Protocol

Single-dose and Randomized, Single-center, Placebo- and Active-controlled, Crossover Study to Assess the Effect of Omecamtiv Mecarbil (OM) on QT/QTc Intervals in Healthy Subjects

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INVESTIGATOR AGREEMENT

I have read the protocol entitled "Single-dose and Randomized, Single-center, Placebo- and Active-controlled, Crossover Study to Assess the Effect of Omecamtiv Mecarbil (OM) on QT/QTc Intervals in Healthy Subjects" (Version 4.0, dated: 23 August 2019), and agree to conduct the study as described herein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

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_____

Signature

Name of Principal Investigator	Date (DD Month YYYY)

STUDY IDENTIFICATION

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SYNOPSIS

Title of study: Single-dose and randomized, single-center, placebo- and active-controlled, crossover study to assess the effect of omecamtiv mecarbil (OM) on QT/QTc intervals in healthy subjects

Objectives:

The primary objective of the study is:

- To assess the effect of a single therapeutic (50 mg) oral dose of OM on the QT/QT interval corrected for heart rate (QTc) interval, relative to placebo, in healthy subjects.

The secondary objectives of the study are:

- To assess the pharmacokinetics (PK) of OM after a single oral dose to healthy subjects.
- To evaluate the effect of OM on other electrocardiogram (ECG) parameters (heart rate [HR], PR and QRS intervals, and treatment-emergent T-wave abnormalities and presence of U-waves).
- To evaluate the plasma concentration-effect relationship for OM on the QT/QTc interval in healthy subjects.
- To evaluate assay sensitivity by evaluation of the positive control, a single 400-mg oral dose of moxifloxacin, on the QT/QTc interval in healthy subjects.
- To evaluate the safety and tolerability of OM after a single oral dose to healthy subjects.

Hypothesis:

The hypothesis is that OM does not prolong QTc intervals after administration of a single 50-mg oral dose and will be safe and well tolerated in healthy subjects.

Study design:

This is a single-center, single-dose (Part A; PK Evaluation Period), and randomized, 3-period, 3-treatment, crossover, single-dose (Part B) study in healthy adult subjects to determine whether OM prolongs the QTc after a single oral dose administration of 50 mg OM. Treatment in Part A will consist of a single 25-mg OM treatment (Treatment 1). Subjects whose resulting maximum observed plasma OM concentration (C_{max}) is ≤ 350 ng/mL will be randomized into Part B, which consists of 3 periods wherein a single treatment is given in each period. Treatments will consist of placebo (Treatment A), OM 50 mg (Treatment B), or moxifloxacin 400 mg (Treatment C). All treatments (Part A and Part B) will be separated by a washout of at least 7 days.

Part A

All subjects will receive Treatment 1. OM treatment will be open-label. Safety and tolerability monitoring will be conducted throughout Part A, and blood samples will be collected to determine plasma OM concentrations. Safety digital ECG recordings will be reviewed by the Investigator or designee on Day -1, and on Day 1 at the following timepoints: predose and at 1, 4, 24, 48, and 120 hours postdose. Pharmacokinetic blood samples for OM will be collected at the following timepoints on Day 1: predose and 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, and 12 hours postdose.

Subjects whose resulting C_{max} is ≤ 350 ng/mL will be randomized into Part B. There will be a minimum of a 7-day washout between treatments in Part A and Part B.

Part B

After completing Part A, eligible subjects will be randomized to receive 3 treatments in 1 of 6 sequences, as follows:

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	C	B	A
6	B	A	C

In Part B, placebo and OM treatments will be double-blinded, moxifloxacin treatment will be open-label, and the core ECG lab will be blinded to all treatment information. Safety and tolerability monitoring will be conducted throughout the study, and blood samples will be collected to determine plasma OM and moxifloxacin concentrations in relevant periods.

In each Part B treatment period, continuous digital ECG recording will be performed for approximately 27 hours, from predose through at least 24 hours postdose, and up to 10 replicate 12-lead ECGs will be extracted at the following timepoints on Day 1: -1.25, -1, and -0.75 hours predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 8, 12, and 24 hours postdose.

In each Part B treatment period, PK blood samples for OM and moxifloxacin will be collected at the following timepoints on Day 1: predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 8, 12, 24, 48, 72, 96, and 120 hours postdose.

Number of subjects:
Approximately 60 to 70 subjects will be enrolled in Part A in order to have 60 subjects (10 per sequence) enrolled in Part B. With approximately 60 subjects in Part B, it is estimated that approximately 48 evaluable subjects will have data from all 3 periods in Part B.

Diagnosis and main criteria for inclusion:
Healthy adult females and males, aged between 18 and 50 years (inclusive) and with a body mass index between 18.0 and 30.0 kg/m^2 (inclusive).

Investigational products, dose, and mode of administration:
Subjects will receive the following single, oral dose under fasting conditions:
Part A

- Treatment 1: 25-mg OM oral solution

Note: Individual subject PK will be measured in Part A. Only subjects with plasma OM maximum concentrations ≤ 350 ng/mL in Part A will be eligible to continue to Part B.

Subjects will receive the following single, oral doses under fasting conditions, according to a randomization schedule generated by a Covance statistician:

Part B

- Treatment A: Placebo oral solution
- Treatment B: 50-mg OM oral solution
- Treatment C: 400-mg moxifloxacin oral tablet

Duration of subject participation in the study:
The total duration of participation in this study will be approximately 55 days, including a screening period of up to 28 days.

Study endpoints:
The primary endpoint is the placebo-corrected change from baseline in QTc interval based on the Fridericia correction (QTcF) (ΔΔQTcF) after OM dosing.
The following are secondary endpoints for this study:

- Pharmacokinetic parameters of OM including, but not limited to, C_{max}, the time of maximum observed concentration (t_{max}), apparent terminal elimination half-life ($t_{1/2}$), apparent volume of distribution (V_Z/F), apparent total plasma clearance (CL/F), area under the concentration-time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t}), AUC from time 0 to infinity (AUC_{inf}), and the percentage of AUC_{inf} due to extrapolation ($\%AUC_{extrap}$)
- ΔΔQTcF after moxifloxacin dosing
- Change-from-baseline heart rate, QTcF, PR and QRS intervals (ΔHR, ΔQTcF, ΔPR, and ΔQRS) after OM dosing
- Concentration-QTc analysis based on ΔΔQTcF after OM dosing
- Placebo-corrected ΔHR, ΔPR, and ΔQRS (ΔΔHR, ΔΔPR, and ΔΔQRS) after OM dosing
- Categorical outliers for QTcF, HR, PR, and QRS after OM dosing
- Frequency of treatment-emergent changes in T-wave morphology and U-wave presence after OM dosing
- Subject incidence of treatment-emergent adverse events (TEAEs)
- Changes in laboratory safety tests, vital signs, and ECGs.

Statistical methods:

Cardiodynamic evaluation:

The primary analysis will be based on by-timepoint analysis to evaluate the effect of OM on ΔΔQTcF at each postdose extraction window using a linear mixed-effect model. The effect of OM on ΔΔHR, ΔΔPR, and ΔΔQRS will also be evaluated using the same modeling approach. An analysis of categorical outliers will be performed for changes in HR, PR, QRS, QTcF, T-wave morphology and U-wave presence. Assay sensitivity will also be evaluated using by-timepoint analysis of the effect of moxifloxacin on ΔΔQTcF using the same model as for the primary analysis.

Pharmacokinetics:

Pharmacokinetic data for OM will be presented and summarized by treatment and at each timepoint when applicable. Graphical summaries of the data may also be presented.

Pharmacokinetic/electrocardiography analyses:

The relationship between OM plasma concentrations and ΔΔQTcF will be evaluated using a linear mixed-effects modeling approach.

Safety:

The number and percentage of subjects reporting any TEAEs will be tabulated by Medical Dictionary for Regulatory Activities system organ class and preferred term and grouped by treatment. Adverse events, serious adverse events, clinical laboratory evaluations, ECGs, and vital signs measurements will be summarized by descriptive statistics.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	angiotensin-converting-enzyme
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
Anti-HBc	hepatitis B core antibody
Anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{inf}	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the plasma concentration-time curve from time 0 to infinity
AV	atrioventricular
BID	twice daily
BP	blood pressure
CFR	Code of Federal Regulations
CI	confidence interval
CK-MB	creatine kinase MB fraction
C_{max}	maximum observed plasma concentration
CRF	case report form
CRO	Contract Research Organization
CV%	coefficient of variation
ΔΔQTcF	time-matched change from baseline in placebo-adjusted QT interval corrected for heart rate based on the Fridericia correction
DILI	drug-induced liver injury
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	End of Study
FAS	full analysis set
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCAb	hepatitis C antibodies
hERG	human ether-à-go-go-related gene
HF	heart failure

HFrEF	heart failure
HIV	human immunodeficiency virus
HIVAb	human immunodeficiency virus antibodies
HR	heart rate
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IP	investigational product
IPIM	Investigational Product Instruction Manual
IRB	institutional review board
IUD	intrauterine device
LS	least squares
MAD	multiple-ascending dose
MDRD	Modified Diet in Renal Disease
MRI	magnetic resonance imaging
OM	omecamtiv mecarbil
PD	pharmacodynamic
$\%AUC_{extrap}$	percentage of area under the concentration-time curve from time 0 to infinity due to extrapolation
PI	Principal Investigator
PK	pharmacokinetic(s)
QD	once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate based on the Fridericia correction
RBC	red blood cell
RR	time interval between two successive R-waves of the QRS signal on the electrocardiogram
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
$t_{1/2}$	apparent terminal elimination half-life
TBL	total bilirubin
TdP	torsades de pointes
TEAE	treatment-emergent adverse event
t_{max}	time of the maximum observed plasma concentration
TQT	thorough QT
ULN	upper limit of normal
WBC	white blood cell

1. INTRODUCTION

Refer to the omecamtiv mecarbil (OM) Investigator's Brochure (IB)[1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and safety profile of omecamtiv mecarbil.

1.1. Study Rationale

The International Council for Harmonisation (ICH) E14 requests that non anti-arrhythmic drugs are tested for their QT liability and proposes that a thorough assessment is performed in healthy volunteers in order to determine whether the potential for QT prolongation needs to be studied further in the patient population. The QT interval represents the duration of ventricular depolarization and subsequent repolarization, and is measured from the beginning of the QRS complex to the end of the T-wave. A delay in cardiac repolarization creates an electrophysiological environment that favors the development of cardiac arrhythmias, most clearly torsades de pointes (TdP), but possibly other ventricular tachyarrhythmias as well. Most drugs that have caused TdP clearly increase both the absolute QT and the QT interval corrected for heart rate (QTc). Because prolongation of the QT/QTc interval is the electrocardiogram (ECG) finding associated with the increased susceptibility to these arrhythmias, an adequate investigation should include characterization of OM's effects on the QT/QTc interval consistent with ICH E14 guidance.

1.2. Background

1.2.1. Disease

Heart failure (HF) is a clinical syndrome marked by impaired cardiac contractility and is the final pathway for a diversity of diseases that afflict the heart.[2] It affects over 26 million people worldwide, over 3.5 million people are newly diagnosed every year, and its prevalence notably increases with age.[3] The rate of cardiovascular mortality or HF re-hospitalization approaches 25% to 30% at 6 months in patients hospitalized for HF.[4]

Heart failure is most often caused by coronary artery disease; other common causes include idiopathic, hypertension, and valvular heart disease.[5] In an attempt to preserve cardiac output, the condition progresses through stages with compensatory mechanisms characterized by increased sympathetic tone and peripheral vasoconstriction, and activation of various neurohormonal pathways. These adaptive properties provide short-term relief but can be damaging with long-term or prolonged activation. Patients experience dyspnea, fatigue, and fluid retention and may eventually develop pulmonary congestion and peripheral edema. Treatment goals are to improve symptoms, prolong survival, and reduce hospital readmissions.[6,7] 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[8]), 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. Current inotropic agents, such as β-adrenergic receptor agonists or

phosphodiesterase inhibitors, work indirectly by activating second messenger signaling pathways to increase cardiac myocyte intracellular calcium resulting in an increase in systolic function. However, these agents can also cause arrhythmias, increase heart rate and oxygen consumption, result in clinically significant hypotension, and have been associated with increased mortality. These adverse effects may be related to their mechanism of action of increasing intracellular calcium.

In contrast to current inotropes, OM directly activates cardiac myosin without affecting intracellular calcium and may therefore improve systolic function without the liabilities of inotropes.

