Title: A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 986 in Healthy Subjects and Heart Failure Patients

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I have read the attached protocol entitled: A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 986 in Healthy Subjects and Heart Failure Patients dated 27 July 2018, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub-investigators (including, if applicable, their spouses [or legal partners] and dependent children)

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

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

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 986 in Healthy Subjects and Heart Failure Patients

Study Phase: 1

Indication: Heart Failure

Primary Objective:

- To evaluate the safety and tolerability of ascending single (Part A) and ascending multiple (Part B) doses of AMG 986 in healthy subjects, who received AMG 986 by constant intravenous (IV) infusion or oral (PO) administration and of ascending multiple PO doses of AMG 986 in heart failure patients (Part C).

Secondary Objectives:

- To characterize AMG 986 pharmacokinetics (PK) after IV infusion and oral administration in healthy subjects and heart failure patients.
- To characterize the pharmacodynamic (PD) effects of AMG 986 in healthy subjects and in heart failure patients.

Exploratory Objectives:

- To characterize AMG 986 excretion in urine.
- To evaluate AMG 986 impact on heart failure prognostic markers in heart failure patients.
- To evaluate AMG 986 impact on endothelial function markers including endothelin-1 (ET-1), angiotensin II (ANG II), and apelin.
- To characterize the effect of AMG 986 administration on free water clearance by the kidney into the urine after multiple doses of AMG 986.
- To evaluate the impact of AMG 986 administration on glucose and lipid metabolism.
- To explore the relationship between changes in QTc and AMG 986 exposure.

Hypotheses:

- AMG 986 will be safe and well tolerated in healthy subjects and in heart failure patients after single and multiple dosing by IV infusion and oral administration.

Primary Endpoint:

- Subject incidence of treatment-emergent adverse events.
- Subject incidence of clinically significant changes in physical examinations, vital signs, laboratory safety tests, and electrocardiograms (ECGs).

Secondary Endpoints:

- AMG 986 PK parameters including, but not limited to, maximum observed concentration (Cmax), the time of maximum observed concentration (tmax), area under the concentration-time curve (AUC), and oral bioavailability.
- Changes over time from baseline in echocardiographic parameters of left ventricular systolic and diastolic functions (left ventricular ejection fraction, fraction shortening, stroke volume, wall thickening, end-systolic and end-diastolic volumes and indexes, septal and lateral e', E/A ratio, E/e' ratio, E wave deceleration time, left atrial volume index) in both healthy subjects and heart failure patients, as well as changes in ventriculo-arterial coupling and global strain in heart failure patients only.

Exploratory Endpoints:

- AMG 986 excretion in urine.
- Characterization of potential metabolites of AMG 986 in plasma and urine (if appropriate).
- Change from baseline in free water clearance in the urine after multiple daily doses of AMG 986 (Part B).
- Change from baseline in fasting glucose and fasting lipid profiles after AMG 986 administration.
- Change from baseline of heart failure prognostic markers, eg, NT-pro-BNP, Troponin, Galectin-3, soluble ST-2, and GDF-15 (Part C)
- Change from baseline of endothelial functional markers, eg, endothelin-1 and angiotensin II, apelin, ADMA and SDMA (Parts B and C)
- Change from baseline for QTc and relationship to AMG 986 exposure.

Study Design: This study is a randomized, placebo-controlled, double-blind, single day ascending dose (SDAD) study (Part A), a multiple daily ascending dose (MDAD) study (Part B), in healthy subjects, and a MDAD study (Part C) in heart failure patients. In Parts A and B of the study, healthy volunteers will receive AMG 986 by continuous IV infusion or by oral administration in a fasted state. IV Infusions will be divided into an initial loading dose (LD) for the first hour followed immediately by a maintenance dose (MD). In Part C of the study, patients with heart failure and either reduced (HFrEF) or preserved (HFpEF) ejection fraction will receive MDAD of IP by once daily oral administration for 21 days.

All available safety and laboratory data will be reviewed in an unblinded fashion by the members of the Dose Level Review Meeting (DLRM) prior to the first dose administration of IP at the higher dose level. For study Part A, PK assessments will be part of each DLRM. For study Parts B and C, vital signs, and all available PK and PD data will also be reviewed at the DLRM. All cohorts in Part B will enroll sequentially after review of safety data at the previous dose level. Both cohorts in Part C (HFrEF cohort and HFpEF cohort) will enroll concurrently after completion of study Part B.

Based on emerging safety and tolerability data and upon assessment by the Principal Investigator (PI), Medical Monitor and Global Safety Officer (DLRM members), cohorts may be removed or additional cohorts may be added. Subject numbers within each cohort may also be increased or decreased based on the decision from the DLRM. Doses to be administered within each cohort may be higher or lower than the last. Dosing of any subject shall not exceed the highest planned IV and PO cohorts.

Refer to the study schema at the end of the protocol synopsis for an overall summary of the study design.

Part A

Part A is a randomized, parallel group, double-blind, SDAD study consisting of 11 cohorts (5 IV infusion dose cohorts and 6 oral dose cohorts). Within each cohort, a total of 8 subjects will be randomized to receive AMG 986 or placebo in a 3:1 ratio.

Starting doses of 0.5 mg by IV infusion lasting 1 hour and 5 mg given by oral administration are planned. The sequence of escalation for IV dosing and PO dosing will partially overlap to achieve step-wise increases in AMG 986 exposure. Dose escalations in Part A will initially be sequential, with AMG 986 dosing to begin at the starting IV dose of 0.5 mg infused over 1 hour, followed by escalation to IV Cohort 2 dosing at 3 mg infused over 1 hour. After the safety and tolerability of AMG 986 in IV Cohort 2 are demonstrated and reviewed at a DLRM, escalation to IV Cohort 3 (6 mg LD + 36 mg MD) and initiation of oral dosing at the proposed 5 mg starting dose will be permitted. Subsequent IV and oral dose cohort escalations and DLRM reviews will occur as shown in the study schema.

After the safety and tolerability of AMG 986 in IV Cohort 4 (20 mg LD + 120 mg MD) and PO Cohort 4 (200 mg) are demonstrated and reviewed at a DLRM, escalation to IV Cohort 5 (60 mg LD + 360 mg MD) and PO Cohort 5 (400 mg) will be permitted. Enrollment for IV Cohorts will end

after IV Cohort 5. After the safety and tolerability of AMG 986 at 400 mg are demonstrated and reviewed at a DLRM, escalation to PO Cohort 6 (650 mg) will be permitted.

A DLRM will be held once safety data through at least 4 days post dose become available for all subjects in a treatment cohort. Escalation to a higher dose within a cohort, between cohorts, and enrollment of Part B, will proceed only when the previous doses have been found to be tolerated and, in the case of initiation of Part B, after drug exposures from the preceding single dose cohorts have been evaluated.

Part B

Part B is a randomized, parallel group, double-blind, MDAD study consisting of 8 cohorts (2 IV infusion dose cohorts and 6 oral dose cohorts). Within each cohort, a total of 8 subjects will be randomized to receive AMG 986 or placebo in a 3:1 ratio. Prior to the transition from Part A to Part B, verification of PK model assumptions is planned as AMG 986 human PK data become available from individual IV and oral single dose cohort escalations in Part A.

In the IV cohorts, AMG 986 will be dosed as a series of IV infusions, each with duration of 24 hours, for 4 consecutive days. On study Day 1, IV infusions will be divided into an initial loading dose infusion for 1 hour followed immediately by a maintenance dose with duration for 23 hours. On study days 2 to 4, maintenance doses will be administered as constant infusions with duration for 24 hours. The transition from SDAD in Part A to MDAD in Part B is planned to occur after confirmation of AMG 986 safety and tolerability in IV Cohort 4 (20 mg LD + 120 mg MD) of Part A. The starting IV dose in Part B at 6 mg (LD) + 38 mg/24 hour (MD; 1.57 mg/h, 36 mg/ 23 h on Day 1 and 38 mg/ 24 h on Days 2-4) infused over 4 days will have been previously evaluated over 24 hours in IV Cohort 3 (6 mg LD + 36 mg MD) of Part A.

In the PO cohorts, AMG 986 will be dosed once daily for 7 consecutive days. Parts A and B will partially overlap for the oral dose cohorts. Transition to the first PO cohort of Part B (5 mg QD) is planned to occur upon a DLRM decision to proceed after the 30 mg PO single dose cohort in Part A has been made. Subsequent oral dose escalations to 200 mg QD will occur in Part B as shown in the study schema. Escalation to 400 mg QD in Part B will be allowed after the safety and tolerability of AMG 986 at 400 and 650 mg in Part A (PO cohorts 5 and 6, respectively) are demonstrated and reviewed at each DLRM. Subsequent oral dose escalations to 400 mg and 650 mg QD will occur in Part B as shown in the study schema.

The safety and tolerability of each dose level (including the last dose cohort) in Part B will be assessed at the DLRM once safety data through at least 4 days post dose become available for all subjects in a treatment cohort. Escalation to a higher dose within a cohort, between cohorts, and enrollment of Part B, will proceed only when the previous doses have been found to be tolerated.

The impact of AMG 986 on PD measures of cardiovascular function in study subjects will be determined using echocardiography and evaluated at each DLRM as data become available.

Sample Size:

- Part A IV Dose Cohorts: 40 subjects (8 subjects per cohort)
- Part A Oral Dose Cohorts: 48 subjects (8 subjects per cohort)
- Part B IV Dose Cohorts: 16 subjects (8 subjects per cohort)
- Part B Oral Dose Cohorts: 48 subjects (8 subjects per cohort)

The above sample sizes, for both Parts A and B, are based on practical considerations and are consistent with the number of subjects enrolled in similar studies.

Part C

A total of up to 40 subjects, 20 with HFrEF and 20 with HFpEF, will be randomized to receive AMG 986 or placebo in a 3:1 ratio (15 treated and 5 placebo). Subjects will receive once daily oral administration of IP at 10 mg for the first 7 days, 30 mg for the next 7 days and 100 mg for the last 7 days.

Summary of Subject Eligibility Criteria:

For Parts A and B: Healthy male and female subjects age 18 to 55 years (inclusive) with body mass index between 18 and 35 kg/m^2 (inclusive).

For Part C:

- Criteria for HFrEF- Patients between the ages of 18 and 85 years with stable NYHA class II or III chronic HF in sinus rhythm on optimal therapy and a left ventricular ejection fraction of ≤ 40% and NT-proBNP level of ≥ 250 pg/mL.
- Criteria for HFpEF- Patients between the ages of 18 and 85 years with stable NYHA class II or III chronic HF, in sinus rhythm on optimal standard of care therapy with a left ventricular ejection fraction of ≥ 50% and NT-proBNP level of ≥ 250 pg/mL.

