). 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 IP (omecamtiv mecarbil or placebo)"?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of investigational product, protocol-required therapies, and/or procedure (including an screening procedure(s)). 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 (eg. administration of investigational product, protocol-required therapies, and/or procedure?)"

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 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 signing of the informed consent until 30 days after the last dose of IP or Safety Follow-up Visit/End of Study, 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 applicable eCRF.

9.2.2.1 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period defined above or after the end of the study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union 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. If the first notification of a serious adverse event is reported to Amgen via the electronic Serious 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 IP (omecamtiv mecarbil or placebo). 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 IP (omecamtiv mecarbil or placebo)?"

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 applicable eCRF (eg, Event eCRF).

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.

In addition, the occurrence of deaths and cardiovascular events will be recorded on specific worksheets by the investigative study center. Source documentation supporting each cardiovascular event will be provided to Amgen or designee by the investigative study center when the event is reported. Each package (worksheet and supporting documentation) will be provided to a CEC for review and adjudication according to the CEC manual. The CEC committee will provide the results of the adjudication to Amgen or designee.

9.2.2.2 Reporting a Safety Endpoint as a Study Endpoint

The investigator is responsible for ensuring that all serious adverse events/adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent or randomization, respectively, through the Safety Follow-up Visit/EOS are reported using the applicable eCRF (eg, Event eCRF), including events that are reported to the CEC committee for adjudication.

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 following the last dose of 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 following the last dose of 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 Endpoints

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

10.1.1.2 Secondary Endpoint

- Changes from baseline in SET by echocardiography at week 16

10.1.1.3 Safety Endpoints

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

10.1.1.4 Exploratory Endpoints

Exploratory endpoints are as follows:

- observed values and change from baseline to assessed timepoints of stroke volume, left ventricular end-systolic diameter (LVESD) and left ventricular end-dyastolic diameter (LVEDD).
- observed values and change from baseline to assessed timepoints of HR
- observed values and change from baseline to assessed timepoints of NT-proBNP
- subject incidence of supraventricular tachycardia and ventricular tachycardia arrhythmias requiring treatment from initiation of IP to EOS
- subject incidence of the following clinical outcome endpoints:
    - cardiovascular death or HF hospitalization until EOS
    - all-cause death or HF hospitalization until EOS
    - all adjudicated events until EOS; events include, but may not be limited to: cardiovascular death, HF, acute myocardial infarction, myocardial ischemia, unstable angina, and resuscitated sudden death
    - new onset atrial fibrillation/flutter
    - all-cause death

10.1.2 Analysis Sets

The PK analysis set (PKAS) includes all randomized subjects who have received at least one dose of omecamtiv mecarbil and have at least one evaluable omecamtiv mecarbil PK parameter (C_{max}, $C_{predose}$). This analysis set will be used for analyses of all the PK endpoints, unless significant protocol deviations have affected the data or if key dosing or sampling information are missing, in which case a modified PKAS will be used.

The full analysis set (FAS) includes all randomized subjects who have received at least one dose of IP (omecamtiv mecarbil or placebo). This set will be used for all analyses of non-PK endpoints.

The completers analysis set is a subset of the FAS and includes subjects who have completed IP administration. The completers analysis set will be used for sensitivity analyses.

10.1.3 Covariates and Subgroups

The stratification factor is presence or absence of atrial fibrillation/flutter. Other baseline covariates include the following:

- age (< 65, ≥ 65)
- sex
- LVEF
- Body mass Index (BMI)
- NT-proBNP
- presence of coronary artery disease
- HF treatment at baseline

10.2 Sample Size Considerations

The primary endpoints of this study are the omecamtiv mecarbil PK parameters. PK parameter's mean will be estimated. Assuming the SDs for C_{max} and AUC are in the range of 40 to 90, a sample size of n= 20 subjects in each treatment group, 19 subjects (assuming 5% subjects out of a total n = 20 subjects per treatment arm are excluded from PKAS) will provide a 2-sided 95% confidence interval (CI) with half width of 18 to 41. The SD estimates are from the predicted steady state PK for 25 mg and 50 mg BID doses for Matrix F1 formulation based on simulations performed using PK data following single dose from study 20090727. Table 4 below presents CI half widths given particular SDs in this range for 19 subjects per treatment group.