1.2.2. Amgen Investigational Product Background: Omecamtiv Mecarbil

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.[9,10]

Omecamtiv mecarbil has been evaluated in 11 Phase 1 studies (Studies CY 1011, CY 1013, CY 1015, CY 1016, CY 1111, CY 1211 [20120255], 20080676, 20090229, 20090727, 20150134, and 20160159), 4 Phase 2a studies in subjects with chronic heart failure with reduced ejection fraction (HFrEF; Studies CY 1121, CY 1221, CY 1124, and CY 1021), 1 Phase 2b study in subjects with acute HF (Study 20100754), and 2 Phase 2b studies in subjects with HFrEF (Studies 20110151 and 20120227). In these studies, the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamic (PD) effects of OM were evaluated with intravenous infusions up to 72 hours and oral dosing up to 20 weeks.

In addition to the above studies, a Phase 3 cardiovascular outcomes study (Study 20110203 [GALACTIC-HF], NCT 02929329) in approximately 8000 subjects is underway to evaluate chronic dosing of the oral MR dosage form of OM for the reduction of cardiovascular death and HF events (defined by an urgent, unscheduled clinic/office/emergency department visit or hospital admission, with a primary diagnosis of HF) in subjects with HFrEF. A second Phase 3 study (CY 1031 [METEORIC-HF], NCT 03759392) is also being conducted to assess the effect of OM on exercise tolerance in subjects with chronic HFrEF and reduced exercise capacity. A summary of completed and ongoing clinical studies for OM is provided in the IB.[1]

The half maximal inhibitory concentration (IC_{50}) for the effect of omecamtiv mecarbil on human ether à go-go related gene (hERG) current was estimated to be 125.5 µM. Omecamtiv mecarbil did not inhibit or prolong QT interval in dogs at therapeutic concentrations.

Following oral solution administration of OM in healthy subjects, the time of maximum observed concentration (t_{max}) is approximately 0.5 hours and apparent terminal elimination half-life ($t_{1/2}$) is approximately 21 hours. Refer to the specific section of the IB for additional information related to the physical, chemical, and pharmaceutical properties and formulations. A detailed description of the chemistry, pharmacology, efficacy, and safety of OM is provided in the IB.[1]

1.2.3. Non-Amgen Non-Investigational Product Background: Moxifloxacin

Moxifloxacin is a broad-spectrum fluoroquinolone antibiotic that binds to and inhibits the hERG IKr α subunit and causes a mean increase of the QTc interval of 6 ms after a single 400-mg oral dose. Moxifloxacin is commonly used as a positive control in thorough QT (TQT) studies to satisfy the requirements of ICH E14.

Refer to the regional manufacturer package insert of AVELOX (moxifloxacin hydrochloride) tablets for additional information.[11]

1.3. Benefit-Risk Assessment

The following benefit-risk assessment supports the conduct of this trial. For more details on identified risks, see Appendix A of the OM IB.[1]

1.3.1. Therapeutic Context

This study will be conducted in healthy subjects without therapeutic intent. In particular, the subjects enrolled in the study would not be expected to benefit from exposure to the treatments used in this study.

1.3.2. Key Benefits

Subjects will not directly benefit from participating in the study. The data from the study will support the development of OM, which may address unmet medical need in the relevant patient population.

1.3.3. Risks

Myocardial ischemia and myocardial infarction have been observed in a healthy subject and in subjects with heart failure in clinical studies and are identified risks of OM. One healthy subject was reported to have signs and symptoms consistent with myocardial infarction following intravenous administration of 1 mg/kg/hr of OM. The subject experienced chest tightness, palpitations, lightheadedness, and feeling hot, in association with tachycardia, ECG changes, and troponin elevation. The maximum observed plasma OM concentration (C_{max}) associated with this event was estimated to be approximately 1540 ng/mL. Echocardiography following this event did not demonstrate any evidence of regional wall motion abnormality and a contrast enhanced cardiac magnetic resonance imaging (MRI) was negative for myocardial infarction/scar.

Excessive exposure to OM may result in prolongation of the systolic ejection time to an extent that reduces diastolic coronary filling. The reduced coronary filling could precipitate myocardial ischemia or infarction. Signs and symptoms of myocardial ischemia or infarction can include, but are not limited to, electrocardiographic changes consistent with myocardial ischemia (ST-segment depression), angina, chest or throat tightness, palpitations and/or tachycardia, lightheadedness, dizziness, hypotension, dyspnea, premature ventricular contractions, and troponin elevation. For more details on identified risks, see Appendix A of the OM IB.[1]

To mitigate the risk of myocardial ischemia or infarction in patients due to excessive exposure during the clinical development program, exposure to OM is controlled (to maintain plasma concentrations lower than 1000 ng/mL) through a PK-based dose adjustment strategy using an oral modified-release formulation to guide appropriate dosing (Section 3.3).

To limit the risk of excessive exposure to healthy subjects in the current study, which utilizes an OM oral solution, Part A will consist of a PK Evaluation Period, in which a 25-mg dose of OM will be given and PK assessed by subject. The mean C_{max} following a 25-mg dose is expected to be approximately 220 ng/mL and, assuming dose proportionality, the exposure following 50 mg is therefore expected to be approximately 440 ng/mL. Only those subjects with $C_{max} \leq 350$ ng/mL in Part A will be eligible to continue to Part B. Therefore, exposure in Part B is not expected to exceed 700 ng/mL, which is 55% lower than the predicted exposure that resulted in the cardiac event in 1 healthy subject.

As a result of administration of moxifloxacin, subjects may experience the following side effects: temporary changes in the electrical activity of the heart, palpitations, inflammation or rupture of the tendons, fainting spells, dizziness or lightheadedness, allergic reactions, nerve damage, convulsions, low blood sugar levels, and rupture or tearing of large blood vessels. However, at the dose level administered in the present trial and the very limited exposure, it is expected that these side effects will be mild in nature. Refer to the adverse reactions section of the regional manufacturer package insert of Avelox.[11]

Safety monitoring: safety assessments throughout the study include adverse event (AE) and serious adverse event (SAE) monitoring, ECGs, clinical examination, vital signs, and clinical chemistry.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESES

2.1. Objectives

The primary objective of the study is:

- To assess the effect of a single therapeutic (50 mg) oral dose of OM on the QT/QTc interval, relative to placebo, in healthy subjects.

The secondary objectives of the study are:

- To assess the PK of OM after a single oral dose to healthy subjects.
- To evaluate the effect of OM on other ECG parameters (hear rate [HR], PR and QRS intervals, and treatment-emergent T-wave abnormalities and presence of U-waves).
- To determine the plasma concentration-effect relationship for OM on the QT/QTc interval in healthy subjects.
- To evaluate assay sensitivity by evaluation of the positive control, a single 400-mg oral dose of moxifloxacin, on the QT/QTc interval in healthy subjects.
- To evaluate the safety and tolerability of OM after a single oral dose to healthy subjects.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary endpoint is the placebo-corrected change from baseline in QT interval corrected for HR based on the Fridericia correction (QTcF) interval (ΔΔQTcF) after OM dosing.

2.2.2. Secondary Endpoints

The following are secondary endpoints for this study:

- Pharmacokinetic parameters of OM including, but not limited to, C_{max}, t_{max}, $t_{1/2}$, apparent volume of distribution (V_Z/F), apparent total plasma clearance (CL/F), area under the concentration-time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t}), AUC from time 0 to infinity (AUC_{inf}), and the percentage of AUC_{inf} due to extrapolation ($\%AUC_{extrap}$)
- ΔΔQTcF after moxifloxacin dosing
- Change-from-baseline HR, QTcF, PR and QRS intervals (ΔHR, ΔQTcF, ΔPR and ΔQRS) after OM dosing
- Concentration-QTc analysis based on ΔΔQTcF after OM dosing
- Placebo-corrected ΔHR, ΔPR and ΔQRS (ΔΔHR, ΔΔPR and ΔΔQRS) after OM dosing
- Categorical outliers for QTcF, HR, PR, and QRS after OM dosing
- Frequency of treatment-emergent changes in T-wave morphology and U-wave presence after OM dosing
- Subject incidence of treatment-emergent adverse events (TEAEs)
- Changes in laboratory safety tests, vital signs, and ECGs.

Other noncompartmental PK parameters may be reported. In addition, plasma concentration will be determined and PK parameters will be calculated for moxifloxacin only if deemed necessary.

2.3. Research Hypothesis

The hypothesis is that OM does not prolong QTc intervals after administration of a single 50-mg oral dose and will be safe and well tolerated in healthy subjects.

3. INVESTIGATIONAL PLAN

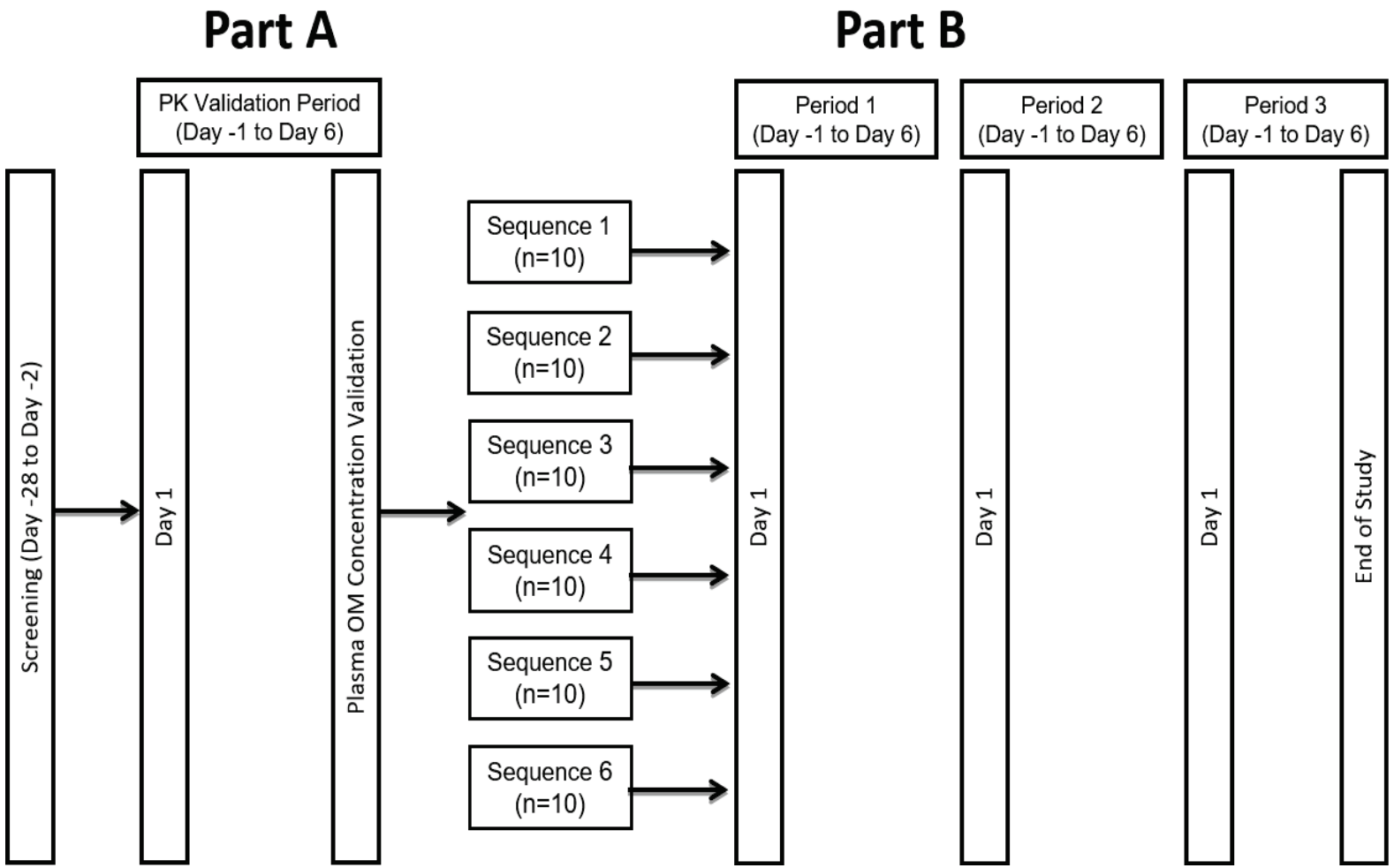
3.1. Overall Study Design and Plan

This will be a single-dose and randomized, single-center, 3-period, 3-treatment crossover study in healthy adult subjects to determine whether OM prolongs the QT/QTc interval after a single oral dose administration of 50 mg OM. The total duration of participation in the study will be approximately 55 days, including the screening period. The study will be conducted at a single clinical site.