For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

Investigational Product

Investigational product for IV infusion will be prepared by an unblinded pharmacist in normal saline bags for loading and maintenance doses (as per instructions provided in the Investigational Product Instruction Manual - IPIM). Investigational product for oral administration will be prepared as tablets in strengths of 5 mg and 25 mg. The oral doses proposed for this study range from 5 mg to 650 mg and the total cumulative daily intravenous doses proposed range from 0.5 mg to 420 mg.

In Part A, subjects will receive AMG 986 or placebo by either IV infusion lasting up to 24 hours or as a single oral dose. The planned IV dose cohorts include IV infusions of 0.5 mg over 1 hour, 3 mg over 1 hour, 6 mg over 1 hour immediately followed by 36 mg over 23 hours, 20 mg over 1 hour immediately followed by 120 mg over 23 hours and 60 mg over 1 hour immediately followed by 360 mg over 23 hours. The planned single oral doses are 5, 30, 100, 200, 400, and 650 mg.

In Part B, subjects will receive AMG 986 or placebo by either IV infusion lasting for 4 days (96 hours, equivalent to 4 repeat 24-hour infusions) or once daily (QD) oral dose administrations for 7 consecutive days. The planned IV dose cohorts include IV infusions of 6 mg over 1 hour immediately followed by 38 mg per day over 4 days (36 mg/ 23 h on Day 1 and 38 mg/ 24 h on Days 2-4) and 60 mg over 1 hour immediately followed by 376 mg per day over 4 days (360 mg/23 h on Day 1 and 376 mg/ 24 h on Days 2-4). Subjects in the IV cohorts will remain in residency at the study site during 4 days of IV infusion administration plus one day of follow up. The planned oral doses are 5, 30, 100, 200, 400, and 650 mg QD for 7 days. Oral dosing will be initiated in the morning at approximately the same time each day. Subjects in the oral cohorts will remain in residency at the study site during 7 days of oral administration plus one day of follow up.

In Part C, subjects will receive AMG 986 or placebo by oral IP for 21 days starting at 10 mg daily for the first 7 days, followed by 30 mg daily for the next seven days, and ending with 100 mg daily for the last 7 days. There are two planned cohorts defined by their heart failure diagnosis of HFrEF and HFpEF, and both cohorts will receive the same dose of IP.

For Parts A, B and C, AMG 986 dose adjustments (if any) will be made on a treatment cohort and not on an individual basis, and will be agreed upon by Amgen in coordination with the investigators. IV dosing regimen may be modified based on emergent PK or safety data.

Control Group: For Parts A, B and C, the control group will be subjects who receive placebo.

Procedures: After informed consent is obtained, all screening procedures and tests establishing eligibility will be performed within 28 days prior to study product administration for the subjects.

Subjects will be admitted to the research facility on Day -1 for further baseline/eligibility assessments.

After completion of all pre-dose procedures on the day of dosing (Day 1), subjects will receive AMG 986 or Placebo. Subjects will reside at the research facility according to the schedule of assessments for the assigned cohort after dosing and then be discharged and provided with instructions to return to the research facility according to the procedures provided in the Schedule of Assessment (Section 7.1).

For a full list of study procedures, including the timing of each procedure, please refer to Schedule of Assessments (Section 7.1).

Statistical Considerations: Data will be analyzed for each Part of the study and each route of administration separately. Descriptive statistics by cohort will be provided for selected demographics, safety, PK, and PD data. After review, data for subjects receiving placebo will be combined across all dose escalation cohorts for each Part and route of administration separately. Descriptive statistics on continuous measurements will include means, medians, 25th and 75th percentiles, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. PK, PD, and clinical lab data will be summarized at each time point when samples are collected.

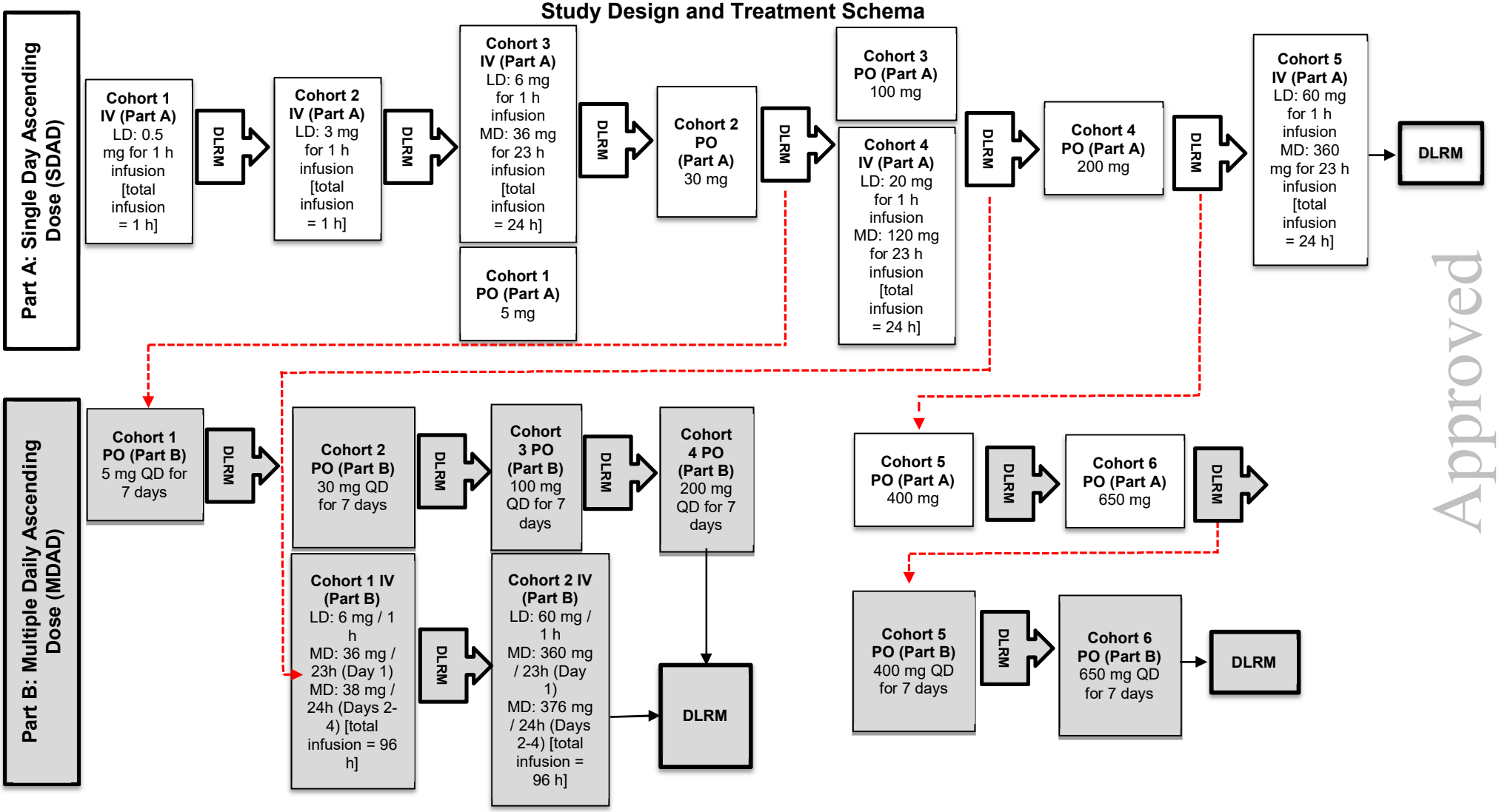
The number and percentage of subjects reporting any treatment-emergent adverse events will be tabulated by system organ class and preferred term, and will be further classified by relationship to treatment. Serious adverse events and clinically significant changes in clinical laboratory test values, ECG, or vital signs will be noted. Both exploratory graphical and model-based PK/PD analyses may be conducted with selected PD markers. Modeling of single-dose PK data obtained in Part A may be used to guide selection of doses and dosing intervals in the multiple-dose segment (Parts B and C).

The sample size for all Parts of the study is based on practical considerations and is consistent with the number of subjects enrolled in similar studies. Approximately 152 healthy subjects (8 subjects per cohort in 19 cohorts for Parts A and B) and up to 40 heart failure patients in Part C are expected to be enrolled. For safety considerations, with up to 144 subjects receiving AMG 986 (114 healthy and 30 patients), there is a 99.94% chance of detecting an adverse event with a true incidence rate of 5% or greater and a 99.99 % chance of detecting a more common adverse event with a true incidence rate of 10%. A rare event with a true incidence rate of 1% will have a chance of 76.48% to being detected with the current sample size.

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

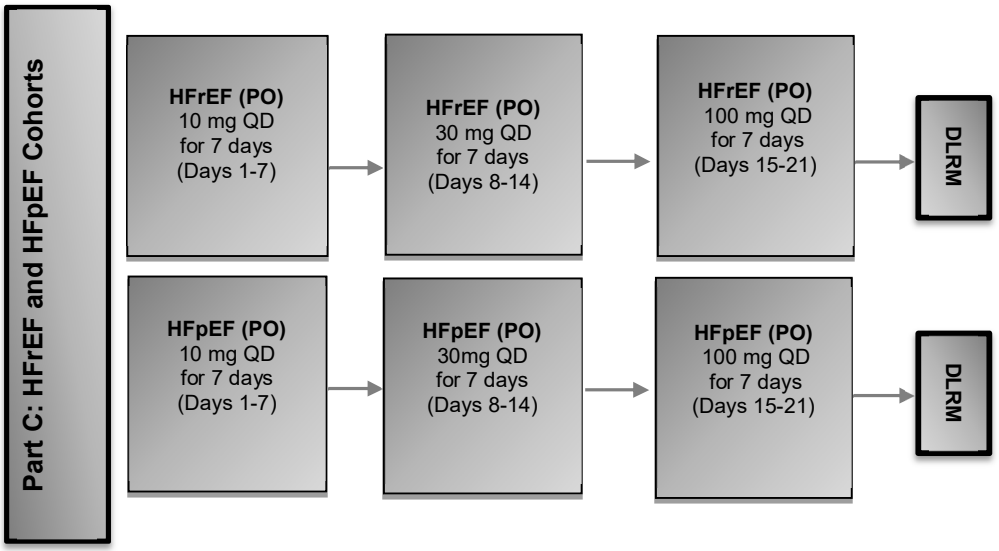
Sponsor: *Amgen, Inc*

Study Design and Treatment Schema



Study Design and Treatment Schema

Part C



Abbreviations:

DLRM = Dose Level Review Meeting
h = Hour
IV = Intravenous
QD = Once Daily Dosing
LD = IV Loading Dose
MD = IV Maintenance Dose
PO = Oral Dose