Table 4. PK Parameter 95% Confidence Intervals

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

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Unless otherwise specified in this section, subjects, site personnel, or Amgen staff and their designees will not have access to unblinding information until the study is formally

unblinded. Unblinded individuals, as designated in this section, are to ensure unblinding information and potentially unblinding data are not distributed to blinded individuals until the study is formally unblinded.

Staff involved in randomized treatment assignment, IP packaging and labeling, biological sample management, and assaying PK samples are unblinded to the treatment assignments in this study, but will not have access to subject-level safety or efficacy data. Staff in Amgen's Clinical Pharmacology Modeling & Simulation who are responsible for PK data analysis and interpretation during the conduct of this study will not have knowledge of subject IDs; samples are labeled by an alias before analysis. The external independent biostatistics group will have access to treatment assignments and will provide unblinded results, including aggregate and subject-level data, to the DMC for data reviews.

10.4 Planned Analyses

10.4.1 Data Monitoring Committee (DMC)

An external independent DMC will formally review the accumulating data from Amgen's ongoing omecamtiv mecarbil studies to facilitate detection of any increased risk for harm to subjects (eg, unexpected PK concentration due to PK variability). The DMC will review unblinded data approximately every month while subjects are receiving IP. Based on the totality of evidence, the DMC will make an overall recommendation to the sponsor whether to continue the study according to the protocol or whether to make any changes (eg, including, but not limited to, dose change or stopping enrollment). To protect the status of the blind and to minimize potential operational bias, analyses for the DMC will be provided by the independent biostatistics group which is external to Amgen and supported by designated Amgen staff (eg, Clinical Pharmacology Lead in Section 10.3), if needed. Details will be provided in the DMC charter.

10.4.2 Primary Analysis

To evaluate the PK, PD, safety, tolerability of omecamtiv mecarbil in Japanese subjects with HF with reduced ejection fraction, the primary analysis will be conducted when all the enrolled subjects in the study either complete the EOS visit (week 20) or terminate the study early. At that time, the database will be cleaned, processed and a snapshot will be taken. At this stage, the study will be unblinded to conduct the primary analysis. The primary analysis will include estimation for all endpoints. No formal hypotheses will be tested in this study and all statistical approaches are hypothesis-generating.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Statistical analyses in this study are descriptive in nature.

Subject disposition, demographics and baseline characteristics will be summarized.

Summary statistics for continuous variables will include number of subjects, mean, median, SD, or standard error, minimum, and maximum. For PK parameters, coefficient of variation will also be included. For categorical variables, frequency and percentage will be presented. Subjects will be analyzed based on their randomized treatment group assignment.

10.5.2 Primary Endpoint

The primary endpoints are the omecamtiv mecarbil PK parameters $C_{predose}$ and AUC, collected in the study (Section 10.1.1.1).

In the PK analysis, all plasma concentrations below the quantifiable limits will be assigned the value of zero. For any data excluded from the analyses, specific reasons will be provided.

Individual omecamtiv mecarbil concentration-time data and summary statistics will be tabulated for omecamtiv mecarbil. Individual, mean, and SD concentration-time data may be plotted. The PKAS will contain all subjects for whom at least one PK parameter (C_{max}, $C_{predose}$) can be adequately estimated. PK parameters will be calculated using non--compartmental methods. Actual dosing and sampling times will be used for calculation of PK parameters. Descriptive statistics will be generated for each PK parameter for each treatment.

Individual PK parameters will be summarized descriptively at each scheduled assessment, in the primary analysis set of PKAS.

10.5.3 Secondary Endpoint

Echocardiographic parameter SET and its change from baseline at week 16 will be summarized by treatment group and scheduled assessment.

In addition, analysis will be performed to explore the potential relationship between omecamtiv mecarbil exposure and changes from baseline in SET. Differences between treatment groups in SET will be estimated via repeated-measures model, with difference estimates and their 95% CIs presented. The model will include the stratification factor,

treatment group, visit and the interaction of treatment group and visit. Subgroup analyses by baseline covariates in Section 10.1.3 will be provided.

10.5.4 Safety Endpoints

10.5.4.1 Adverse Events

The current Medical Dictionary for Regulatory Activities (MedDRA) version at the time of the data lock will be used to code all adverse events (AE) 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.