The overall duration for individual subjects may vary depending on timing of sample shipment and analysis for Part A of the study, to confirm eligibility for Part B.

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic



Note: All study treatments will be separated by a washout period of at least 7 days (including between Part A and Part B).

Potential subjects will be asked to read and sign an Informed Consent Form (ICF). After informed consent is obtained, screening procedures and tests to establish subject eligibility to enter the study will be performed within 28 days before Day 1 in Part A (PK Evaluation Period). Study procedures are summarized in the Schedule of Assessments in Appendix 6. Adverse events and SAEs will be recorded from the time the ICF is signed.

Approximately 60 to 70 subjects will be enrolled in Part A in order to have 60 subjects (10 per sequence) enrolled in Part B. With approximately 60 subjects in Part B, it is estimated that approximately 48 evaluable subjects will have data from all 3 periods in Part B.

Treatment in Part A will consist of a single 25-mg OM oral dose (Treatment 1), after which subjects whose resulting C_{max} is $\leq$ 350 ng/mL will be randomized into Part B. Part B consists of 3 periods, in which a single treatment is given in each period. Treatments in Part B will consist of placebo (Treatment A), OM 50 mg (Treatment B), and moxifloxacin 400 mg (Treatment C). All study treatments (Part A and Part B/Period 1, Period 2 and Period 3) will be separated by a washout of at least 7 days.

Part A

- Treatment 1: 25-mg OM oral solution

A subject will be considered enrolled once he/she is deemed eligible by the Investigator and has received the first dose administration in Part A.

Subjects will be admitted to the research facility on Day -1 in Part A, at which time baseline procedures will be performed according to the Schedule of Assessments in Appendix 6. After an overnight fast of at least 10 hours, subjects will be administered treatment with 250 mL of water. No food will be allowed for at least 4 hours postdose. Water is allowed as desired except for 1 hour before and after drug administration.

Subjects will stay at the research facility until Day 3, and study assessments will be performed according to the Schedule of Assessments in Appendix 6. PK samples will be collected to determine plasma OM concentrations according to the Schedule of Assessments in Appendix 6. Subjects will be discharged after completion of Day 3 activities and will return for a safety follow-up visit on Day 6. PK results from Part A will be available prior to Part B. For subjects whose resulting C_{max} in Part A is > 350 ng/mL, the Day 6 visit will be considered their End of Study (EOS) visit.

Part B

- Treatment A: Placebo oral solution
- Treatment B: 50-mg OM oral solution
- Treatment C: 400-mg moxifloxacin oral tablet

After completing Part A, eligible subjects will be randomized to receive 3 treatments in 1 of 6 sequences, as follows:

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	C	B	A
6	B	A	C

Subjects will be admitted to the research facility on Day -1 of Period 1 in Part B, at which time Check-in procedures will be performed according to the Schedule of Assessments in Appendix 6. After an overnight fast of at least 10 hours, subjects will be administered treatment with 250 mL of water. No food will be allowed for at least 4 hours postdose. Water is allowed as desired except for 1 hour before and after drug administration. Placebo and OM treatments will be double-blinded and moxifloxacin treatment will be open-label. Subjects will receive standardized meals at approximately the same time.

Subjects will stay at the research facility throughout Part B, and study assessments will be performed according to the Schedule of Assessments in Appendix 6, including continuous ECG recording, digital ECG extractions, and PK sample collections to determine plasma OM and moxifloxacin concentrations. Additionally, standard safety assessments, including 12-lead ECGs and vital signs monitoring, will be performed and safety and tolerability monitoring will be conducted throughout the study. Subjects will be discharged after completion of Day 6 activities in Period 3.

All study treatments will be separated by a washout period of at least 7 days (including between Part A and Part B).

The EOS visit will complete a subject's participation in this study after Period 3. If there is a clinically significant clinical or laboratory abnormality that requires monitoring, the subject will be followed until resolution of the abnormality or until it is considered stable. If possible, EOS procedures will be performed on subjects who withdraw early from the study.

The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint, for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early. The planned primary completion date is the date when the last subject has completed the assessments on Day 6 of Period 3 in Part B.

The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

3.2. Discussion of Study Design

The purpose of this study is to evaluate the potential for OM to cause QT prolongation. As OM exposure affects cardiac contractility, the primary endpoint for this study will be the QTcF. A supratherapeutic dose of OM is unable to be administered due to the step-wise titration scheme needed to optimize OM dose and safety concerns in healthy subjects. A

crossover design has been selected, with subjects acting as their own controls to minimize inter-subject variability.

This study will be double-blinded for OM and placebo to control for bias in safety assessments, including safety ECGs, and open-label for moxifloxacin as the QTc effects and AEs of this drug are well characterized. The central ECG laboratory and ECG readers will be blinded to treatment sequence, timepoint, and subject.

The anticipated C_{max} resulting from the 50-mg OM dose used for the assessment of QTc effects will be consistent with that in Phase 3 and will be below 1200 ng/mL. However, to provide further assurance that subjects will not exceed 1200 ng/mL, this study incorporates an initial PK assessment at 25 mg to confirm that individual C_{max} values do not exceed 350 ng/mL; given the linear PK of OM, a subject with $C_{max} \leq 350$ ng/mL at 25 mg would be expected to have predicted exposure no higher than 700 ng/mL at 50 mg, and therefore below 1200 ng/mL.

This study will be conducted using healthy subjects to eliminate potential variables known to have an effect on ECG parameters (eg, concomitant drugs, diseases). Subjects will be randomized to treatment in an effort to ensure that baseline characteristics are evenly distributed across treatment sequences. The sample size in this study is driven by the need to perform a by-timepoint statistical analysis of the primary endpoint per the ICH E14 guidance.

Moxifloxacin will be included as a positive control to validate the sensitivity of the assay to detect small increases from baseline in QTc. Following single oral doses of 400 mg moxifloxacin, a QTc increase of 6 ms has occurred at t_{max}.[11] Moxifloxacin plasma samples will be collected and concentrations may be measured, but PK vs QTc modeling will not be performed, as the QT effects of moxifloxacin are well-known.

3.3. Selection of Doses in the Study

According to ICH E14, the highest therapeutic dose and a supratherapeutic dose are recommended for the QT/QTc study. The OM dose in ongoing Phase 3 studies is individualized using a PK-based titration to avoid excessive OM exposures (> 1200 ng/mL). The observed mean (standard deviation; SD) steady state C_{max} from a Phase 2 study (20110151) for 25 mg BID and 50 mg BID are 193 (58.5) ng/mL and 492 (115) ng/mL, respectively. A supratherapeutic dose will not be evaluated due to the identified risk of myocardial ischemia or infarction.

Based on Study 20160159, the 25-mg oral solution formulation resulted in a mean (SD) C_{max} of 220 (71.2) ng/mL after a single dose administration in healthy subjects. This exposure is well below the 1200 ng/mL threshold and the dose is proximal to the 50-mg dose, such that it is anticipated to provide a very reliable prediction of the C_{max} of 50 mg, given the linear PK of OM.

In Part B, OM treatment will be a 50-mg single dose of oral solution. The 50-mg oral solution dose should achieve therapeutic concentrations (range of 300 to 700 ng/mL). Moxifloxacin 400 mg is associated with an observed 6 ms increase in the mean placebo- and baseline-corrected QTc interval, which is within the range required by ICH.[17]

In summary, to attain clinically relevant concentrations, a single dose of 50 mg oral solution will be administered for the purpose of evaluating the proarrhythmic potential of OM as reflected by change in the QTc interval in healthy subjects.

4. SELECTION OF STUDY POPULATION

The Investigator will be expected to maintain a screening log of all potential study candidates, which includes limited information about the potential candidate (eg, date of screening).

Before any study-specific activities/procedures may be performed, the appropriate written informed consent must be obtained (see Appendix 5).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, will not be provided.

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the Screening visit or as otherwise stated:

1. Subject has provided informed consent before initiation of any study-specific activities/procedures.
2. Healthy male or healthy female subjects ≥ 18 to ≤ 50 years of age.
3. No history or evidence of clinically relevant medical disorders as determined by the Investigator at Screening.
4. Physical examination at Screening and vital signs, clinical laboratory values, and ECGs at Screening and Day -1 of each period are clinically acceptable to the Investigator.
5. Body mass index (BMI) ≥ 18.0 kg/m^2 and ≤ 30.0 kg/m^2.
6. Willing to maintain current general diet and physical activity regimen.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the Screening visit unless otherwise stated:

1. History or evidence of clinically significant disorder, condition, or disease not otherwise excluded that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
2. Any users of tobacco- or nicotine-containing products within 6 months before Day -1 of Part A.
3. History suggestive of esophageal (including esophageal spasm, esophagitis), gastric, or duodenal ulceration or bowel disease (including, but not limited to, peptic ulceration, gastrointestinal bleeding, ulcerative colitis, Crohn's disease, or irritable bowel syndrome); or a history of gastrointestinal surgery other than uncomplicated appendectomy.

4. History or current signs or symptoms of cardiovascular disease, including but not limited to myocardial infarction, congenital heart disease, valvular heart disease, coronary revascularization, or angina.
5. Known substance abuse (eg, alcohol, licit or illicit drugs) within 1 year prior to Screening.
6. Subjects with poor peripheral venous access.
7. Use of any medications/substances outside the allowed timeframes as specified in Section 6.1.2.
8. Currently receiving treatment in another investigational device or drug study, or less than 3 months, or 5 half-lives if longer, prior to receiving the first dose of study drug. Other investigational procedures while participating in this study are excluded.
9. Donated blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening.
10. Subjects who were previously exposed to OM.
11. Hepatic impairment defined by a total bilirubin (TBL) ≥ 1.2 times the upper limit of normal (ULN), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > ULN (and confirmed upon repeat).
12. Systolic blood pressure (BP) > 140 mmHg or < 90 mmHg, or diastolic BP > 90 mmHg.
13. QTcF interval > 450 msec in male or > 470 msec in female or history/evidence of long QT syndrome, or PR of ≥ 200 msec; or 2nd degree atrioventricular (AV) block or 3rd degree AV block, or heart rate > 100 bpm (and confirmed upon repeat, except 2nd or 3rd degree AV block, which are exclusionary based on a single finding).
14. Troponin I or creatine kinase MB fraction (CK-MB) > ULN at Screening or Check-in for Part A or B.
15. Estimated glomerular filtration rate (eGFR) < 80 mL/min/1.73 m^2 at Screening as calculated by the Modified Diet in Renal Disease (MDRD) equation;
16. Any positive test for drugs, cotinine (tobacco or nicotine use), and/or alcohol use.
17. Positive hepatitis panel and/or positive human immunodeficiency virus test. Subjects whose results are compatible with prior immunization may be included.
18. Subject has known sensitivity to any of the products or components to be administered during dosing, including history of hypersensitivity to moxifloxacin or any member of the quinolone class of antibacterials.
19. History of tendon rupture or connective tissue disorders.
20. Female subjects with a positive pregnancy test.
21. Female subjects lactating/breastfeeding or who plans to breastfeed during the study through 90 days after the EOS visit.
22. Unwilling to adhere to contraceptive requirements through 90 days after the EOS visit (see Appendix 7).

23. Unwilling to abstain from sperm and ovum donation through 90 days after the EOS visit.
24. Male subjects with a female partner of childbearing potential and not willing to inform his partner of his participation in this clinical study.
25. Male subjects with a pregnant partner or partner planning to become pregnant while the subject is on study through 90 days after the EOS visit.
26. Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the subject and Investigator's knowledge.

If generic screening was performed within the specified study screening window, selected study-specific procedures will be repeated either at an additional Screening visit or on admission to the Clinical Research Unit on Day -1 of Part A.

4.3. Screen Failures and Rescreening

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study due to not meeting eligibility criteria. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious Adverse Events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Screen failures may only be rescreened once at the discretion of the Investigator in consultation with the Sponsor.

4.4. Subject Number and Identification

Subjects will be given a unique identification number used at Screening. Subjects will be assigned a subject number at the time of dosing in Part A. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, Subjects 0101, 0102, 0103). Replacement subjects (Section 4.5) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 0101).

Subjects meeting the PK Evaluation criteria will continue on to Part B, and will be randomized to a treatment sequence and given a randomization number on Day 1 of Part B Period 1.