Study Glossary

Abbreviation or Term	Definition/Explanation
AE	Adverse Event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANA	Anti-nuclear antibody
APJ	apelin receptor
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{24h}	area under the concentration-time curve from time 0 to 24 hours
BMI	body mass index
BP	blood pressure
CL	Clearance
C_{max}	maximum observed concentration
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug induced liver injury
DLRM	dose level review meeting
DLRT	dose level review team
dP/dtmax	Maximal rate of left ventricular systolic pressure increase
ECG	Electrocardiogram
CRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
end of study for individual subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
end of treatment	defined as the last assessment for the protocol specified treatment phase of the study for an individual subject
end of study (primary completion)	defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint
end of study (end of trial)	defined as when the last subject is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts
Enrollment	When the investigator decides that the subject has met all eligibility criteria
FIH	first-in-human
GCP	good clinical practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen

Abbreviation or Term	Definition/Explanation
hERG	human Ether-à-go-go-Related Gene
HepCAb	hepatitis C antibody
HFrEF	heart failure with reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HIV	human immunodeficiency virus
HR	heart rate
IC_{50}	concentration at which 50% of the maximum inhibition is observed
ICF	informed consent form
ICH	International Conference on Harmonization
INR	international normalized ratio
IP	investigational product
IPIM	investigational product instruction manual
I_{Kr}	delayed rectifier potassium current
IUD	intrauterine device
IV	Intravenous
LD	Loading dose
MDAD	Multiple Daily Ascending Dose for the oral route and multiple 24 hour infusions that follow an initial loading dose on Day 1
MD	Maintenance dose
MDRD	Modification of Diet in Renal Disease
NASH	Nonalcoholic Fatty Liver Disease including Steatohepatitis
NOAEL	No observed adverse effect level
NOEL	No observed effect level
PD	Pharmacodynamics
PDE5	Phosphodiesterase 5
PK	Pharmacokinetics
PO	Oral dose
QD	Once daily dosing
Randomization	Once eligibility into the study has been confirmed, the subject will be randomized on Day 1 to receive either AMG 986 or placebo
SAE	Serious Adverse Event
SAER	Serious Adverse Event Report Form
SDAD	Single Day Ascending Dose for the oral route and single 24 hour infusion divided into an initial loading dose plus a maintenance dose for the intravenous route

Abbreviation or Term	Definition/Explanation
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
study Day 1	defined as the first day that protocol specified investigational product/protocol-required therapies is/are administered to the subject
TBL	total bilirubin
T_{max}	time of maximum concentration
ULN	upper limit of normal
Vss	steady-state volume of distribution

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1. OBJECTIVES

1.1 Primary

- To evaluate the safety and tolerability of ascending single (Part A) and ascending multiple (Part B) doses of AMG 986 in healthy subjects, who received AMG 986 by constant intravenous (IV) infusion or oral (PO) administration, and of ascending multiple PO doses of AMG 986 in heart failure patients (Part C).

1.2 Secondary

- To characterize AMG 986 pharmacokinetics (PK) after IV infusion and PO administration in healthy subjects and heart failure patients.

  To characterize the pharmacodynamic (PD) effects of AMG 986 in healthy subjects and in heart failure patients.

1.3 Exploratory

- To characterize AMG 986 excretion in urine.
- To characterize potential metabolite(s) of AMG 986 in plasma and urine (if appropriate).
- To evaluate AMG 986 impact on heart failure prognostic markers in heart failure patients.
- To evaluate AMG 986 impact on endothelial function markers including endothelin-1 (ET-1), angiotensin II (ANG II), and apelin.
- To characterize the effect of AMG 986 administration on free water clearance by the kidney into the urine.
- To evaluate the impact of AMG 986 administration on glucose and lipid metabolism.
- To explore the relationship between changes in QTc and AMG 986 exposure.

2. BACKGROUND AND RATIONALE

AMG 986 is a novel apelin receptor (APJ) small molecule agonist that binds and activates APJ receptor to improve cardiac function by increasing left ventricular contractile function and cardiac reserve without a significant impact on heart rate. AMG 986 is being developed as a potential treatment for heart failure.

2.1 Disease

Heart failure (HF) refers to a clinical condition in which the cardiac output is insufficient to meet the metabolic needs of body organs and is marked by cardiac systolic and/or diastolic dysfunction. Heart failure with predominantly systolic dysfunction, which is identifiable as decreased contraction, is more aptly described as heart failure with reduced ejection fraction (HFrEF). Alternatively, heart failure with a predominantly diastolic component, identifiable by decreased relaxation, is referred to as heart failure with preserved ejection fraction (HFpEF). Common to both types of heart failure is

uncoupling of left ventricular and arterial interaction. In an attempt to preserve cardiac output, a series of compensatory changes occur over time, which include increased sympathetic tone and peripheral vasoconstriction, as well as activation of the renin-angiotensin-aldosterone system as key features.

Heart failure is a common and debilitating disease, affecting almost 6 million Americans, or more than 2% of the United States population (McMurray and Pfeffer, 2005; Roger et al, 2012). However, cumulative evidence from epidemiologic studies shows that there has been only modest improvement in the prognosis of HF over the past 40 years despite numerous clinical advances (Khand et al, 2000). With a 1-year rate of cardiovascular mortality or HF hospitalizations of 30% to 40% in patients recently hospitalized for HF, symptomatic HF is associated with a worse prognosis than the majority of cancers.

Heart failure is a progressive disorder with a natural history punctuated by frequent recurrent hospitalizations and ultimately death. Long-term goals of HF therapy are to implement chronic interventions that decrease death and hospital readmission (Jessup et al, 2009; McMurray et al, 2012), both of which occur frequently (Lloyd-Jones et al, 2010). More recently, efforts have been made in developing therapies that improve cardiac reserve, symptoms of HF and functional capacity. While several interventions have been shown to reduce the rate of HF hospitalizations and improve mortality, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta-blockers, aldosterone antagonists, and biventricular pacing (Krum and Teerlink, 2011), mortality and morbidity still remain high. In addition, these available treatments that are aimed at diverse targets often fail to control symptoms or restore quality of life.

AMG 986 was developed to explore the therapeutic potential associated with the APJ pathway. AMG 986 is a long-acting small-molecule agonist that binds to the APJ receptor and activates $G_{\alpha i}$ and beta-arrestin with sub-nM potency.

AMG 986 may have therapeutic potential for both HFrEF and HFpEF.

2.2 Amgen Investigational Product Background

2.2.1 Pharmacology

Nonclinical Pharmacology

The cardiovascular effects of AMG 986 *in vivo* were studied in both rodent and canine models. In the ZSF1 rat (a model reproducing diastolic heart failure), AMG 986

increased cardiac contractile reserve, ejection fraction and stroke volume. Improvements in ventriculo-arterial coupling were also observed in ZSF1 rats. In a canine heart failure model (tachypacing), AMG 986 improved left ventricular contractile function without affecting heart rate. These nonclinical findings support the hypothesis that AMG 986 would be beneficial in addressing the underlying pathophysiology of heart failure in patients with either reduced or preserved ejection fraction. Details of AMG 986 nonclinical pharmacology are summarized in the AMG 986 Investigator's Brochure.

2.2.2 Pharmacokinetics

Non-clinical Pharmacokinetics

AMG 986 PK after single IV or oral dose administration was characterized in male CD1 mice, male Sprague-Dawley rats, male beagle dogs, and male cynomolgus monkeys. Following a single IV dose, the clearance (CL) of AMG 986 was low in mouse and dog and moderate in rat and monkey, relative to hepatic blood flow. Estimates of apparent steady-state volume of distribution (Vss) were variable across species and mean estimates of elimination half-life (t1/2,z) ranged from 2.26 hours in mice to 7.47 hours in monkeys. Metabolism was the primary pathway of AMG 986 clearance in rats. After single oral dosing in rats and dogs, AMG 986 was rapidly absorbed with peak concentrations achieved within 0.25 to 0.5 hours and oral bioavailability was approximately 73% in rats and 98% in dogs.

AMG 986 was highly bound to plasma protein and did not preferentially distribute into blood cells when assessed in vitro across species. AMG 986 was 99.6% bound in human plasma. The metabolism of AMG 986 in vitro was principally catalyzed by human CYP3A. Oxidized metabolites of AMG 986 were formed across species with no unique human metabolites observed in liver microsome and hepatocyte incubations.

AMG 986 was an inducer of CYP3A4 in vitro at clinically relevant AMG 986 concentrations, as determined by increases in CYP3A4 mRNA levels in primary human hepatocytes. AMG 986 was not an inhibitor in vitro of any of the major drug metabolizing human CYP enzymes. AMG 986 was characterized in vitro as a substrate of P-glycoprotein (P-gp) and organic anion-transporting polypeptide 1B3 (OATP1B3) transporters. Details of AMG 986 nonclinical pharmacokinetics are summarized in the AMG 986 Investigator's Brochure.

Predictions of Human Pharmacokinetics

Human PK parameters were predicted using in vitro and in vivo nonclinical data. AMG 986 CL and V_{ss} in humans were predicted to be 45.0 mL/h/kg and 463 mL/kg,

respectively, with a projected half-life in plasma of approximately 12 hours. Bioavailability after oral dosing was predicted to be 85%.

A linear two-compartment PK model with first-order elimination was used to estimate human exposures and simulate concentration-time profiles after AMG 986 administration by constant IV infusion. The same PK model with first-order absorption was used to estimate human exposures and perform simulations at the oral doses planned for the study.

Human PK model predictions were used to support selections of IV and oral doses, as described in Section 2.7 of the protocol.

2.2.3 Toxicology

Nonclinical Toxicology

The nonclinical toxicology package for AMG 986 included repeat dose toxicology studies with both oral (up to 6-months in duration in rats and 9-months in duration in dogs) and IV (14-day studies in rat and dog) dose routes and genetic toxicology, phototoxicity and safety pharmacology studies.

Repeat Dose Toxicology Studies:

The no-observed-adverse effect-levels (NOAEL) in all of the repeat dose oral and IV toxicology studies in rat and dog were the highest doses evaluated. For the 28-day oral studies, the no-observed-effect-levels (NOEL) in rats was 1000 mg/kg/day (limit dose) and the NOAEL in dogs (based on clinical signs of emesis) was 300 mg/kg/day. Estimates of AUC_{24h} exposures in rats at the NOEL dose and dogs at the NOAEL dose were 150-fold and 219-fold greater than observed human exposure at the 5 mg oral dose and 2.2-fold and 3.2-fold greater than the observed human exposure at 650 mg, respectively (Table 3). The margins from the toxicology studies support administration of the oral dose up to 650 mg planned for the current study.

In developmental and reproductive toxicology studies in rats and rabbits, oral administration of AMG 986 resulted in embryo-fetal toxicity and malformations. In rats, AMG 986-related fetal tail abnormalities and skeletal dysmorphogenesis were observed. In rabbits there were abortions, lower maternal body weights/ body weight gains associated with decreases in embryo-fetal survival, and external, visceral and skeletal malformations.