10.5.4.2 Safety Laboratory Tests

The analyses of safety laboratory endpoints will include summary statistics at each scheduled assessment by cohort and treatment group. Shifts in grades of safety laboratory values between baseline and the most extreme post-baseline values will be tabulated by cohort and treatment group.

10.5.4.3 Vital Signs

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

10.5.4.4 Electrocardiogram

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters.

Subjects' maximum change from baseline in QT Fridericia corrected 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.

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 appropriate Amgen representative to the investigator. The written informed consent document is to be prepared in the language(s) of the potential subject 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 IPs 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 or 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 or 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 eCRF 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 or 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 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 and by what mechanism, after termination of the study and before the product is available commercially.

12.2 Study Documentation and Archive

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

Source documents are original documents, data, and records from which the subject's eCRF 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.

eCRF entries may be considered source data if the eCRF is the site of the original recording (ie, there is no other written or electronic record of data).

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 should include the following:

- subject files containing completed eCRFs, informed consent forms, and subject identification list
- study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation, and all correspondence to and from the IRB/IEC and Amgen

- IP-related correspondence including Proof of Receipts, Investigational Product Accountability Records, Return of Investigational Product for Destruction Forms, Final Investigational Product Reconciliation Statement, 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, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen Clinical Monitor and/or appropriate Amgen representative 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 Clinical Monitor and/or appropriate Amgen representative is to have access to subject medical records and other study-related records needed to verify the entries in the eCRFs.

The investigator agrees to cooperate with the Amgen Clinical Monitor and/or appropriate Amgen representative to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, 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 eCRFs must be maintained and readily available.
- Updates to eCRFs 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 and/or site notifications are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer. Additional queries may be sent out by the CEC and, upon resolution, will be closed by the CEC.

- The investigator signs only the Investigator Verification Form for this EDC study. This signature indicates that investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content.

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.

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

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, the investigator will solicit input and assistance from Amgen staff as appropriate.

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, 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; and (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. If permitted under applicable regional laws and regulatory guidelines, subjects may be compensated for other inconveniences not associated with study-related injuries (eg, travel costs).

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. As of the protocol date, the CTCAE is available at the following link:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Potential Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or 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 appropriate eCRF (eg, Event eCRF) 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.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(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 investigational product(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, haptoglobin lactate dehydrogenase, and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for pharmacokinetic 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 investigational product(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 eCRFs.

Appendix B. Sample Serious Adverse Event Report Form

Sample eSAE Contingency Report Form

A **Study # 20120227** **AMG 423** **(omecamtiv mecarbil)**	**Electronic Adverse Event Contingency Report Form** **For Restricted Use**

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?**	**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)

FORM-056006 (variant)
Form Created: 05 JUN 2015

Version 6.0 Effective Date 07 JUL 2014

A **Study # 20120227** **AMG 423** **(omecamtiv mecarbil)**	**Electronic Adverse Event Contingency Report Form** **For Restricted Use**

	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**	Dose Start Date **(Day Month Year)**						Lot # ☐ **Unknown** Serial # ☐ Unavailable / Unknown
		Dose Start Time **(24-hr clock)**						
		Action Taken with Product ☐ Still being Administered ☐ Permanently discontinued ☐ Withheld						

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✓	 Yes✓	Continuing No✓	 Yes✓	Dose	Route	Freq.	Treatment Med No✓	 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										

A **Study # 20120227** **AMG 423** **(omecamtiv mecarbil)**	**Electronic Adverse Event Contingency Report Form** **For Restricted Use**

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: 20120227

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: 20120227

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: _____

Appendix D. Excluded Medications and Foods

CYP3A4 Inducers	CYP3A4 Inhibitors
Carbamazipine	Amprenavir
Dexamethasone	Cobicistat
Efavirenz	Cyclosporine
Etravirine	Clarithromycin
Nevirapine	Delaviridine
Phenobarbital	Erythromycin
Phenytoin	Grapefruit juice
Rifabutin	Indinavir
Rifampicin	Itraconazole
St. John's wort	Nelfinavir
	Ritonavir
	Saquinivir
	Telaprevir
	Verapamil
	Voriconazole