Subjects will be identified only by subject number on all trial documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.5. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee)

- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn from dosing, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all EOS assessments, if possible (Appendix 6). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of adverse events thought to be related to the study treatment will generally not be replaced.

4.6. Study Termination

The Sponsor may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP. Both the Sponsor and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement (CTA). The Investigator is to notify the institutional review board (IRB)/independent ethics committee (IEC) in writing of the study's completion or early termination and send a copy of the notification to the Sponsor. Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply IP and by what mechanism, after termination of the study.

In addition, the study may be terminated by the Sponsor at any time and for any reason. If the Sponsor decides to terminate the study, they will inform the Investigator as soon as possible.

4.7. Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product 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 investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Assessments (Appendix 6) including different options of Follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on study to ensure safety surveillance and/or collection of outcome data.

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- Decision by the Sponsor
- Lost to Follow-up
- Death
- Protocol deviation
- Noncompliance
- Adverse events
- Subject request
- Pregnancy

In addition, a subject must be discontinued from study treatment if either of the following occur:

- QTcF > 500 ms (as confirmed by 2 ECGs taken within 1 hour)
- Increase in QTcF > 60 ms compared to predose baseline.

5. STUDY TREATMENTS

Study treatment is defined as any IP, non-investigational product (non-IP), placebo, or medical device intended to be administered to a study subject according to the study protocol.

Note that in several countries, IP and non-IP are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

5.1. Investigational Products

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 1.

Table 1: Study Treatments

Study Treatment Name	Amgen Investigational Product: Omecamtiv Mecarbil (OM)	Amgen Investigational Product: Placebo Water	Non-Amgen Non-Investigational Product: Moxifloxacin
Dosage Formulation	Oral solution	Water	Oral tablets
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	25 mg (Part A); single dose 50 mg (Part B); single dose	Not applicable; single dose	400 mg; single dose
Route of Administration	Oral	Oral	Oral
Accountability	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's case report form (CRF).	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's CRF.	The quantity administered, date administered, and lot number of product is to be recorded on each subject's CRF.
Dosing Instructions	The Principal Investigator/designee will administer the treatment after the completion of all predose procedures and after a fast of at least 10 hours.	The Principal Investigator/designee will administer the treatment after the completion of all predose procedures and after a fast of at least 10 hours.	The Principal Investigator/designee will administer the treatment after the completion of all predose procedures and after a fast of at least 10 hours. One tablet should be taken with 8 oz. of water. Tablet should not be broken or chewed.

All supplies of IP, both bulk and subject-specific, will be stored in accordance with the manufacturer's or pharmacy's instructions. Until dispensed to the subjects, the study drugs will be stored at the study site in a location that is locked with restricted access.

5.1.1. Dose Modification

Dose modification is not permitted with this study.

5.1.2. Guidance for Signs or Symptoms Consistent with Myocardial Ischemia or Infarction

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. A series of troponin samples should be analyzed at the local laboratory if possible. If possible, a series of samples for CK-MB should be collected for analysis by the local laboratory, and a series of 12-lead ECGs should be collected until the symptoms have reverted or a diagnosis has been established. Amgen will be notified of any subject experiencing clinical signs or symptoms of myocardial ischemia or infarction.

5.1.3. Treatment of Overdose

Excessive exposure to OM may result in prolongation of the systolic ejection time to an extent that reduces diastolic coronary filling. The reduced coronary filling could precipitate myocardial ischemia or infarction.

No antidote for OM currently exists. In the event of an overdose, health care providers should be especially vigilant for signs and symptoms of myocardial ischemia and should treat as clinically indicated.

5.1.4. Medical Devices

No investigational medical device(s) will be used in this study.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care. Non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by the Sponsor (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

5.1.5. 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 or device after it is released for distribution to market or clinic by either Amgen (Sponsor) or by distributors and partners for whom Amgen manufactures the material. This includes any investigational product (OM) provisioned and/or repackaged/modified by the Sponsor.

Any product complaints associated with an IP (OM) supplied by Amgen (Sponsor) are to be reported according to the instructions provided in the IPIM.

5.2. Non-Amgen Non-investigational Product

Moxifloxacin hydrochloride non-IP will be used in this study (see Section 1.2.3).

5.3. Study Treatment Administration

For each treatment period, subjects will fast overnight from food (not including water) for at least 10 hours. Each dose of study treatment (moxifloxacin, OM, placebo) will be administered orally. Except as part of the dose administration, subjects will restrict their consumption of water for 1 hour predose and for 1 hour postdose; at all other times during the study, subjects may consume water ad libitum. Subjects will continue fasting for at least 4 hours postdose.

Subjects will be dosed in numerical order while standing. As soon as possible after dosing, subjects will be instructed to lie down supine or semi-recumbent and will remain supine or semi-recumbent for 2 hours after treatment administration, except as necessitated by the study procedures or occurrence of an AE.

All study treatments will be separated by a washout period of at least 7 days (including between Part A and Part B).

Additional details on the study treatment administration will be provided in the IPIM.

5.4. Randomization

A subject number will be assigned at the time of dosing in Part A. Subjects meeting the PK Evaluation criteria will continue on to Part B, and will be randomized to a treatment sequence on Day 1 of Part B Period 1. The randomization date is to be documented in the subject's medical record and on the enrollment eCRF. A computer-generated randomization schedule and emergency code-break envelopes will be provided to the clinical site. Randomization details will be included in the randomization specification.

5.5. Blinding

This is a partially double-blind study. Part A will be open-label. In Part B, placebo and OM treatments will be double-blinded, moxifloxacin treatment will be open-label, and the core ECG lab will be blinded to all treatment information. Except for the moxifloxacin treatment in one of 3 periods in Part B, treatment assignment will be blinded to all subjects, site personnel, the Medical Monitor, Clinical Research Associate(s), as described below. The bioanalytical lab and Amgen Clinical Pharmacology Modeling Simulation group will be unblinded, and there will additionally be an unblinded Clinical Research Associate.

5.5.1. Site Personnel Access to Individual Treatment Assignments

A subject's assigned treatment sequence in Part B is to only be unblinded by the Investigator when knowledge of the treatment other than moxifloxacin in any given period is essential for the further management of the subject on this study or may potentially impact the safety of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation. It is encouraged that the Study Manager be notified before the blind is broken unless the Investigator believes that identification of the study treatment is required for a medical emergency. If this is not possible, the Study Manager must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

5.5.2. Access to Individual Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information is not to be distributed to the study team, investigators, or subjects before the study being formally unblinded (eg, the formal unblinding may occur at the final analysis rather than during the primary analysis) except as specified (eg, Section 5.5.1).

The bioanalytical laboratory will be unblinded and receive the randomization schedule to facilitate analysis of the required concentration samples.

If an SAE or significant event occurs in a subject (eg, suspected unexpected serious adverse reaction [SUSAR]) and the Sponsor determines that knowledge of the subject's treatment sequence may be necessary to protect the safety of other subjects in this or other studies of

OM, the Sponsor (or designee) may be unblinded to that subject's assigned treatment sequence following the same procedures as in Section 5.5.1.

5.6. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory of OM, placebo, and moxifloxacin will be performed.

6. STUDY RESTRICTIONS

6.1. PRIOR AND CONCOMITANT THERAPIES

6.1.1. Prior Therapies

Prior therapies that were being taken/used from 30 days before enrollment through the first dose of study treatment will be recorded.

6.1.2. Concomitant Therapies

Concomitant therapies are to be recorded from first dose of IP through the EOS, during each visit and as specified in the Schedule of Assessments in Appendix 6. Any concomitant medication use reported throughout the study will be recorded in the source documents and the eCRF. The therapy name, indication, dose, unit, frequency, route, start date, and stop date will be recorded.

The following medications/substances are prohibited for the periods stated:

Medication/Substance Type[a,b]	**Examples (including, but not limited to)**	**Restriction Period Start**	**Restriction Period End**
Over-the-counter or prescription medications	Antacids, H2-blockers, proton pump inhibitors, inhibitors of CYP3A4, CYP2D6 or P-glycoprotein (P-gp), aspirin, non-steroidal anti-inflammatory drugs (NSAIDS)	Within 14 days or 5 half-lives (whichever is longer) prior to receiving the dose in Part A	EOS visit

Substances known to affect drug metabolism (CYP inducers)	Rifampin, corticosteroids, anticonvulsants	Within 30 days or 5 half-lives (whichever is longer) prior to receiving the dose in Part A	EOS visit
Substances known to affect drug metabolism (Inhibitors of CYP3A4 or P-gp)	Ketoconazole, itraconazole, human immunodeficiency virus (HIV) protease inhibitors, nefazodone, cyclosporine, erythromycin, clindamycin, tetracycline, clarithromycin	Within 14 days or 5 half-lives (whichever is longer) prior to receiving the dose in Part A	EOS visit
Substances known to affect drug metabolism (Inhibitors of CYP2D6)	Fluoxetine, paroxetine, bupropion, quinidine, cinacalcet	Within 14 days or 5 half-lives (whichever is longer) prior to receiving the dose in Part A	EOS visit

a Acetaminophen (up to 2 g per day) for analgesia and hormone replacement therapy (eg, estrogen, thyroid) will be allowed.

b All herbal medicines (eg, St. John's wort), vitamins, and supplements consumed by the subject within the 30 days before receiving the first dose of OM, and continuing use, if applicable, will be reviewed by the Investigator.

Subjects will refrain from use of any prescription or nonprescription medications/products during the study until the EOS visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent. Throughout the study, the Investigator may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care.

6.2. Diet

While confined at the clinical site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. The clinical site will provide standardized meals, in addition to light snacks and drinks to the subjects during the in-residency period. The timing and composition of the meals for individual subjects should be the same between periods. For safety laboratory tests, subjects will be fasted at least 8 hours before collection of blood samples at Check-in for Parts A and B. Subjects will fast overnight at least 10 hours prior to dose administration, and will continue fasting for at least 4 hours after.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to Day -1 of Part A until after the EOS visit.

Caffeine-containing foods and beverages will not be allowed from 7 days before each visit (including Screening) and while confined to the research unit.

Subjects must refrain from alcohol consumption within 48 hours before Check-in for each period and while confined to the research unit. For the remainder of the study, the use of alcohol by subjects should be limited to no more than 1 unit per day for females and 2 units per day for males (1 unit being equivalent to 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of 80 proof distilled spirits).

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine -containing products within 6 months prior to Screening until the EOS visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 72 hours before each blood collection for clinical laboratory tests. Subjects should otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, and platelets from 6 weeks prior to Screening until 3 months after the EOS visit.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- continuous ECG extraction window
- pharmacokinetic blood samples
- safety assessments
- any other procedures.

7.1. General Assessments

7.1.1. Demographics

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

7.1.2. Medical History

At timepoints specified in Appendix 6, the Investigator or designee will collect a complete medical and surgical history. Medical history will include information on the subject's concurrent medical conditions and any events occurring prior to the first dose of study treatment. All findings will be recorded on the medical history eCRF.

7.1.3. Physical Measurements

Height (in centimeters) and weight (in kilograms) should be measured without shoes. Body mass index should be calculated using the following formula:

BMI (kg/m^2) = weight (kg)/[height (cm)/100]^2

7.2. Electrocardiography Assessments

7.2.1. Continuous 12-lead Electrocardiogram Recording

In Part B, continuous 12-lead digital ECG recording will be performed as specified in Appendix 6. The continuous 12-lead digital ECG data will be stored onto SD memory cards. The ECGs to be used in the analyses will be selected by predetermined timepoints as defined in Appendix 6 and will be read centrally by ERT.

The following principles will be followed in ERT's core laboratory:

- ECG analysts are blinded to the subject, visit, and treatment allocation.
- Baseline and on-treatment ECGs for a particular subject will be over-read on the same lead and will be analyzed by the same reader.

The primary analysis lead is lead II. If lead II is not analyzable, then the primary lead of analysis will be changed to another lead for the entire subject data set.

The 12-lead ECGs will be extracted in up to 10 replicates at the predefined timepoints with subjects resting for at least 10 minutes prior to and 5 minutes after each nominal time.

7.2.1.1. TQT Plus Extraction Technique

Ten 14-second digital 12-lead ECG tracings will be extracted from the continuous recordings using the 'TQT Plus method', a computer-assisted and statistical process utilized by ERT. The method enables extraction of ECGs with the lowest HR variability and noise within the protocol-specified extraction time window (eg, the HR and QT changes from beat to beat in the range of < 10%). At each protocol-specified timepoint, 10 ECG replicates will be

extracted from a 5-minute "ECG window" (typically, the last 5 minutes of the 15-minute period when the subject is maintained in a supine or semi-recumbent quiet position).