AMG 986 was negative in both in vitro and in vivo genetic toxicology studies and in an in vitro phototoxicity assay.

Safety Pharmacology:

The NOEL for effects on neurobehavioral and respiratory function in rats was 1000 mg/kg (single oral dose). In an anesthetized beagle dog cardiovascular (CV) study, with IV dose administration in a cumulative dose escalation design, AMG 986-related CV effects were limited to small dose-independent increases (~10%) in the rate of left ventricular pressure rise in early systole (dP/dtmax) and similar increases (~10%) in mean blood pressure at plasma concentrations greater than 1.34 µg/mL. In the conscious dog telemetry study, there were no AMG 986-related effects on hemodynamics (blood pressure and heart rate) or ECG parameters (PR, QRS, QT or heart rate-corrected QTc intervals [individual subject correction method]) after single oral doses up to 300 mg/kg (telemetry monitoring for at least 24 hours). No effects on QT/QTc interval were observed in the anesthetized dog study or the conscious dog telemetry study. Further, there were no changes in QTc interval in the 28-day oral dog toxicology (ECGs assessed in weeks 2 and 4) or in the 14-day IV dog toxicology study.

The IC_{50} value for inhibitory effect of AMG 986 on hERG current (I_{Kr} current; potassium channel in human ventricles primarily responsible for repolarization) was estimated to be $>$ 300 µM (157 µg/mL, unbound concentration), approximately 1000X higher than the predicted human maximum unbound concentrations at an oral dose of 650 mg and approximately 5000X higher than the highest planned IV infusion dose (60 mg loading dose + 360 mg/24 hours maintenance dose).

Details of AMG 986 nonclinical toxicology are summarized in the AMG 986 Investigator's Brochure.

2.3 Clinical Experience

The AMG 986 clinical program thus far consists of 5 studies (4 ongoing, 1 completed). In addition to ongoing Study 20150183, there are three phase 1, open-label, single-dose studies of AMG 986, including, Study 20150186 (renal impairment), Study 20150187 (healthy Japanese subjects), and Study 20170553 (tablet vs capsule formulation). Enrollment and dosing have been completed for all 3 of these studies. Study 20150185 is a completed, phase 1, open-label study to evaluate the effect of food and concomitant itraconazole administration on the pharmacokinetics of AMG 986 in heathy subjects.

Overall, up to the 01 June 2018 cutoff date, data from these 5 studies indicate that AMG 986 has an acceptable safety and tolerability profile at all doses tested in healthy subjects, in subjects with heart failure who have been evaluated thus far, in healthy

Japanese subjects, and in subjects with renal impairment. No serious or fatal adverse events have been reported, most reported adverse events in these studies were CTCAE grade 1, and no trends or specific safety concerns have been identified based on the types and frequency of adverse events that have occurred.

Refer to the AMG 986 Investigator's Brochure for details on AMG 986 clinical experience.

2.4 Risk/Benefit Assessment

2.4.1 Risk Assessment

AMG 986 has an identified risk of embryo-fetal toxicity and malformations. In developmental and reproductive toxicology studies in rats and rabbits, oral administration of AMG 986 resulted in abortions, embryo-fetal toxicity and external, visceral and skeletal malformations. Women of childbearing potential are not eligible to participate in this study, and male subjects must agree to practice an acceptable method of effective birth control and not donate sperm while on study and through 11 weeks after receiving the last dose of AMG 986. These inclusion/exclusion criteria will mitigate the risk of embryo-fetal toxicity.

AMG 986 has a potential risk of causing changes in blood pressure. Studies have shown that the principal effect of the apelin/APJ system is to counterbalance the renin-angiotension-aldosterone system, and apelin affects vascular tone and blood pressure. AMG 986-related cardiovascular changes in the nonclinical program were limited to modest and reversible decreases in mean blood pressure at the highest IV dose in the rat and small dose-independent increases in mean blood pressure in the anesthesized dog. Subjects will be closely monitored for changes in cardiovascular parameters, such as blood pressure, heart rate, and ECG measurements, and for signs and symptoms suggesting adverse events.

The nonclinical (toxicology and safety pharmacology) package suggests a safe profile for the initiation of clinical trials with AMG 986. Genetic toxicology and photosafety evaluations indicated that AMG 986 is not genotoxic or phototoxic. No AMG 986-related toxicity was identified in the rat or dog toxicology studies that were conducted with oral (6- and 9-months duration in rats and dogs, respectively) or IV (14-day studies) dose administration. The AUC-based exposure margins based on NO(A)EL doses from the rat and dog toxicology studies support the planned oral and IV infusion clinical dose ranges. Additionally, no AMG 986-related effects in the safety pharmacology studies were identified, including data indicating that QTc interval prolongation risk is low.

As of 01 June 2018, safety and tolerability data on clinical exposure to AMG 986 from FIH study 20150183 were available and reviewed for 19 fully implemented cohorts of 8 to 9 healthy subjects each. The subjects reviewed included those who received single oral doses of AMG 986 up to 650 mg, oral doses of AMG 986 up to 650 mg for 7 consecutive days, IV-infused doses of AMG 986 up to 24 hours (loading doses up to 60 mg over 1 hour followed by maintenance doses up to 360 mg over 23 hours), IV-infused doses of AMG 986 over 4 days (loading dose up to 60 mg over 1 hour followed by maintenance doses up to 360 mg over 23 hours and subsequent maintenance doses up to 376 mg over 24 hours for 3 additional days), and placebo.

There was a total of 116 subjects who received AMG 986 and 38 subjects who received placebo. Of these 154 subjects, 151 completed the investigational product, and 3 subjects withdrew after receiving investigational product due to subject request and not related to an adverse event.

For these 154 subjects there were no serious adverse events and no adverse events with fatal outcome. There were no adverse events from the cardiac disorders system organ class. Twenty-three subjects (14.9%) were reported to have treatment emergent adverse events during double-blind treatment. The most common event was headache, which occurred in 8 subjects (5.2%). The event of headache was reported as a common terminology criteria for adverse events (CTCAE) severity grade 1 in 7 of the subjects, and CTCAE grade 2 in 1 subject. The majority of the adverse events were CTCAE grade 1 events. There were 7 CTCAE grade 2 events (the only grade 2 event that occurred in more than 1 subject was toothache), and no grade 3 events. One CTCAE grade 4 event was reported; this event (blood creatine phosphokinase increased as high as 9927 U/L) occurred in a [redacted]-year-old [redacted] subject in the 650 mg PO multiple dose cohort on study day 5, was nonserious, resulted in no action/change to the investigational product administration, was not associated with clinical symptoms (eg, myalgia) or worsening renal function tests, occurred concurrently with a CTCAE grade 2 event of aspartate aminotransferase increased and a grade 1 event of alanine aminotransferase increased, did not require any treatment, and was reported as resolved on study day 29 (22 days after the last dose of investigational product).Overall, the prevalence of adverse events was comparable across all the cohorts and did not show higher incidence with increasing doses. The adverse event terms represented a variety of system organ classes and did not suggest a trend or indicate a specific safety concern.

After each dose cohort completed and before any dose escalation, an aggregate evaluation of adverse events, vital signs, ECG and laboratory parameters was performed in unblinded DLRMs. No clinically meaningful individual subject changes in vital signs (including blood pressure) were identified within or across any of the 19 cohorts. There were no notable variations in vital signs with increasing doses of AMG 986 throughout the study. Additionally, no trends in laboratory or ECG abnormalities (eg- QTc interval) were detected.

Additionally, data from 12 heart failure subjects enrolled in study 20150183 were available and reviewed. Eight subjects received oral doses of AMG 986 for 21 days (consisting of consecutive doses of 10, 30, and 100 mg for 7 days each) and 4 subjects received placebo. Four of the 12 subjects (33.3%) reported treatment-emergent adverse events during the double-blind treatment. No serious or fatal adverse events were reported. There was no discontinuation of investigational product due to an adverse event. All the events were CTCAE grade 1 events.

Refer to the AMG 986 Investigator's Brochure for further details on AMG 986 clinical experience.

In summary, the clinical experience accumulated with AMG 986 to date suggests that the administration of AMG 986 results in no safety concern up to the doses tested.

Taken together, the non-clinical data and clinical experience accumulated with AMG 986 suggest that the administration of AMG 986 at the proposed scheme is safe. All doses tested thus far were generally well tolerated and an acceptable safety profile was observed. Pregnant women should not take AMG 986.

2.4.2 Benefit Assessment

Patients enrolled in part C of the study will be treated with stable, optimal pharmacological therapy for a minimum of 4 weeks prior to randomization. Patients will be randomized to receive AMG 986 or a matching placebo. It is expected that patients participating in this study may derive benefits overall from the care and monitoring from the experts in the field. Those patients receiving AMG 986 may benefit from the additional positive contribution of AMG 986 on their disease.

2.4.3 Overall Benefit/Risk Assessment

The nonclinical (toxicology and safety pharmacology) package suggests a safe profile for the initiation of clinical trials with AMG 986. The AUC-based exposure margins based on NO(A)EL doses from the rat and dog toxicology studies support the planned

dose ranges. To date, the clinical experience accumulated with AMG 986 provides evidence that the administration of AMG 986 has an acceptable safety profile in all doses tested.

Considering the mechanism of action of AMG 986, the nonclinical safety profile, and the acceptable tolerability and safety of AMG 986 in humans thus far, together with the risk mitigation measures taken for the proposed study, the benefit/risk profile for AMG 986 in study 20150183 is positive.

2.5 Non-Amgen Medicinal Product Background

Not applicable for this study.

2.6 Pediatric Risk Assessment

Not applicable for this study.

2.7 Rationale

This study will evaluate the safety, tolerability, PK and PD of AMG 986 in healthy male and female subjects, and in heart failure patients with reduced (HFrEF) or preserved (HFpEF) ejection fraction, after AMG 986 dosing by IV or oral routes of administration. In all Parts of the study, healthy subjects and heart failure patients will receive investigational product in a fasted state.

IV infusion doses planned for the FIH study will be divided into an initial loading dose (LD) for the first hour followed immediately by a maintenance dose (MD) over the remainder of the dosing interval. Total continuous infusion up to 24 hours is planned for Part A of the study and up to 96 hours is planned for Part B. For Part C, heart failure patients will receive only oral IP once daily for up to 21 days.

The proposed loading dose infusion is supported by the planned use of AMG 986 in acute clinical settings and its anticipated rapid onset of pharmacological response. Selection of a 1 hour loading dose infusion will allow rapid titration to therapeutic concentration levels. Establishment of therapeutic concentrations early in the treatment course would also take advantage of the rapid rate of pharmacological response anticipated for AMG 986. Systemic apelin administration was shown within minutes to cause reductions in peripheral vascular resistance accompanied by increases in cardiac output in healthy subjects (Japp et al, 2010).

AMG 986 oral tablet administration is planned as a single dose in Part A of the study and as a once-daily (QD) dosing for 7 consecutive days in Part B and for 21 days in Part C.

Rationale for Dose Selection in Part A

Selection of the dose range for evaluation in healthy subject cohorts who receive AMG 986 by IV infusion or by single oral administration was based on model predictions of human exposure, target exposure associated with a 10% increase in ejection fraction in an ischemic heart failure dog model, and observed exposures in GLP toxicology studies.

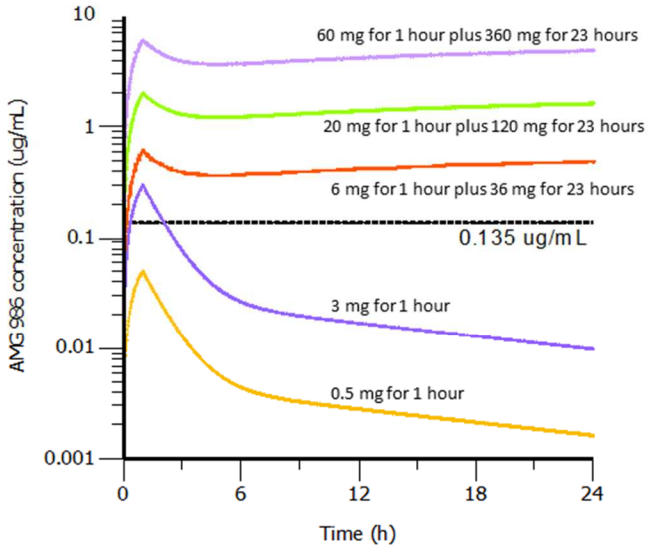
IV Cohorts 1 to 5:

The IV dose regimen proposed for Part A of the study will start at 0.5 mg administered as a 1-hour infusion. Escalation of IV doses will continue with 3 mg infused over 1 hour. The IV cohorts 1 and 2 will be comprised of a single 1 hour infusion without a maintenance dose. Subsequent escalation of IV cohorts will continue with 6 mg over 1 hour (LD) followed by infusion of 36 mg over 23 hours (MD; 1.57 mg/hour); with 20 mg over 1 hour (LD) followed by infusion of 120 mg over 23 hours (MD; 5.22 mg/hour); and 60 mg over 1 hour (LD) followed by infusion of 360 mg over 23 hours (MD; 15.7 mg/hour).

A clinical starting IV dose of 0.5 mg infused over 1 hour is not expected to elicit pharmacological activity based on observations in normal healthy dogs (Study 118965). In healthy subjects an IV dose of 0.5 mg infused over 1 hour is predicted to achieve a maximum plasma concentration of 0.0501 μg/mL (Table 1), approximately one-half the nonclinical target plasma concentration of 0.135 μg/mL (0.258 μM) associated with a 10% increase in both ejection fraction and fractional shortening in the dog heart failure model. Model predictions of human maximal exposures for the next IV cohort dose of 3 mg infused over 1 hour is anticipated to approximate the target concentration associated with cardiovascular function improvement in the dog model (Figure 1).

Relative to human exposure predictions at the starting single IV dose, mean AUC_{24h} exposures achieved at IV NOEL doses in the 14 day toxicology studies in male rats (300 mg/kg/day) and in dogs (100 mg/kg/day; sexes combined) were approximately 7090-fold and 4550-fold greater than human AUC_{24h} exposure predicted at the 0.5 mg IV starting dose, respectively. At the highest planned clinical IV dose, AUC_{24h} and C_{max} exposures in male rats and in dogs at NOEL doses were approximately 11-fold and 6.7-fold greater than human AUC_{24h} exposure and 48-fold and 20-fold greater than human C_{max} exposure predicted for infusions at 60 mg LD for 1 hour followed by 360 mg MD for 23 hours, respectively (Table 1).

Figure 1. Part A Predicted Human AMG 986 Concentration-time Profiles After Single 24 Hour Intravenous Infusions of AMG 986 Comprised of an Initial Loading Dose (IV Cohorts 1-5) and Immediately Followed by a Maintenance Dose (IV Cohorts 3-5)



Group	Intravenous Infusion Dose
cohort 1 IV	0.5 mg for 1 hour
cohort 2 IV	3 mg for 1 hour
cohort 3 IV	6 mg for 1 hour plus 36 mg for 23 hours
cohort 4 IV	20 mg for 1 hour plus 120 mg for 23 hours
cohort 5 IV	60 mg for 1 hour plus 360 mg for 23 hours

AMG 986 PK profiles (solid lines) and concentration target at 0.135 µg/mL associated with 10% increase in ejection fraction and fractional shortening in the dog heart failure model (reference line)

Table 1. Predicted Human Exposures After AMG 986 IV Infusion Over one day and Ratios Relative to Exposures at NOEL IV Doses in 14-Day rat and dog Toxicology Studies

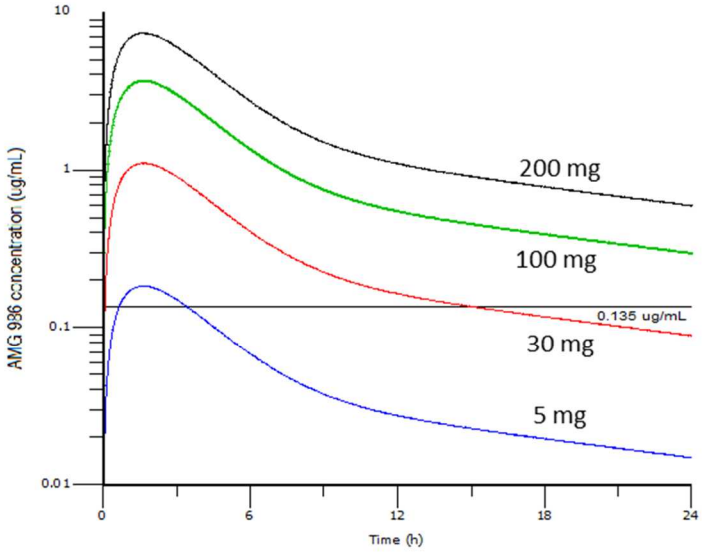
Clinical IV Dose		[1]Predicted Human PK		[2]Exposure Ratios	
LD (mg/ 1 h)	MD (mg/ 23 h)	Day 1 AUC_{24h} (µg*h/mL)	Day 1 C_{max} (µg/mL)	[3]Rat-Human Exposure Ratios ([5]AUC_{24h}; C_{max})	[4]Dog-Human Exposure Ratios ([5]AUC_{24h}; C_{max})
0.5	0	0.151	0.0501	7090; 5750	4550; 2440
3	0	0.908	0.300	1180; 960	757; 407
6	36	10.2	0.601	105; 479	67; 203
20	120	34.0	2.00	32; 144	20; 61
60	360	102	6.01	11; 48	6.7; 20

[1] Human PK predictions using a linear 2-compartment model with clearance (45 mL/h/kg) and apparent steady-state volume of distribution (463 mL/kg) parameters. Estimate of elimination half-life was approximately 12 hours.
[2] Exposure ratios calculated as Rat (Dog) / Human
[3] Mean of observed C_{max} and AUC_{24h} exposures at NOEL IV dose (300 mg/kg/day) on day 14 in male rats were 288 ug/mL and 1070 ug.h/mL, respectively. (Study: 120832)
[4] Mean of observed C_{max} and AUC_{24h} exposures at NOEL IV dose (100 mg/kg/day) on day 14 in dogs (sexes combined) were 122 ug/mL and 687 ug.h/mL, respectively. (Study: 120833)
[5] AUC exposure ratio calculated as rat (dog) day 14 AUC_{24h} / human day 1 AUC_{24h}
Abbreviations: Area under concentration-time curve from time 0 to 24 h after dosing, AUC_{24h}; maximum concentration, C_{max}; intravenous, IV; loading dose LD; maintenance dose, MD; no observed effect level, NOEL

Oral Cohorts 1 to 4:

The proposed single oral dose regimen for Part A will be 5, 30, 100 and 200 mg. Relative to human exposure predictions at the starting single oral dose, mean AUC_{24h} exposures achieved at an oral NOEL dose in male rats (1000 mg/kg/day) and NOAEL dose in dogs (300 mg/kg/day; sexes combined) in the 28-day toxicology studies were approximately 297-fold and 434-fold greater than human AUC_{24h} exposure predicted at the 5 mg oral starting dose, respectively. At the highest planned single oral dose in the clinic, AUC_{24h} and C_{max} exposures in male rats at a NOEL dose and in dogs at a NOAEL dose were approximately 7.4-fold and 11-fold greater than human AUC_{24h} exposure and 20-fold and 14-fold greater than human C_{max} exposure predicted at 200 mg single oral administration, respectively (Table 2). Model predictions of human maximal exposures at the starting dose of 5 mg are anticipated to approximate the target concentration associated with cardiovascular function improvement in the dog model (Figure 2).

Figure 2. Part A Predicted Human AMG 986 Concentration-time Profiles by Treatment Group Following a Single Oral Dose of AMG 986



Group	Oral Dose
cohort 1 PO	5 mg
cohort 2 PO	30 mg
cohort 3 PO	100 mg
cohort 4 PO	200 mg

AMG 986 PK profiles (solid lines) and concentration target at 0.135 µg/mL associated with 10% increase in ejection fraction and fractional shortening in the dog heart failure model (reference line)

Table 2. Predicted Human Exposures After AMG 986 Single Oral Dosing and Ratios Relative to Exposures at NO(A)EL Oral Doses in 1-month rat and dog Toxicology Studies

Clinical Dose	[1]Predicted Human PK		[2]Exposure Ratios	
Oral Dose (mg)	Day 1 AUC_{24h} (µg*h/mL)	Day 1 C_{max} (µg/mL)	[3]Rat-Human Exposure Ratios ([5]AUC_{24h}; C_{max})	[4]Dog-Human Exposure Ratios ([5]AUC_{24h}; C_{max})
5	1.24	0.180	297; 783	434; 543
30	7.42	1.08	50; 131	73; 91
100	24.7	3.61	15; 39	22; 27
200	49.5	7.21	7.4; 20	11; 14