7.2.1.2. Expert-Precision QT Analysis

Expert-precision QT analysis will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates. Statistical quality control procedures are used to review and assess all beats and identify "high" and "low" confidence beats using several criteria, including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely).
- Time interval between 2 successive R-waves of the QRS signal on the electrocardiogram (RR) values exceeding or below certain thresholds (biologically unlikely).
- Rapid changes in QT, QTc or RR from beat to beat.

Measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates that are deemed "high confidence" will be performed using COMPAS software. All low-confidence beats will be reviewed manually and adjudicated using pass-fail criteria. The final QC assessment will be performed by a cardiologist. The beats found acceptable by manual review will be included in the analysis. The median QT, QTc, and RR value from each extracted replicate will be calculated, and then the mean of all available medians from a nominal timepoint will be used as the subject's reportable value at that timepoint.

Categorical T-wave morphology analysis (Table 2) and the measurement of PR and QRS intervals will be performed manually in 3 of the 10 ECG replicates at each timepoint. Each fiducial point (onset of P-wave, onset of Q-wave, offset of S-wave, and offset of T-wave) will be electronically marked.

Table 2: T-wave Morphology Categories (Assessed Manually)

Category	Description
Normal T-wave	Any T-wave not meeting any criterion below
Flat T-waves	T amplitude < 1 mm (either positive or negative) including flat isoelectric line
Notched T-wave (+)	Presence of notch(es) of at least 0.05 mV amplitude on ascending or descending arm of the positive T-wave
Biphasic	T-wave that contains a second component with an opposite phase that is at least 0.1 mV deep (both positive and negative/positive and polyphasic T-waves included)
Normal T-wave (-)	T amplitude that is negative, without biphasic T-wave or notches

Category	Description
Notched T-wave (-)	Presence of notch(es) of at least 0.05 mV amplitude on descending or ascending arm of the negative T-wave

In addition to the T-wave categorical analysis, the presence of abnormal U-waves is to be noted.

7.2.2. Safety 12-Lead Electrocardiogram

Standard safety 12-lead ECGs will be recorded at the times indicated in the Schedule of Assessments in Appendix 6 in each treatment period after the subject has been supine or semi-recumbent and at rest for at least 5 minutes to detect any immediate ECG effects for subject safety. These ECGs will be viewed by the Investigator locally, with the Investigator only blinded to OM or placebo treatment.

Any on-therapy ECG with a QTcF > 500 ms (as defined by automatically measured intervals) should be confirmed by a second ECG taken within 1 hour. If the second safety ECG confirms a QTcF > 500 ms, the subject should be discontinued from the study.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests that a more detailed assessment of ECGs is required.

7.2.3. Telemetry

Cardiac rhythm monitoring will be done by telemetry at the times indicated in Appendix 6.

7.3. Pharmacokinetic Assessments

7.3.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples for analysis of plasma OM and moxifloxacin concentrations will be obtained from all subjects in each treatment period of this study to ensure uniform study conditions. Analyses for OM will be performed on samples from subjects who receive OM and analyses for moxifloxacin may be performed (if needed) on samples from subjects who receive moxifloxacin. No analysis of blood samples taken from subjects during the placebo treatment period is planned. All other samples will be saved for analysis if needed.

Blood samples (approximately 1 × 4 mL) for OM and for moxifloxacin (approximately 1 × 2 mL) will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 6. Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.3.2. Analytical Methodology

Plasma concentrations of OM and potentially moxifloxacin will be determined using a validated analytical procedure. Specifics of the analytical method will be provided in separate Bioanalytical Reports.

7.4. Safety and Tolerability Assessments

7.4.1. Adverse Events and Serious Adverse Events: Time period and Frequency for Collecting and Reporting Safety Event Information

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF until the subject's completion of the study. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as "How have you been feeling since you were last asked?", at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

Adverse Events

Adverse events possibly related to any study procedures are reported from signing of the ICF. All other AEs are reported after the first dose of study treatment. The Investigator is responsible for ensuring that all AEs observed by the Investigator or reported by the subject that occur from signing of the ICF or after the first dose of study treatment as specified above, through the end of the study are reported using the appropriate eCRF.

The AE grading scale to be used in this study will be the Amgen Standard Grading Scale and is described in Appendix 1.

The investigator is responsible for ensuring that all AEs observed by the investigator or reported by the subject from first dose of study treatment through the last dose of study treatment or through the end of study visit, **whichever is later,** are recorded/reported using the appropriate eCRF.

Serious Adverse Events

The investigator is responsible for ensuring that all SAEs observed by the investigator or reported by the subject that occur after signing of the ICF through 30 days after the last dose of study treatment, are recorded/ reported using the appropriate eCRF **and** recorded/reported on the paper-based Serious Adverse Event Report Form (described in Appendix 1).

All SAEs will be collected, recorded and reported to Amgen (Sponsor) within 24 hours of the investigator's knowledge of the event. The investigator will submit any updated SAE data to Amgen (Sponsor) within 24 hours of it being available.

Any AEs and remedial action required will be recorded in the subject's source data. The nature, time of onset, duration, and severity will be documented, together with the Investigator's (or designee's) opinion of the relationship to study drug.

Serious Adverse Events After the Protocol-Required Reporting Period

There is no requirement to monitor study subjects for SAEs following the protocol-required reporting period or after end of study. However, these SAEs can be reported to Amgen. Per

local requirements in some countries, investigators are required to report SAEs that they become aware of after end of study. If SAEs are reported, the investigator is to report them to the Sponsor within 24 hours following the investigator's knowledge of the event using the paper-based Serious Adverse Event Report Form.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the Sponsor's safety database as clinical trial cases and handled accordingly based on relationship to investigational product (OM).

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs and SAEs will be followed, where possible, until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up. This will be completed at the Investigator's (or designee's) discretion.

All new information for previously reported SAEs must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the SAE must be consistent with that recorded on the appropriate eCRF.

Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of an SAE, this information must be submitted to the Sponsor.

Prompt notification by the investigator to the sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Part B of the study - to comply with worldwide reporting regulations for SAEs, the treatment assignment of subjects who develop serious, unexpected, and related AEs may be unblinded

by Amgen before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team, as appropriate. Investigators will receive notification of related SAE reports sent to regulatory authorities in accordance with local requirements.

Safety Monitoring Plan

Subject safety will be routinely monitored as defined in the Sponsor's safety surveillance and signal management processes.

7.4.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 6. Clinical laboratory evaluations are listed in Appendix 3.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 6. For all female subjects, a pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

The Investigator (or designee) is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the appropriate CRF. The Investigator (or designee) must determine 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 [or designee's] judgment) are not to be recorded as AEs. However, laboratory value changes that require treatment or adjustment in current therapy are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as AEs.

7.4.3. Vital Signs

Supine (or semi-recumbent) BP, supine (or semi-recumbent) pulse rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests that a more detailed assessment of vital signs is required.

Vital signs measurements will be taken singly and will be repeated once if outside the relevant clinical reference range.

Subjects must be supine or semi-recumbent for at least 5 minutes before BP and pulse rate measurements.

7.4.4. Physical Examination

A full physical examination and symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 6.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

With approximately 60 enrolled subjects, it is estimated that approximately 48 evaluable subjects will have data from all 3 periods in Part B.

Based on the calculation of the sample size for a TQT study[12], assuming a 1-sided 5% significance level and a within-subject standard deviation (SD) of 7 msec for ΔQTcF, and a true mean difference of 3 msec in ΔQTcF between OM and placebo, a sample size of 48 evaluable subjects would be expected to provide 99.5% power to demonstrate that the upper bounds of all the 2-sided 90% confidence intervals (CIs) on ΔΔQTcF will fall below 10 msec for up to 8 timepoints. With the within-subject SD of 8 msec and other similar assumptions, the power will decrease to 96.5%.

Determination of sample size for assay sensitivity:

Assuming a 1-sided 5% significance level and a within-subject SD of 7 msec for ΔQTcF, a sample size of 48 evaluable subjects will provide a power of 99.9% to exclude a mean difference of 5 msec in ΔQTcF between moxifloxacin and placebo groups from the lower bound of the 2-sided 90% CI on ΔΔQTcF at at least 1 of the 3 prespecified timepoints. With the within-subject SD of 8 msec and other similar assumptions, the power will decrease to 99%.

8.2. Analysis Populations

The full analysis set (FAS) includes all randomized subjects who have received at least 1 dose of each study treatment (OM, moxifloxacin, and placebo).

The PK population will include all subjects who received at least 1 dose of OM and have evaluable PK data. Any subject who experiences emesis within 4 hours of dosing or diarrhea within 24 hours of dosing may be excluded from the PK analysis.

The QT/QTc analysis set will include all subjects in FAS with measurements at baseline as well as on-treatment with at least 1 postdose timepoint with a valid ΔQTcF value in Part B. The QT/QTc analysis set will be used for the by-timepoint and categorical analyses of cardiodynamic ECG parameters.

The PK/QTc analysis set will include all subjects who are in both the QT/QTc and PK analysis sets with at least 1 pair of postdose PK and QTcF data from the same timepoint. The PK/QTc analysis set will be used for the concentration-QTc analysis in Part B.

The safety analysis set will include all subjects who receive at least 1 dose of study treatment.

8.3. Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the EOS, as defined in Section 3.1.

8.3.1. Primary Analysis

Primary analysis will be conducted after all subjects have either completed all the scheduled study visits or have early terminated from the study. At that time, the database will be cleaned, processed, and locked. Based on the locked data, cardiodynamic, PK, and safety analyses will be performed.

8.3.2. General Considerations

Summary statistics for continuous variables will include number of subjects, mean, median, SD or standard error, minimum, and maximum. For categorical variables, frequency and percentage will be given.

Safety data will be analyzed and reported by treatment (OM, placebo, or moxifloxacin).

Statistical inferences will be provided for analyses of primary endpoints. Unless specified otherwise, all statistical tests are 2-sided with a significance level of 0.05; no statistical inference and imputation will be conducted for analyses of safety endpoints.

8.3.3. Cardiodynamic ECG Assessments

The Cardiac SAP will provide details on the planned electrocardiography analyses.

8.3.3.1. Baseline for Cardiodynamic ECG Assessments

For all continuous ECG parameters from each period, baseline will be the average of the measured ECG intervals from the 3 predose timepoints (-1.25, -1, and -0.75 hours) for the respective period.

8.3.3.2. Primary Cardiodynamic Analysis

The primary analysis of the QT/QTc data will be the "by-timepoint" analysis for QTcF, based on a linear mixed-effects model with ΔQTcF as the dependent variable; period, sequence, time (categorical), treatment (OM, moxifloxacin, and placebo), and time-by-treatment interaction as fixed effects; and baseline QTcF as a covariate. An unstructured covariance matrix will be specified for the repeated measures at timepoints for subject within-treatment period. If the model with an unstructured covariance matrix fails to converge, other covariance matrices such as compound symmetry and autoregressive will be considered. The model will also include a subject-specific random effect. If the fixed effects for period and/or sequence should prove to be nonsignificant (ie, if the p-value > 0.1), these effects may be removed from the model and the analysis will be repeated without those covariates. From this analysis, the least squares (LS) mean and 2-sided 90% CI will be calculated for the contrast "OM versus placebo" at each postdose timepoint, separately. If the upper bound of the CI lies below 10 msec for all postdose timepoints, OM will be concluded not to have a significant effect on QT interval prolongation.

8.3.3.3. Secondary Cardiodynamic Analyses

For HR, PR, and QRS intervals, the analysis will be based on the change-from-baseline post-dosing (ΔHR, ΔPR, and ΔQRS). The same model will be used as described for QTcF in

the by-timepoint analysis. The LS mean, standard error, and 90% CI from the statistical modeling for both change-from-baseline and placebo-corrected change-from-baseline values will be listed in tables and graphically displayed.

8.3.3.4. Assay Sensitivity

The analysis to show assay sensitivity will be based on the change-from-baseline post-dosing QTcF of moxifloxacin. The same model will be used as described for the primary analysis. For the timepoints 2, 3, and 4 hours after dose administration, the contrast in treatment ΔΔQTcF = "moxifloxacin – placebo" will be tested against the 1-sided null hypothesis ΔΔQTcF ≤ 5 msec at the 5% level. Multiplicity will be controlled using the Hochberg procedure.[13] If after this procedure QTc (ΔΔQTcF) is significantly larger than 5 msec for at least 1 timepoint, assay sensitivity will be considered shown. In addition, 2-sided 90% CIs will be obtained for the contrast at all timepoints and used in the figures.