[1] Human PK predictions using a linear 2-compartment model with clearance (45 mL/h/kg), apparent steady-state volume of distribution (463 mL/kg) and oral bioavailability (85%) parameters.
[2] Exposure ratios calculated as Rat (Dog) / Human
[3] Mean of observed C_{max} and AUC_{24h} exposures at NOEL PO dose (1000 mg/kg/day) on day 28 in male rats were 141 ug/mL and 368 ug.h/mL, respectively. (Study: 118964)
[4] Mean of observed C_{max} and AUC_{24h} exposures at NOAEL PO dose (300 mg/kg/day) on day 28 in dogs (sexes combined) were 97.7 ug/mL and 538 ug.h/mL, respectively. (Study: 118965)
[5] AUC exposure ratio calculated as rat (dog) day 28 AUC_{24h} / human day 1 AUC_{24h}
Abbreviations: Area under concentration-time curve from time 0 to 24h after dosing, AUC_{24h}; maximum concentration, C_{max}; loading dose LD; maintenance dose, MD; no observed (adverse) effect level NO(A)EL; oral, PO

Oral Cohorts 5 and 6:

After confirmation of safety and tolerability of oral AMG 986 at doses that range from 5 to 200 mg in Parts A and B, further escalations in dose are planned. The proposed single oral dose regimen extended for Part A will be 400 and 650 mg. Selection of the extended range of oral doses was based on the following: (1) acceptable safety and tolerability of oral does up to 200 mg, (2) observed AMG 986 PK results and (3) exposure margins projected for AUC exposures up to 650 mg relative to exposures observed at NOEL and NOAEL doses in GLP toxicology studies. Although dose proportionality was not formally evaluated in the FIH study, increases in AUC and C_{max} exposures appeared to be linear and proportional to dose over the 5 to 200 mg oral dose range tested. Assuming dose proportional increases in AMG 986 exposure at 650 mg, estimates of AUC_{24h} exposures in rats at the NOEL dose and dogs at the NOAEL dose were approximately 1.4-fold and 2.0-fold greater than the predicted human exposure at 650 mg, respectively. Estimates of AUC_{24h} exposures in rats at the NOEL dose and dogs at the NOAEL dose were 2.2-fold and 3.2-fold greater than the observed human exposure at the 650 mg oral dose, respectively (Table 3).

Table 3. Preliminary Observed AMG 986 PK Estimates in Healthy Subjects After Single Oral Dose Administration and Exposure Margins

Dose (mg)	Obs/ Pred	C_{max} (ng/mL) (CV%)	AUC_{inf} (ng*h/mL) (CV%)	[1]Rat-Human Ratio C_{max}	[1]Rat-Human Ratio AUC	[2]Dog-Human Ratio C_{max}	[2]Dog-Human Ratio AUC
5	Obs	334 (22)	2460 (34)	422X	150X	293X	219X
30	Obs	1850 (33)	12600 (25)	76X	29X	53X	43X
100	Obs	5760 (24)	34100 (5)	24X	11X	17X	16X
200	Obs	12200 (34)	85600 (33)	12X	4X	8X	6X
400	Obs	16200 (33)	102000 (53)	9X	3.6X	6X	5.3X
650	Obs	18400 (35)	169000 (61)	8X	2.2X	5.3X	3.2X

[1] Ratio of mean observed C_{max} and AUC_{24h} exposure at NOEL PO dose (1000 mg/kg/day; Study: 118964) on day 28 in male rats (141 ug/mL and 368 ug.h/mL, respectively) and human observed or predicted C_{max} and AUC_{inf} estimates.
[2] Ratio of mean observed C_{max} and AUC_{24h} exposure at NOAEL PO dose (300 mg/kg/day; Study: 118965) on day 28 in dogs (sexes combined; 97.7 ug/mL and 538 ug.h/mL, respectively) and human observed or predicted C_{max} and AUC_{inf} estimates.
[3] Predictions of human C_{max} and AUC_{inf} exposures were estimated by linear regression of observed data
Abbreviations: AUC_{24h}=area under the curve from 0h to 24h; AUC_{inf}=area under the curve from 0h to infinity; C_{max}=maximum concentration; CV%=coefficient of variation; Obs=observed; Pred=predicted

Rationale for Dose Selection in Part B

Prior to the transition from Part A to Part B, verification of PK model assumptions is planned as AMG 986 human PK data become available from individual IV and oral single dose cohort escalations in Part A. The IV dose regimen proposed for Part B of the study will include multiple 24 hour infusions administered for 4 consecutive days at a starting dose of 6 mg over 1 hour (LD) plus 38 mg/ 24 hours (MD; 1.57 mg/h, 36 mg/ 23 h on Day 1 and 38 mg/ 24 h on Days 2-4). A second IV cohort is proposed at 60 mg over 1 hour (LD) plus 376 mg/ 24 hours (MD; 15.7 mg/h, 360 mg/ 23 h on Day 1 and 376 mg/ 24 h on Days 2-4. The proposed once-daily (QD) oral dose regimen for Part B will be 5, 30, 100, 200, 400, and 650 mg QD for 7 consecutive days.

After confirmation of safety and tolerability of oral AMG 986 at doses that range from 5 to 200 mg in Parts A and B, further escalations in dose are planned. The proposed multiple oral dose regimen extended for Part B will be 400 mg QD and 650 mg QD for 7 consecutive days.

The planned dose escalation schedules for Part B may be modified based on treatment-emergent data (Part A or Part B safety and/or PK data). Dose adjustments, if

any, will be made for a full treatment cohort and not on an individual basis. Any dose adjustments will be agreed upon by Amgen in coordination with the investigator(s).

Rationale for Dose Selection in Part C

The starting dose of 10 mg by oral route daily in Part C was based on:

- Safety and tolerability observed with an up to 200 mg single oral dose in healthy subjects, as described in the Risk Assessment section (2.3).
- Pharmacodynamic response (change in stroke volume) measured (by echocardiography) at the 5 mg and 30 mg oral single and multiple doses in healthy volunteers.

In order to evaluate a potential effect of AMG 986 in patient subjects with heart failure, a starting dose of 10 mg has been proposed that is considered safe and could also potentially be sufficient to elicit a pharmacodynamic response by echocardiography.

Prior to the transition from Part B to Part C, verification of the safety, tolerability and PK model assumptions are planned as data become available from individual IV and oral multiple dose cohort escalations in Part B. Subjects will receive AMG 986 by oral administration at a dose of 10 mg daily for the first 7 days followed by 30 mg daily for the next 7 days and ending with 100 mg daily for the last 7 days.

The planned dose schedules for Part C may be modified based on treatment-emergent data (Part A or Part B safety and/or PK data). Pre-dosing adjustments, if any, will be made for a full treatment cohort and not on an individual basis. Any dose adjustments will be agreed upon by Amgen in coordination with the investigator(s).

2.8 Clinical Hypotheses

AMG 986 will be safe and well tolerated in healthy subjects and in heart failure patients after single and multiple dosing by IV infusion and oral administration.

3. EXPERIMENTAL PLAN

3.1 Study Design

This study is a randomized, placebo-controlled, double-blind, single day (Part A) and multiple daily (Part B) ascending dose study in healthy male and female adult subjects, between 18 and 55 years of age. Subjects will receive AMG 986 by IV infusion or by oral administration. In Parts A and B of the study, healthy subjects will receive investigational product in a fasted state. In Part C of the study, patients between the ages of 18 to 85 years with heart failure and either reduced (HFrEF) or preserved (HFpEF) ejection fraction will receive ascending doses of IP by once daily oral

administration for 21 days. The overall study design is described by a study schema at the end of the protocol synopsis section. The study endpoints are defined in Section 10.1.1.

At the conclusion of each cohort, a DLRM will convene to review all available data in an unblinded fashion in order to evaluate AMG 986 safety and tolerability before advancing to the next dose cohort. In support of escalation to the next planned dose level, a review of AMG 986 exposure and dose predictions will be conducted using available PK data from all dose cohorts.

Based on emerging safety and tolerability data and upon assessment by the DLRM members, cohorts may be removed or additional cohorts may be added. Subject numbers within each cohort may also be increased or decreased based on the decision from the DLRM. Doses to be administered within each cohort may be higher or lower than the last. Dosing of any subject shall not exceed the highest planned IV and PO cohorts for Parts A and B. (Refer to Table 7).

Part A.

Part A will consist of 5 IV infusion dose cohorts and 6 PO dose cohorts. Within each cohort, a total of 8 subjects will be randomized to receive AMG 986 or placebo in a 3:1 ratio. Subjects of IV dose cohorts will be in residence for at least 48 hours. Subjects of PO dose cohorts will be in residence for at least 24 hours.

IV dosing will occur by an infusion lasting 24 hours. Infusions will be divided into an initial loading dose for the first hour followed immediately by a maintenance dose for the remainder. Subjects in the first two IV dose cohorts will receive a loading dose only with no maintenance dose. Subjects in the oral dose cohorts will receive AMG 986 as a single oral administration. The sequence of escalation for IV dosing and PO dosing will partially overlap to achieve step-wise increases in AMG 986 exposure.

In Part A of the study, AMG 986 safety and tolerability will be evaluated at an unblinded DLRM before advancing to the next dose cohort. In support of escalation to the next planned dose level, a review of AMG 986 exposure and dose predictions will be conducted using available PK data from all dose cohorts. At the conclusion of each cohort, predictions of exposure and dose will be reviewed using PK data from the most recent cohort. A review of AMG 986 safety and tolerability will adhere to these guidelines during each DLRM governing dose escalations in Part A beginning with the

starting dose cohort (cohort 1 IV, 0.5 mg) through cohort 5 IV (60 mg LD + 360 mg MD), as shown in the study schema at the end of the protocol synopsis section.

Dose escalations in Part A will initially be sequential, with AMG 986 dosing to begin at the starting IV dose of 0.5 mg infused over 1 hour, followed by escalation to IV cohort 2 dosing at 3 mg infused over 1 hour. After the safety and tolerability of AMG 986 in IV Cohort 2 are demonstrated and reviewed at a DLRM, escalation to IV Cohort 3 and initiation of oral dosing at the proposed 5 mg starting dose will be permitted.

After the safety and tolerability of AMG 986 in IV Cohort 4 (20 mg LD + 120 mg MD) is demonstrated and reviewed at a DLRM, escalation to IV Cohort 5 (60 mg LD + 360 mg MD) will be permitted. After the safety and tolerability of AMG 986 in PO Cohort 4 (200 mg) is demonstrated and reviewed at a DLRM, escalation to PO Cohort 5 (400 mg) will be permitted. Enrollment for IV Cohorts will end after IV Cohort 5. After the safety and tolerability of AMG 986 (at 400 mg) are demonstrated and reviewed at a DLRM, escalation to PO Cohort 6 (650 mg) will be permitted.