8.3.3.5. Categorical Analyses

The results for categorical outliers, T-wave morphology, and U-wave presence will be summarized in frequency tables with counts and percentages for both number of subjects and number of timepoints. For categorical outliers, the number (percentage) of subjects as well as timepoints that had increases in absolute QTcF values > 450 and ≤ 480 msec, > 480 and ≤ 500 msec, or > 500 msec, and changes from predose baseline of > 30 and ≤ 60 msec, or > 60 msec; increase in PR from predose baseline > 25% to a PR > 200 msec; increase in QRS from predose baseline > 25% to a QRS > 120 msec; decrease in HR from predose baseline > 25% to a HR < 50 bpm; and increase in HR from predose baseline >25% to a HR > 100 bpm will be determined. For T-wave morphology and U-wave presence, the analyses will be focused on change from baseline (ie, treatment-emergent changes).

Outliers for HR and PR, QRS, QT, and QTc intervals will be summarized. New ECG morphological changes will be summarized. "New" means not present on any baseline ECG and becomes present on at least 1 on-treatment ECG.

8.3.4. Pharmacokinetic Analyses

The plasma PK parameters of OM will be calculated using standard noncompartmental methods. Plasma concentrations and PK parameters for OM and potentially plasma concentrations for moxifloxacin will be summarized by descriptive statistics. No formal statistical analyses are planned.

The following PK parameters will be calculated whenever possible, based on the plasma concentrations of OM:

C_{max}	maximum observed concentration
t_{max}	time to maximum observed concentration
AUC_{0-t}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC_{inf}	area under the concentration-time curve from time 0 to infinity

$\%AUC_{extrap}$	percentage of AUC_{inf} that is due to extrapolation
$t_{1/2}$	apparent terminal elimination half-life
CL/F	apparent total plasma clearance
V_Z/F	apparent volume of distribution

Other PK parameters may also be calculated. Moxifloxacin plasma samples may be assayed and PK parameters will be calculated only if deemed necessary.

8.3.5. Pharmacokinetic/Electrocardiography Analyses

The Cardiac SAP will provide details on the planned PK/electrocardiography analyses.

The concentration-QTc analysis, based on ΔΔQTcF, will be reported separately. That is, for the placebo adjustment, the individual ΔQTcF for placebo calculated at a specific timepoint is subtracted from ΔQTcF for the same subject on OM at the same timepoint to generate ΔΔQTcF. The relationship between OM plasma concentration and ΔΔQTcF will be investigated by linear mixed-effects modeling with ΔΔQTcF as the dependent variable, time-matched concentration of OM as the explanatory variate, centered baseline QTcF (ie, baseline QTcF for individual subject subtracting the population mean baseline QTcF for all subjects in the same period) as an additional covariate, a fixed intercept, and subject as a random effect for both intercept and slope, when applicable.

The geometric mean of the individual C_{max} values for subjects on each of the active dose groups will be determined, respectively. The predicted population average ΔΔQTcF (ie, slope estimate × concentration + intercept) and its corresponding 2-sided 90% CI at the observed geometric mean C_{max} of OM will be obtained.

The plot of the observed median-quantile OM concentrations and associated mean ΔΔQTcF (2-sided 90% CI) together with the regression line presenting the predicted ΔΔQTcF (2-sided 90% CI; as described by Tornøe et al)[14] will be used to evaluate the adequacy of the model fit to the assumption of linearity and the impact on quantifying the exposure response. For evaluation of the heart rate-corrected QT interval, a scatter plot and a quantile plot of QTcF and RR intervals by treatment with regression line and a linear mixed-effects line (90% CI), respectively, will also be given. Additional exploratory analyses (via graphical displays and/or model fitting) will include accounting for a delayed effect (hysteresis) and the justification for the choice of PD model (linear versus nonlinear) as follows.

8.3.5.1. Investigation of Hysteresis

Hysteresis will be assessed based on joint graphical displays of the LS mean difference between ΔQTcF under OM and under placebo (ΔΔQTcF) for each postdose timepoint and the mean concentrations of OM at the same timepoints. In addition, hysteresis plots will be given for LS mean ΔΔQTcF and the mean concentrations. If a QT effect (ΔΔQTcF) > 10 msec cannot be excluded from the by-timepoint analysis and if a delay between peak ΔΔQTcF and peak plasma concentration in the plot (ΔΔQTcF versus OM) of more than 1 hour is observed, other C-QTc models, such as a model with an effect compartment, may be explored. With the

provision stated above, hysteresis will be assumed if the curve of hysteresis plot shows a counterclockwise loop.

8.3.5.2. Appropriateness of a Linear Model

To assess the appropriateness of a linear model, normal Q-Q plots for the standardized residuals and random effects, and plots of standardized residuals versus concentration and versus fitted values and versus centered baseline QTcF will be produced. The scatter plots of standardized residuals versus concentration and versus centered baseline QTcF by LOESS fitting (ie, locally weighted scatter plot smoothing as described by Cleveland)[15] will also be produced with optimal smoothing parameters selected by the Akaike information criterion with a correction.[16] A scatter plot of observed concentration and ΔΔQTcF with LOESS line (90% CI) and linear regression line will also be provided to check the assumption of linear concentration-QTc relationship. If there is an indication that a linear model is inappropriate, additional models will be fitted, in particular, an E_{max} model.

The concentration-QTc analysis will then be repeated for the model found to best accommodate the nonlinearity detected.

8.4. Safety Analyses

8.4.1. Adverse Events

The number and percentage of subjects reporting any TEAEs will be tabulated by Medical Dictionary for Regulatory Activities system organ class and preferred term. Tables of fatal AEs, SAEs, AEs leading to withdrawal from IP or other protocol-required therapies, and significant TEAEs will also be provided. Subject-level data may be provided instead of tables if the subject incidence is low.

8.4.2. Clinical Laboratory Tests

Key safety laboratory endpoints will be summarized in descriptive statistics. Details will be provided in the SAP.

8.4.3. Vital Signs

The analyses of vital signs, including systolic BP, diastolic BP, pulse, and temperature, will be summarized using the descriptive statistics at each scheduled timepoint.

8.4.4. Physical Measurements

The analyses of height, weight, and BMI measurements will include summary statistics at baseline.

8.4.5. Safety 12-Lead Electrocardiograms

Summaries over time and/or changes from baseline over time will be provided for all safety ECG parameters. Subjects' maximum change from baseline in QTcF 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.

8.5. Interim Analysis

No interim analyses are planned for this study.

9. REFERENCES

1. Omecamtiv mecarbil (AMG 423) Investigator's Brochure. Edition 14.1. Thousand Oaks, CA: Amgen Inc.; 26 October 2018.

2. Hilfiker-Kleiner D, Landmesser U, Drexler H. Molecular mechanisms in heart failure. Focus on cardiac hypertrophy, inflammation, angiogenesis, and apoptosis. *J Am Coll Cardiol*. 2006;48: Suppl A:A56-66.

3. López-Sendón J. The heart failure epidemic. *Medicographia*. 2011;33:363-369.

4. Konstam M, Gheorghiade M, Burnett J, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA*. 2007;297:1319-31.

5. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol.* 2014;63:1123-33.

6. Yancy C, Jessup M, Bozkurt B, et al. ACCF/AHA guideline for the management of heart failure: A report on the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circ*. 2013;128:e240-e327.

7. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016;37:2129-2200/ Corrigendum in *Eur Heart J*. 2017; ehx158. doi: 10.1093/eurheartj/ehx158.

8. Krum H, Teerlink JR. Medical therapy for chronic heart failure. *Lancet*. 2011;378:713-21.

9. Teerlink JR, Clarke CP, Saikali KG, et al. Dose-dependent augmentation of cardiac systolic function with the selective cardiac myosin activator, omecamtiv mecarbil: a first-in-man study. *Lancet*. 2011;378:667-75.

10. Malik FI, Hartman JJ, Elias KA, et al. Cardiac myosin activation: a potential therapeutic approach for systolic heart failure. *Science*. 2011;331:1439-43.

11. Avelox [package insert]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2016.

12. Zhang J and Machado SG. Statistical issues including design and sample size calculation in thorough QT/QTc studies. *J Biopharm Stat*. 2008;18(3):451-67.

13. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*. 1988;75:800-02.

14. Tornøe CW, Garnett CE, Wang Y, Florian J, Li M, Gobburu JV. Creation of a knowledge management system for QT analyses. *J Clin Pharmacol.* 2011;51(7):1035-42.

15. Cleveland WS. Robust locally weighted regression and smoothing scatter plots. *J Amer Statist Assoc.* 1979;74(368):829-36.

16. Hurvich, CM, Simonoff, JS, and Tsai, CL. Smoothing parameter selection in nonparametric regression using an improved Akaike information criterion. *J Roy Statist Soc Ser B.* 1998;60(2):271-93.

17. ICH E14. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. May 2005. Available: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/the-clinical-evaluation-of-qtqtc-interval-prolongation-and-proarrhythmic-potential-for-non-antiarrh.html.

10. APPENDICES

Appendix 1: Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event (AE) is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE event if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening • The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event • Medical or scientific judgment is to be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events, and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

• When an AE or SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
• The Investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (CRF).
  o Additionally, the Investigator is required to report a fatal event on the appropriate CRF.
• The Investigator must assign the following adverse event attributes:
  o Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  o Dates of onset and resolution (if resolved);
  o Severity (or toxicity defined below);
  o Assessment of relatedness to Amgen investigational product (IP): (OM/placebo), Non-Amgen protocol-required therapy (Moxifloxacin) and/or study-mandated procedures; and
  o Action taken.
• If the severity of an AE changes from the date of onset to the date of resolution, record as a single event with the worst severity on the appropriate CRF.
• It is not acceptable for the Investigator to send photocopies of the subject's medical records to Sponsor in lieu of completion of the appropriate CRF page.
• If specifically requested, the Investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.
• The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The Investigator will make an assessment of severity for each AE and SAE reported during the study. The assessment of severity will be based on: **The Amgen Standard Grading Scale as show below:**

Grade	Definition

MILD	Aware of sign or symptom, but easily tolerated
MODERATE	Discomfort enough to cause interference with usual activity
SEVERE[a]	Incapacitating, with inability to work or do usual activity

[a] An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between IP (OM/placebo), protocol-required therapy (Moxifloxacin) and/or study-mandated procedure and each occurrence of AE/SAE.
- Relatedness means that there are facts or reasons to support a relationship between IP and the event.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from IP/protocol-required therapies because of an SAE, this information must be submitted to Amgen.

- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide Amgen with a copy of any post-mortem findings including histopathology.

- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Paper Case Report Form (SAER Form)
• Facsimile transmission of the Serious Adverse Event Report Form (see Figure 2) is the preferred method to transmit this information. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the Serious Adverse Event Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.

Figure 2: Sample Serious Adverse Event Report Form

AMGEN 20090231 Covance Study#: 8405952 omecamtiv mecarbil (AMG 423)	Clinical Trial Serious Adverse Event Report - Phase 1- 4 *Notify Amgen (Sponsor) Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

Amgen (Sponsor) UK Safety Fax Number: 08000 284223

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year
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. SERIOUS ADVERSE EVENT - ***Information in this section must also be entered on the Serious Adverse Event Summary CRF***

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day_____ Month_____Year_____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *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	SAE Onset Time (24 hr clock)	Date Ended Day Month Year	SAE Stop Time (24 hr clock)	Check only if event occurred before first dose of IP	Enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the event may have been caused by Amgen IP: omcamtiv mecarbil (AMG 423) If yes see section 10 No ✓	Yes✓	Outcome of Event 01 Resolved 02 Resolving 03 Not Resolved 04 Fatal	Check only if event is related to study procedure *eg, biopsy*

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required hospitalization; **04** Prolonged hospitalization; **05** Persistent or significant disability / incapacity; **06** Congenital anomaly / birth defect; **07** Other medically important serious event

4. HOSPITALIZATION

	Date and Time Admitted Day Month Year	Time (24H)	Day Month Year	Date and Time Discharged Time (24H)
Was subject hospitalized or was hospitalization prolonged due to this event? ☐No ☐Yes, **If yes, please complete date(s) and time(s):**				

5. INVESTIGATIONAL PRODUCT (IP)

Provide dosing details including date and time of the first dose and the dose just prior to or at event onset, and action taken (for the latest dose).

omecamtiv mecarbil (AMG 423)		Date and Time of First Dose		Date and Time of Latest Dose Prior to, or at time of Event and Action Taken with Product			Dose	Frequency	Lot # & Serial #
Open Label - (Part A) ☐✓ Blinded – (Part B) ☐✓	**Oral** *Solution* **Dosing**	Day / Month / Year	Time (24H)	Day / Month / Year	Time (24H)	Action Taken			Lot # _____ ☐ Unknown Serial # _____ ☐ Unknown

Action Taken with Product Codes: **01** Still being administered; **02** Permanently discontinued; **03** Withheld

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AMGEN 20090231 Covance Study#: 8405952 omecamtiv mecarbil (AMG 423)	**Clinical Trial Serious Adverse Event Report - Phase 1- 4** ***Notify Amgen (Sponsor) Within 24 Hours of knowledge of the event***	❑New ❑Follow-up

Site Number	Subject ID Number

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

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

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

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

Date and Time (Day Month Year)	Test / Unit / Time (24H)	Result									
	Test										
	Unit										
	Time (24H)										

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

Date and Time (Day Month Year)	Time (24H)	Additional Tests	Results	Units

AMGEN 20090231 Covance Study#: 8405952 *omecamtiv mecarbil (AMG 423)*	**Clinical Trial Serious Adverse Event Report - Phase 1- 4** ***Notify Amgen (Sponsor) Within 24 Hours of knowledge of the event***	❑New ❑Follow-up

	Site Number	Subject ID Number	

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

Signature of Investigator or Designee _____ *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.*	Title	Date

Appendix 2: Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments (Appendix 6) 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 before 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.