Table 4. Intravenous Infusion and Oral Dose Escalations for Part A

	Intravenous Infusion (up to 24 hours)		Oral Administration (single dose)	
Cohort	LD (mg/1 hour)	MD (mg/23 hours)	Cohort	Dose (mg)
Cohort 1 IV (Part A)	0.5	0	Cohort 1 PO (Part A)	5
Cohort 2 IV (Part A)	3	0	Cohort 2 PO (Part A)	30
Cohort 3 IV (Part A)	6	36	Cohort 3 PO (Part A)	100
Cohort 4 IV (Part A)	20	120	Cohort 4 PO (Part A)	200
Cohort 5 IV (Part A)	60	360	Cohort 5 PO (Part A)	400
			Cohort 6 PO (Part A)	650

The safety and tolerability of each dose level (including the final IV and PO dose cohorts) in Part A will be assessed after all subjects have been enrolled and followed through at least for 4 days post dose.

Part B.

Part B will consist of 2 IV infusion dose cohorts and 6 PO dose cohorts. Within each cohort, a total of 8 subjects will be randomized to receive AMG 986 or placebo in a 3:1 ratio.

In Part B of the study, AMG 986 safety and tolerability will be evaluated at a DLRM before advancing to the next dose cohort. In support of escalation to the next planned dose level, AMG 986 exposure and dose predictions will be updated using available PK data that will include observed PK exposure after single day dosing in Part A of the study. Predictions of AMG 986 exposure anticipated for cohort 2 IV (60 mg LD + 360 mg/ 23 hours MD on Day 1 and 376 mg/24 hours MD on Days 2-4) will be reviewed using available PK data from cohort 1 IV (6 mg LD + 36 mg/ 23 hours MD on Day 1 and 38 mg/24 hours MD on Days 2-4).

In the IV cohorts, AMG 986 will be dosed as a series of IV infusions, each with duration of 24 hours, for 4 consecutive days. Subjects of the IV dose cohorts will be in residence for up to 24 hours after the completion of IV infusions. On study Day 1, IV infusions will be divided into an initial loading dose infusion for 1 hour followed immediately by a maintenance dose with duration for 23 hours. On study days 2 to 4, maintenance doses will be administered as constant infusions with duration for 24 hours.

The transition from ascending single day doses in Part A to ascending multiple daily doses in Part B is planned to occur after confirmation of AMG 986 safety and tolerability in IV Cohort 4 of Part A. The starting IV dose in Part B at 6 mg (LD) + 36 mg/ 23 hours MD on Day 1 and 38 mg/24 hours MD on Days 2-4 will have been previously evaluated over 24 hours in IV Cohort 3 of Part A. The rationale for an earlier partial overlap between IV dose cohorts in Parts A and B is supported by the anticipated exposure, safety and tolerability of AMG 986 in IV Cohort 4 of Part A at 20 mg (LD) + 120 mg (MD).

In the PO cohorts, AMG 986 will be dosed once daily for 7 consecutive days. Subjects of the PO dose cohorts will be in residence for at least 24 hours after the completion of the last dose on day 7.

Parts A and B will partially overlap for the oral dose cohorts. Transition to the first PO cohorts of Part B (5 mg QD) is planned to occur upon a DLRM decision to proceed after the 30 mg PO single dose cohort in Part A has been made. Subsequent oral dose escalations to 200 mg QD will occur in Part B as shown in the study schema. Escalation to 400 mg QD in Part B will be allowed after the safety and tolerability of AMG 986 at both 400 and 650 mg in Part A (PO cohorts 5 and 6, respectively) are demonstrated and reviewed at each DLRM.

Table 5. Intravenous Infusion and Oral Dose Escalations for Part B

Intravenous Infusion (for 4 days)			Oral Administration (once daily for 7 days)	
Cohort	Day 1 LD (mg/1 hour)	MD (mg/24 hours)	Cohort	Dose (mg)
Cohort 1 IV (Part B)	6	38 [a]	Cohort 1 PO (Part B)	5
Cohort 2 IV (Part B)	60	376 [b]	Cohort 2 PO (Part B)	30
			Cohort 3 PO (Part B)	100
			Cohort 4 PO (Part B)	200
			Cohort 5 PO (Part B)	400
			Cohort 6 PO (Part B)	650

a. Cohort 1 IV (Part B)
LD: 6 mg / 1 h
MD: 36 mg / 23h (Day 1)
MD: 38 mg / 24h (Days 2-4)
[total infusion = 96 h]

b. Cohort 2 IV (Part B)
LD: 60 mg / 1 h
MD: 360 mg / 23h (Day 1)
MD: 376 mg / 24h (Days 2-4)
[total infusion = 96 h]

The safety and tolerability of each dose level (including the final IV and PO dose cohorts) in Part B will be assessed after all subjects have been enrolled and followed through at least 4 days post dose.

Part C.

Part C will consist of 2 PO dose cohorts, one cohort for HFrEF patients and one cohort for HFpEF patients. Within each cohort, 20 subjects will be randomized to receive AMG 986 or placebo in a 3:1 ratio. Subjects will receive AMG 986 by oral administration at a dose of 10 mg daily for the first 7 days followed by 30 mg daily for the next 7 days and ending with 100 mg daily for the last 7 days for a total of 21 days of treatment. In Part C of the study, AMG 986 safety and tolerability will be evaluated at the end of the 21 day dosing period in an unblinded DLRM.

Table 6. Dose Regimen for HFrEF and HFpEF Patient Subjects in Part C

Day(s)	Route	AMG 986 Dose
1-7	PO	10 mg daily
8-14	PO	30 mg daily
15-21	PO	100 mg daily

3.2 Number of Sites

This study will be conducted in 15 or more sites in the United States, Europe, Canada and Asia. Additional sites and/or countries could be added as necessary to complete enrollment.

3.3 Number of Subjects

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

Approximately 152 healthy volunteer subjects and 40 heart failure patient subjects will be enrolled into the study. In Part A PO Dose Cohorts, 8 subjects per cohort will be enrolled for a total of 48 subjects across 6 cohorts. In Part A IV Dose Cohorts, 8 subjects per cohort will be enrolled for a total of 40 subjects across 5 cohorts. In Part B PO Dose Cohorts, 8 subjects per cohort will be enrolled for a total of 48 subjects across 6 cohorts. In Part B IV Dose Cohorts, 8 subjects per cohort will be enrolled for a total of 16 subjects across 2 cohorts. In Part C, up to 20 HFrEF patient subjects and up to 20 HFpEF patient subjects will be enrolled.

- Part A IV Dose Cohorts: 40 subjects (8 subjects per cohort)
- Part A PO Dose Cohorts: 48 subjects (8 subjects per cohort)
- Part B IV Dose Cohorts: 16 subjects (8 subjects per cohort)
- Part B PO Dose Cohorts: 48 subjects (8 subjects per cohort)
- Part C HFrEF cohort: Up to 20 HF patient subjects
- Part C HFpEF cohort: Up to 20 HF patient subjects

3.4 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study prior to receiving AMG 986 will be replaced at the discretion of the Amgen Medical Monitor and Principal Investigator. Subjects who are withdrawn or removed from treatment or the study may be replaced. This decision will be made by the Amgen Medical Monitor in consultation with the Principal Investigator and the Amgen Global Safety Officer.

The new subject will receive the identical treatment as the replaced subject, but will be assigned a replacement randomization number associated with this new record.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

For both healthy volunteer subjects and heart failure patient subjects, the planned length of participation in the study is approximately 58 days, which includes a 28 day screening period followed by 30 days on study.

3.5.2 End of Study

The EOS is the last planned clinic visit for each subject enrolled in this study, which is at Day 30.

Primary Completion: the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis;

End of Trial: the time when the last subject is assessed or receives an intervention for evaluation in the study.

4. SUBJECT ELIGIBILITY

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

4.1 Inclusion Criteria

101 Subject has provided informed consent prior to initiation of any study-specific activities/procedures.

102 Male and female subjects ≥ 18 to ≤ 55 years old with no history or evidence of clinically relevant medical disorders as determined by the investigator and the Amgen physician (Parts A and B only)

103 Body mass index (BMI) between 18 and 35 kg/m2, inclusive, at screening.

104 Physical examination including vital signs, clinical laboratory values, and ECGs are clinically acceptable to the investigator. Abnormal findings for healthy volunteers and unexpected findings for heart failure patient subjects will be discussed with Amgen prior to study enrollment.

105 Women must be of non-reproductive potential (ie, postmenopausal)

1. Age of ≥ 55 years with no menses for at least 12 months OR
2. Age of < 55 years with no menses for at least 12 months AND with postmenopausal gonadotropin levels (follicle-stimulating hormone levels > 40 IU/L or according to the definition of “postmenopausal range” for the laboratory involved) OR
3. History of hysterectomy OR
4. History of bilateral oophorectomy.

106 Men must agree to practice an acceptable method of effective birth control while on study through 11 weeks after receiving the last dose of investigational product (AMG 986 or placebo). Acceptable methods of effective birth control include sexual abstinence; vasectomy and testing that shows there are no sperm in the semen; or a condom with spermicide (men) in combination with barrier methods (diaphragm, cervical cap or cervical sponge), hormonal birth control or IUS (women).

107 Men must be willing to abstain from sperm donation while on study through 11 weeks after receiving the last dose of investigational product (AMG 986 or placebo).

108 This inclusion criterion only applies to Parts B and C cohorts. Before inclusion in the study, subjects will undergo a screening echocardiogram to ensure that the following parameters can be accurately measured: left ventricular end-systolic and end-diastolic volumes, left atrial end-systolic and end-diastolic volumes, ejection fraction, fraction shortening, and end-systolic septal and posterior wall thickness.

For Part C

Additional Inclusion Criteria for HFrEF Patients

109 Subject must be of age 18 to 85 years, have a diagnosis of HF confirmed by medical records for ≥ 3 months, and be in stable condition for at least 4 weeks.

110 Left ventricular ejection fraction (LVEF) ≤ 40% confirmed by echocardiogram, radionuclide ventriculography, cardiac magnetic resonance imaging, or contrast ventriculography within 12 months prior to randomization.

111 NYHA class II or III at screening

112 Sinus rhythm

113 NT-proBNP level ≥ 250 pg/ml

114 Patients will be treated with stable, optimal pharmacological therapy for a minimum of 4 weeks prior to randomization. Treatment of HFrEF includes at least beta-blockers (carvedilol, metoprolol succinate or bisoprolol) and a RAAS inhibitor (ACEi, ARB or sacubitril/valsartan).

Additional Inclusion Criteria for HFpEF patients

115 Subject must be of age of 18 to 85 years, have a diagnosis of HF confirmed by medical records for ≥ 3 months, and be in stable condition for at least 4 weeks.

116 Left ventricular ejection fraction (LVEF) ≥50% confirmed by echocardiogram, radionuclide ventriculography, cardiac magnetic resonance imaging, or contrast ventriculography within 12 months prior to randomization.

117 Left ventricular ejection fraction (LVEF) never ≤ 40% in the past

118 NYHA class II or III at screening

119 Sinus rhythm

120 NT-proBNP level ≥ 250 pg/ml

121 Patients will be treated with stable, optimal pharmacological therapy for a minimum of 4 weeks prior to randomization. Treatment of HFpEF includes at least a daily dose of diuretics equivalent to furosemide 40 mg.