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

The subject retains the right to request that the sample material be destroyed by contacting the Investigator. Following the request from the subject, the Investigator is to provide the Sponsor with the required study and subject number so that any remaining 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 before 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 Appendix 5 for subject confidentiality.

Appendix 3: Clinical Laboratory Evaluations

Clinical chemistry[a]:	**Hematology[a]:**	**Urinalysis:**
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Cholesterol Creatinine Direct bilirubin Gamma-glutamyl transferase Glucose Inorganic phosphate Potassium Sodium Total bilirubin Total protein Urea Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Ketones pH Protein Specific gravity Urobilinogen Microscopic examination
Serology[b]:	**Drug screen[c]:**	
Hepatitis B core antibody Hepatitis B surface antigen Hepatitis B surface antibody Hepatitis C antibody Human immunodeficiency virus (HIV-1 and HIV-2) antibodies	Including, but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Cotinine Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Tricyclic antidepressants Alcohol breath test	
Hormone panel - females only:	**Other tests:**	
Follicle-stimulating hormone[b] (postmenopausal females only) Serum pregnancy test (human chorionic gonadotropin)[d] Urine pregnancy test[e]	Troponin I Creatine kinase-MB[f]	

[a] Blood samples for clinical chemistry and hematology.
[b] Only analyzed at Screening.
[c] Only analyzed at Screening and at Check-in of each period.
[d] Performed at Screening for all females.
[e] Performed for all females at each Check-in and the Follow-up/End of Study visit. A positive urine pregnancy test will be confirmed with a serum pregnancy test.
[f] CK-MB at post-baseline timepoints also to be collected if possible in the event of a suspected coronary event.

Appendix 4: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Serology	3.5	1	3.5
Safety laboratory tests	7.5	7	52.5
OM pharmacokinetics	4	27	108
Moxifloxacin pharmacokinetics	2	16	32
Placebo blood sampling[a]	4	16	64
Troponin-I sampling	2.5	16	40
Total:			300

a Blood samples will be collected but not analyzed for the placebo treatment period.

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will be less than 500 mL.

Any blood sample collected according to the Schedule of Assessments 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.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents must be submitted to an Ethics Committee (EC) by the Investigator and reviewed and approved by the EC before the study is initiated. A copy of the written approval of the protocol and ICF must be received by the Sponsor (Amgen Inc.) before recruitment of subjects into the study and shipment of Amgen investigational product (IP).

Amgen may amend the protocol at any time. Any protocol amendments will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any nonsubstantial changes, as defined by regulatory requirements. The Investigator must send a copy of the approval letter from the EC and amended protocol Investigator's Signature page to Amgen before implementation of the protocol amendment at their site.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC.
- Obtaining annual EC approval/renewal throughout the duration of the study. Copies of the Investigator's reports and the EC continuance of approval must be sent to Amgen.
- Notifying the EC of serious adverse events (SAE) or other significant safety findings as required by EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR; if applicable), ICH guidelines, the EC, European regulation 536/2014 for clinical studies, and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

An initial sample ICF will be provided for the Investigator (or designee) to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the Study Manager to the Investigator. The written ICF is to be prepared in the language(s) of the potential study participant population.

The Investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any IP(s) is/are administered and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative (defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study) will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and the EC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

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

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records.

Subjects must be re-consented to the most current version of the ICF during their participation in the study.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF must be provided to the subject or the subject's legally authorized representative.

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 ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood. (Refer to ICH E6 GCP guideline, Section 4.8.9).

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

Subject Data Protection

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

A subject will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the electronic case report form (eCRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For SAEs reported to Amgen, subjects are to be identified by their unique subject identification number and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the Investigator, except as described below.

In compliance with 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/EC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The Investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential information of the Sponsor. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor. The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- All data collected at the Clinical Research Unit is recorded on source documents prior to entry in the eCRF. The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.

- The Sponsor or Contract Research Organization (CRO) is responsible for the data management of this study including quality checking of the data. Predefined, agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

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

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Sponsor or CRO electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each subject who is enrolled in the study, according to the eCRF completion instructions. The Sponsor or CRO will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The Investigator is to

notify the Independent Ethics Committee in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen IP(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen IP(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially

Publications

To coordinate dissemination of data from this study, the Investigator will obtain input and assistance from Amgen staff as appropriate.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to 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 need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must 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 must qualify for authorship, and all those who qualify are to be listed. Each author must 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.

Appendix 6: Schedule of Assessments

Table 3: Schedule of Assessments

Activity	Screening	Part A													Follow-up/EOS[b]
Day	Within -28 days of Day 1	-1	1										2	3	6
Time (hours)[a]			**Predose**	**0.25**	**0.5**	**0.75**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**48**	**120**
Clinical Research Unit Residency		X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]	
Outpatient Visit	X															X
GENERAL AND SAFETY ASSESSMENTS																
Informed consent	X															
Eligibility	X	X														
Medical history	X	X[d]														
Demographics	X															
Height	X															
Body weight	X															X
BMI	X															
ECG – standard safety	X	X	X				X			X				X	X	X
Vital signs (BP, HR)	X	X	X				X			X				X	X	X
Vital signs (temp)	X	X	X				X			X				X	X	X
Physical exam	X															X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[e]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LABORATORY PROCEDURES																
Clinical chemistry	X	X														X
Hematology	X	X														X
eGFR[g]	X															
Urinalysis	X	X														X
Pregnancy test (females only)[h]	X	X														X
FSH (females only)[i]	X															
Troponin I	X	X	X				X			X				X		X
CK-MB	X	X														X
Drug, alcohol, and cotinine screen	X	X														

Activity	Screening	Part A														Follow-up/EOS[b]
Day	Within -28 days of Day 1	-1	1											2	3	6
Time (hours)[a]			**Predose**	**0.25**	**0.5**	**0.75**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**48**	**120**
Clinical Research Unit Residency		X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]	
Outpatient Visit	X															X
HIVAb, HBsAg, anti-HBs, anti-HBc, HCAb	X															
OM plasma PK[j]			X	X	X	X	X	X	X	X	X	X	X			
TREATMENT[k]																
OM			X													
PK EVALUATION																
Determine subject eligibility for Part B of study																X[l]

Abbreviations: AE = adverse event; anti-HBs = hepatitis B surface antibody; anti-HBc = hepatitis B core antibody; BMI = body mass index; BP = blood pressure; CK-MB = creatine kinase MB fraction; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = End of Study; FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; HCAb = hepatitis C antibody; HIVAb = human immunodeficiency virus antibody; HR = heart rate; ICF = Informed Consent Form; MDRD = Modified Diet in Renal Disease; OM = omecamtiv mecarbil; PK = pharmacokinetic; Temp = temperature; SAE = serious adverse event.

a Time (in hours) is relative to treatment administration.
b Subjects will return to the clinic on Day 6 for safety evaluations. For subjects with maximum OM plasma concentrations > 350 ng/mL, the completion of these procedures will be considered the End of Study (EOS). Subjects who withdraw or early terminate prior to Day 6 should also return for Day 6 procedures, if possible.
c Subjects may be discharged from the unit after all assessments are completed.
d Medical history since Screening.
e Adverse events (AEs) are collected from the time of the first dose of study treatment until EOS. Events occurring prior to dosing will be reported as baseline signs and symptoms or medical history, as applicable.
f Serious adverse events (SAEs) are collected from the time the ICF is signed until 30 days after the last dose.
g eGFR will be calculated using the MDRD equation.
h Serum pregnancy test at Screening. Urine pregnancy tests will be used on Day -1 and at Follow-up/EOS.
i FSH must be measured for all females to confirm postmenopausal status.
j Pharmacokinetic (PK) samples should be collected within 5 minutes. Samples collected outside of this window should still be collected and recorded as protocol deviations.
k Treatment will be administered after all predose procedures are completed and after at least a 10-hour fast.
l Subjects with maximum plasma OM concentrations ≤ 350 ng/mL will be eligible to continue to Part B. Due to logistics of sample shipping and analysis, this may occur after Day 6 (but prior to Part B).

Activity	Part B: Treatment Periods 1 – 3																			End of period/ Study[b]
Day in Period 1	-1	1														2	3	4	5	6
Day in Period 2	-1	1														2	3	4	5	6
Day in Period 3	-1	1														2	3	4	5	6 (EOS)
Time (hours)[a]		**-1.25**	**-1**	**-0.75**	**Predose**	**0.25**	**0.5**	**0.75**	**1**	**1.5**	**2**	**3**	**4**	**8**	**12**	**24**	**48**	**72**	**96**	**120**
Clinical Research Unit Residency	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
GENERAL AND SAFETY ASSESSMENTS																				
Randomization					X[c]															
Vital signs (BP, HR)	X				X[i]	X	X	X	X	X	X						X			X
Vital signs (temp)	X				X[i]															X[d]
ECG – standard safety	X				X[i]				X				X		X	X	X			X[d]
ECG[e] – extraction windows		X	X	X		X	X	X	X	X	X	X	X	X	X	X				
ECG – telemetry monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Physical exam																				X[d]
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LABORATORY PROCEDURES																				
Clinical chemistry	X																			X[d]
Hematology	X																			X[d]
Urinalysis	X																			X[d]
Pregnancy test (females only)[h]	X																			X[d]
Troponin I	X[n]				X				X				X			X				X[d]
CK-MB	X[n]																			
Drug, alcohol, and cotinine screen	X																			
OM plasma PK[l]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Moxifloxacin plasma PK[l]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TREATMENT[j,k]																				
OM, Moxifloxacin, or Placebo					X															

BMI = body mass index; BP = blood pressure; CK-MB = creatine kinase MB fraction; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; FSH = follicle-stimulating hormone; anti-HBs = hepatitis B surface antibody; anti-HBc = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCAb = hepatitis C antibody; HIVAb = human immunodeficiency virus antibody; HR = heart rate; OM = omecamtiv mecarbil; PK = pharmacokinetic; Temp = temperature.

a Time (in hours) is relative to treatment administration during each period.
b Subjects may be discharged from the unit after all assessments are completed in Period 3. Subjects who withdraw or terminate early should have EOS procedures performed, if possible.
c Subjects will be randomized to a treatment sequence prior to dosing in Period 1.
d Assessment to be performed at EOS only or if a subject is withdrawn early from the study.
e ECGs will be extracted from the continuous 12-lead digital ECG recording as noted. The recording will be performed for approximately 27 hours in total. Subjects should lie down in a quiet room for at least 10 minutes before and 5 minutes after each extraction at the timepoints listed.
f Adverse events (AEs) are collected from the time of the first dose of study treatment to EOS. Events occurring prior to the first dose in Part B but after dosing in Part A will be reported as occurring in Part A.
g Serious adverse events (SAEs) are collected from the time the ICF is signed until 30 days after the last dose.
h Urine pregnancy tests will be used on Day -1 of each dosing period and at EOS.
i Predose vital signs measurements and safety ECGs are to be performed prior to the start of continuous cardiac monitoring.
j Treatments will be separated by a washout period of ≥ 7 days.
k Treatment will be administered after all predose procedures are completed and after at least a 10-hour fast.
l Pharmacokinetic (PK) samples should be collected within 5 minutes after the completion of the digital ECG extraction window through 24 hours postdose and within ± 2 hours of the digital ECG extraction windows after 24 hours postdose. Samples collected outside of this window should still be collected and recorded as protocol deviations.
n Collect only on Day -1 of Period 1.

Appendix 7: Contraceptive Guidance and Collection of Pregnancy and Lactation Information

All subjects must receive pregnancy prevention counseling and be advised of the risk to the fetus if they conceive a child during treatment and for 90 days after the Follow-up visit.

Additional medications given during the study may alter the contraceptive requirements. The Investigator must discuss these contraceptive changes with the subject.

Definitions

Women of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Non-Child-Bearing Potential:

1. **Surgically sterile:** Females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** Females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 1 highly effective method of contraception and a barrier method (male or female) from the time of signing the Informed Consent Form (ICF) until 90 days after the Follow-up visit.

Primary (highly effective) methods of contraception include:

- Hormonal injection (as prescribed)
- Combined oral contraceptive pill or progestin/progestogen-only pill associated with inhibition of ovulation (as prescribed)
- Combined hormonal patch (as prescribed)

- Combined hormonal vaginal ring (as prescribed)
- Surgical method performed at least 3 months prior to the Screening visit
    - Bilateral tubal ligation with confirmation of surgical success
    - Regulatory approved hysteroscopic bilateral tubal occlusion with confirmation of occlusion of the fallopian tubes
- Hormonal implant
- Hormonal or non-hormonal intrauterine device (IUD or IUS)
- Vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject)

Secondary (barrier) methods of contraception include:

- Male condom with spermicide
- Female condom with spermicide
- Over-the-counter sponge with spermicide
- Cervical cap with spermicide (as prescribed)
- Diaphragm with spermicide (as prescribed).

Female subjects of childbearing potential should refrain from donation of ova from the time of signing the ICF until 90 days after the EOS visit.

Male Subjects

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception by female partner from Check-in until 90 days after the Follow-up visit. Acceptable methods of contraception for female partners include:

- Hormonal injection
- Combined oral contraceptive pill or progestin/progestogen-only pill
- Combined hormonal patch
- Combined hormonal vaginal ring
- Surgical method (bilateral tubal ligation or regulatory approved hysteroscopic bilateral tubal occlusion)
- Hormonal implant
- Hormonal or non-hormonal IUD
- Over-the-counter sponge with spermicide
- Cervical cap with spermicide
- Diaphragm with spermicide.

Male subjects are required to refrain from donation of sperm from the time of signing the ICF until 90 days after the EOS visit.

Sexual Abstinence

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a subject who is abstinent at the time of signing the ICF becomes sexually active they must agree to use contraception as described previously.

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the ICF until 90 days after the EOS visit.

Same-sex Relationships

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

Subjects in same-sex relationships at the time of signing the ICF must agree to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 90 days after the EOS visit.

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 90 days after the Follow-up visit.
- Information will be recorded on the Pregnancy Notification Form (see Figure 3). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the Investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 90 days after the Follow-up visit. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event (AE) or serious adverse event (SAE), any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an AE or SAE. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an AE but still must be reported to the Sponsor as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as an SAE (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death, or there is a fetal or neonatal congenital anomaly) the Investigator will report the event as an SAE.
- Any SAE occurring as a result of a post-study pregnancy, which is considered reasonably related to the study treatment by the Investigator, will be reported to Amgen Global Patient Safety. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 7.1 for details).

Male Subjects with Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 90 days after the Follow-up visit, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 3) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The Investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- The Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 90 days after the Follow-up visit.
- Information will be recorded on the Lactation Notification Form (Figure 4) and submitted to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event.
- Study treatment will be discontinued if the female subject breastfeeds during the study.
- With the female subject's signed authorization for release of mother and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 90 days after the Follow-up visit.

Figure 3: Pregnancy Notification Form

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: Amgen Protocol Reference Number: 20090231, Covance Study Number: 8405952

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 age (at onset):**____(in years)

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 last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Figure 4: Lactation Notification Form

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: Amgen Protocol Reference Number: 20090231, Covance Study Number: 8405952

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 age (at onset):**____(in years)

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:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Appendix 8: Hepatotoxicity: Suggested Actions and Follow-up Assessments

Subjects with normal hepatic function at Screening who experience aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3x upper limit of normal (ULN) or subjects with elevated values before drug exposure who have a 2-fold increase above baseline values (as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009) are to undergo clinical assessments and a period of "close observation" until abnormalities return to normal or to the subject's baseline level as described below.

Clinical Assessments and Observation

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (BIL) (total and direct), and INR within 24 hours
- In cases of total bilirubin (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.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin (Ig)G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- 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 nonprescription medicines and herbal and dietary supplements), plants, and mushrooms
    - Viral serologies
    - Creatine phosphokinase, haptoglobin, lactate dehydrogenase and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist).

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the Investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all IP(s) and protocol-required therapies.

The potential drug-induced liver injury (DILI) event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.

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 heart failure, 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
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, ie cases of AST or ALT > 3x ULN and concurrent TBL > 2x ULN or INR > 1.5 (for subjects not on anticoagulation therapy) without evidence of alternative cause of the elevations, require the following:

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

Other events of hepatotoxicity and potential DILI are to be reported as SAEs if they meet the criteria for an SAE defined in Appendix 1.

Summary of Amended Protocol Changes

Single-dose and Randomized, Single-center, Placebo- and Active-controlled, Crossover Study to Assess the Effect of Omecamtiv Mecarbil (OM) on QT/QTc Intervals in Healthy Subjects

Protocol Amendment 3 Status: Final
Protocol Amendment 3 Date: 23 August 2019
Protocol Amendment 2 Date: 07 August 2019
Protocol Amendment 1 Date: 19 July 2019
Original Protocol Date: 30 May 2019

Clinical Phase: 1

Investigational Product: omecamtiv mecarbil (AMG 423)

Amgen Protocol Reference Number: 20090231
Covance Study Number: 8405952
EudraCT Number: 2018-003157-19

Sponsor:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320

The protocol is being amended to reflect the additional blood volume needed for troponin-I sample collections due to a change in analysis method (CPS Labs instead of I-Stat method). Additionally, the blood volume table in Appendix 4 is being updated to reflect the total number of troponin I sample collections.

Other changes include: the protocol version and date were updated throughout the protocol to reflect the amendment status, the Confidentiality Statement was updated for consistency with other studies in the development program, the volume of water to be given with dosing was

updated to 250 mL for consistency with the Investigational Product Instruction Manual, and the Medical Monitor was clarified to be the out-of-hours contact for clinic staff.

A detailed summary of changes is presented below:

Title Page

The title page was updated to reflect the new protocol version and effective date.

Confidentiality Statement

Previously read:

> This document contains confidential information of Amgen Inc.
>
> This document must not be disclosed to anyone other than the site study staff and members of the institutional review board/independent ethics committee/institutional scientific review board or equivalent.
>
> The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.
>
> If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: US sites, 1-800-77-AMGEN; Canadian sites, 1-866-50-AMGEN; European/UK sites, +44(0) 1223 436441; Amgen's general number in the US, 1-805-447-1000.

Now reads:

> This document contains confidential information of Amgen Inc.
>
> This document must not be disclosed to anyone other than the site study staff and members of the ~~institutional review board/independent ethics committee/institutional scientific review board~~ **Institutional Review Board/Independent Ethics Committee/Institutional Scientific Review Board** or equivalent.
>
> The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.
>
> If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: US sites, 1-800-77-AMGEN; Canadian sites, 1-866-50-AMGEN; ~~European/UK sites, +44(0) 1223 436441;~~ Amgen's general number in the US, 1-805-447-1000.

Study Identification

Previously read:

Medical Monitor	[redacted] MD Executive Medical Director Covance Clinical Pharmacology Services 3402 Kinsman Boulevard Madison, Wisconsin 53704 USA Tel (Office): [redacted] Tel (Mobile): [redacted]

Now reads:

Medical Monitor **(Out of Hours Contact)**	[redacted] MD Executive Medical Director Covance Clinical Pharmacology Services 3402 Kinsman Boulevard Madison, Wisconsin 53704 USA Tel (Office): [redacted] Tel (Mobile): [redacted]

Section 3.1: Overall Study Design and Plan (Part A)

Previously read:

After an overnight fast of at least 10 hours, subjects will be administered treatment with 240 mL (8 fluid ounces) of water.

Now reads:

After an overnight fast of at least 10 hours, subjects will be administered treatment with ~~240~~**250** mL ~~(8 fluid ounces)~~ of water.

Section 3.1: Overall Study Design and Plan (Part B)

Previously read:

After an overnight fast of at least 10 hours, subjects will be administered treatment with 240 mL (8 fluid ounces) of water.

Now reads:

After an overnight fast of at least 10 hours, subjects will be administered treatment with ~~240~~**250** mL ~~(8 fluid ounces)~~ of water.

Appendix 4: Total Blood Volume

Previously read:

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Serology	3.5	1	3.5
Safety laboratory tests	7.5	7	52.5
OM pharmacokinetics	4	27	108
Moxifloxacin pharmacokinetics	2	16	32
Placebo blood sampling[a]	4	16	64
Troponin-I sampling	1	13	13
Total:			273

Now reads:

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Serology	3.5	1	3.5
Safety laboratory tests	7.5	7	52.5
OM pharmacokinetics	4	27	108
Moxifloxacin pharmacokinetics	2	16	32
Placebo blood sampling[a]	4	16	64
Troponin-I sampling	**~~1~~2.5**	**~~13~~16**	**~~13~~40**
Total:			**~~273~~300**

Summary of Amended Protocol Changes

Single-dose and Randomized, Single-center, Placebo- and Active-controlled, Crossover Study to Assess the Effect of Omecamtiv Mecarbil (OM) on QT/QTc Intervals in Healthy Subjects

Protocol Amendment 2 Status: Final
Protocol Amendment 2 Date: 07 August 2019
Protocol Amendment 1 Date: 19 July 2019
Original Protocol Date: 30 May 2019

Clinical Phase: 1

Investigational Product: omecamtiv mecarbil (AMG 423)

Amgen Protocol Reference Number: 20090231
Covance Study Number: 8405952
EudraCT Number: 2018-003157-19

Sponsor:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320

The protocol is being amended to comply with MHRA requirement to clarify in the appropriate protocol section that a subject must be discontinued from study treatment if QTcF > 500 ms (as confirmed by 2 ECGs taken within 1 hour) or if increase in QTcF > 60 ms compared to predose baseline is observed.

The protocol version and date were also updated throughout the protocol to reflect the amendment status.

Summary of Amended Protocol Changes

Single-dose and Randomized, Single-center, Placebo- and Active-controlled, Crossover Study to Assess the Effect of Omecamtiv Mecarbil (OM) on QT/QTc Intervals in Healthy Subjects

Protocol Amendment 1 Status: Final
Protocol Amendment 1 Date: 19 July 2019
Original Protocol Date: 30 May 2019

Clinical Phase: 1

Investigational Product: omecamtiv mecarbil (AMG 423)

Amgen Protocol Reference Number: 20090231
Covance Study Number: 8405952
EudraCT Number: 2018-003157-19

Sponsor:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320

The protocol is being amended primarily in response to MHRA recommendations to further ensure selection of healthy subjects and to ensure the safety and privacy of study subjects. Major changes include:

1. Additional troponin-I sample collections have been added to Parts A and B of the study corresponding with safety electrocardiograms (ECGs) at the following Day 1 timepoints: predose and 1, 4, and 24 hours postdose. An additional standard safety ECG was added at 1 hour postdose on Day 1 of Part B, and a troponin-I sample collection was added to End of Study (EOS) or early withdrawal in Part B. These samples will be analyzed and reviewed along with the other safety data as described in the protocol to ensure selection of healthy subjects and to protect subject safety.

2. The blood volume table was updated to reflect the additional troponin-I sample collections.
3. The upper age limit of potential subjects has been decreased to 50 years from 55.
4. The section “Subject Data Protection” was updated so that subject initials will not be included in information sent to the sponsor as part of serious adverse event (SAE) reporting, in accordance with guidance on subject privacy protections.

Minor changes include:

1. The protocol version and date were updated throughout the protocol.
2. Typographical and/or formatting errors were corrected, as necessary.
3. Minor editorial updates were made for consistency with other studies in the same development program.