122 For subjects in Parts A, B and C: Women must have negative results for both the screening (serum) and day -1 (serum or urine) pregnancy tests

4.2 Exclusion Criteria

201 Currently receiving treatment in another investigational device or drug study, or less than 30 days or 5 half-lives (whichever is longer), since ending treatment on another investigational device or drug study(s) prior to receiving the first dose of investigational product (AMG 986 or placebo).

202 Female subjects who are lactating/breastfeeding or who plan to breastfeed while on study through 11 weeks after receiving the last dose of investigational product (AMG 986 or placebo).

203 Male subjects with partners who are pregnant or planning to become pregnant while the subject is on study through 11 weeks after receiving the last dose of investigational product (AMG 986 or placebo).

204 Female subjects of reproductive potential.

205 Subjects in Parts A and B of the study: estimated glomerular filtration rate (eGFR) within the screening period of less than 60 mL/min/1.73m^2 as calculated using the estimated Modification of Diet in Renal Disease (MDRD) formula.

206 Current or prior malignancy within 5 years of randomization, with the exception of non-melanoma skin cancers, cervical or breast ductal carcinoma in situ, and adenocarcinoma of the prostate Stage I or IIa (defined as T1, T2a or T2b, N0, M0 with documented serum PSA < 20 ng/mL and Gleason score ≤ 7) per the American Joint Committee on Cancer (AJCC) primary tumor, regional lymph nodes, and distant metastasis system.

207 Positive results for Human Immunodeficiency Virus (HIV), antibodies, hepatitis B surface antigen (HBsAg), or hepatitis C antibodies (HepCAb).

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

209 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge.

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

211 Subject previously has entered this study or has been previously exposed to AMG 986.

212 Concurrent or prior use of strong CYP3A4 inhibitors within 14 days of study Day 1, including (not limited to): macrolide antibiotics (eg, clarithromycin, telithromycin), antifungals (eg, itraconazole, voriconazole), antivirals (eg, ritonavir, saquinavir, indinavir, nelfinavir), nefazodone.

213 Concurrent or prior ingestion of grapefruit or grapefruit products and other foods that are known to inhibit CYP3A4 within 7 days of study Day 1.

214 Concurrent or prior use of strong CYP3A4 inducers within 28 days of study Day 1, Including (not limited to): phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital. Subjects should also not take St John's Wort.

215 Concurrent or prior use of strong P-glycoprotein inhibitors within 28 days of study Day 1, including (not limited to): elacridar and valspodar.

216 All herbal supplements, vitamins, and nutritional supplements taken within the last 30 days prior to dosing on Day 1 (and continued use, if appropriate), must be reviewed and approved by the PI and Amgen Medical Monitor.

217 For subjects enrolled under Amendments 1-6, inclusive: QTc > 450 msec or history/evidence of long QT syndrome.

218 Planned elective surgery within 30 days of study completion or before return of red blood cell parameters to normal values.

219 Blood donation ≥ 500 mL within 60 days of Day 1.

220 Systolic blood pressure > 150 mm Hg or < 90 mm Hg, or diastolic blood pressure > 95 mm Hg or < 60 mm Hg, assessed on 2 separate occasions prior to enrollment (Parts A and B only).

221 Heart rate ≥ 100 beats per minute after 5 minutes of rest or an untreated symptomatic bradyarrhythmia within 1 month prior to enrollment.

222 **For Parts A and B:** Troponin I at screening > upper limit of normal (ULN).

223 In the opinion of the Investigator, a condition that compromises the ability of the subject to give written informed consent or to comply with study procedures.

224 Unwilling or unable to abstain from nicotine or tobacco containing products (including but not limited to: snuff, chewing tobacco, cigars, cigarettes, pipes, or nicotine patches) throughout the screening period and for the duration of the study.

225 Subjects who are unwilling or unable to limit alcohol consumption to 1 units/day (1 unit = 1 drink and 1 drink is equivalent to 12 ounces of regular beer, 8 to 9 ounces of malt liquor, 5 ounces of wine or 1.5 ounces of 80 proof distilled spirits).

226 Subjects with a positive urine drug screen or alcohol breath test.

227 Known history of drug or alcohol abuse.

228 Concurrent use of Phosphodiesterase 5 (PDE5) inhibitors including (not limited to) avanafil, sildenafil, tadalafil, vardenafil.

229 Concurrent use of vasodilators by healthy subjects in Parts A and B that could in the opinion of the investigator potentially lead to a drop in blood pressure in combination with investigational product.

230 Severe uncorrected valvular heart disease, or hypertrophic obstructive cardiomyopathy, active myocarditis, constrictive pericarditis, or clinically significant congenital heart disease.

231 For subjects in Part C of the study: estimated glomerular filtration rate (eGFR) within the screening period of less than 30 mL/min/1.732m^2 as calculated using the Modification of Diet in Renal Disease (MDRD) formula.

232 For subjects in Part C of the study: Systolic blood pressure > 160 mm Hg or < 100 mm Hg, or diastolic blood pressure > 110 mm Hg or < 60 mm Hg, assessed on 2 separate occasions prior to enrollment.

233 For subjects in Part C of the study: Troponin I > ULN if there is also evidence of an acute cardiovascular event.

234 For subjects enrolled in Part C under Amendment 7: QTc > 500 msec or history/evidence of long QT syndrome.

5. SUBJECT ENROLLMENT

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

All subjects must personally sign and date the informed consent form before commencement of study-specific activities/procedures.

The Investigator is to document the enrollment decision and date, in the subject's medical record and in/on the enrollment CRF.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The Investigator is to document the enrollment decision and date, in the subject's medical record and in/on the enrollment CRF.

Provided all eligibility criteria have been met, subjects will be asked to return to the research facility for admission on Day -1 (Baseline Visit) where additional assessments will be performed to confirm that the subject remains eligible for the study. If subject eligibility is confirmed, the subject will be randomized on Day 1 to receive either AMG 986 or universal placebo.

Each subject who enters into the screening period for the study (defined as the point when the subject signs and dates the IRB approved consent form) receives a unique subject identification number before any study procedures are performed. The subject

identification number will be assigned manually. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

The identification number will be 11 digits: the first 3 are the protocol identifier (183), the next 5 digits represent the site number, which consists of the 2-digit country code (66) and 3-digit study-specific site number (001), and the last 3 digits are assigned in sequential order as subjects are screened (eg, 001, 002, 003, etc.). Thus, the first subject screened at site 66001 would be 18366001001, and the second subject would be 18366001002, and so forth.

If the investigator has any questions regarding a subject's eligibility, he/she should contact the Amgen Medical Monitor. The site is to document the enrollment date in the subject's medical record and the electronic case report form (CRF).

Rescreening will be allowed for this study on a case-by-case basis at the discretion of the Amgen Medical Monitor in consultation with the Principal Investigator.

5.1 Randomization/Treatment Assignment

In study Parts A and B, 8 subjects will be enrolled in each cohort and will be randomized such that 6 subjects receive AMG 986 and 2 subjects receive placebo (3:1 ratio). In study Part C, up to 20 patient subjects will be enrolled in each of 2 cohorts to receive AMG 986 or placebo in a 3:1 ratio. Randomization to AMG 986 or placebo will be based on a randomization schedule (following a sentinel dosing design) prepared by Amgen before the start of the study. In all cohorts, eligible subjects will be randomized prior to dosing on Day 1 (day of investigational product AMG 986 or placebo administration). They will receive a unique randomization number and will be assigned to receive either AMG 986 or placebo. Once eligibility for study participation has been confirmed (based on data collected during the Screening visit and Day -1), a randomization number will be assigned in sequential order in which eligibility was met. At no time will the same randomization number be assigned to more than one subject. No more than 2 sentinel subjects will be dosed and observed for at least 24 hours before the remaining subjects in the cohort are dosed, provided there are no safety or tolerability concerns as assessed by the Principal Investigator (Part A and B).

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

5.2 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should only be unblinded by the investigator when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of subjects currently enrolled or subjects in subsequent cohorts. Unblinding at the study site for any other reason will be considered a protocol deviation. An unblinded pharmacist (and/or qualified designee) will have access to the treatment assignment and will be responsible for preparing the appropriate treatment based on the randomization list provided by Amgen (Part A and B) and from IVRS in Part C. Emergency unblinding at the site level for subject safety reasons will be done by the unblinded pharmacist upon investigator's request. The unblinded pharmacist will be responsible for securing any unblinded pharmacy records in a secure location.

It is encouraged that the Amgen Medical Monitor and/or Clinical 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. In this case, the Amgen Trial Manager must be notified within 24 hours after breaking the blind.

Treatment assignments will be unblinded after final lock. Upon receipt of written authorization from Amgen to unblind, the unblinded pharmacist will release the specified unblinded pharmacy records to site staff designated to enter the subject Package Lot Number (PLN) into each subject's Investigational Product Administration CRF.

6. TREATMENT PROCEDURES

6.1 Classification of Product and/or Medical Device

The Amgen investigational product and/or placebo used in this study include: AMG 986 and placebo.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 986 and placebo.

6.2 Investigational Product

All investigational products will be administered at the research facility by a qualified staff member.

A physician or qualified designee must be available at the time of administration of investigational product.

6.2.1 Amgen Investigational Product AMG 986 and Placebo

AMG 986 for PO administration will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical investigational product distribution procedures.
AMG 986 for PO administration will be presented as tablets available in 15-count bottles.

Placebo for PO administration will be presented in identical containers and stored/packaged the same as AMG 986.

AMG 986 for IV infusion will be manufactured by Integrity Bio Inc., and distributed using Amgen clinical investigational product distribution procedures. AMG 986 for IV infusion will be supplied with 4 mL deliverable volume in a single use 5 cc CZ® resin vial stored at or below 25°C, protected from light. AMG 986 is formulated as a sterile solution for infusion at a concentration of 10 mg/mL in 100 mM glycine at pH 9.4. Placebo for IV administration will be 0.9% w/v sodium chloride/ saline solution.

6.2.1.1 Dosage, Administration, and Schedule

In Parts A and B of the study, healthy subjects will receive investigational product (AMG 986 or placebo) in a fasted state. Subjects in the IV dose cohorts of Parts A and B will receive investigational product on an empty stomach (no food or liquids, except water, at least 2 hours prior to initial IV infusion) and refrain from food and liquid (except water) intake until after completion of the initial 1 hour infusion loading dose on study Day 1. Subjects in the PO dose cohorts of Parts A and B will receive investigational product on an empty stomach (no food or liquids, except water, at least 2 hours prior to drug administration) and refrain from food and liquid (except water) intake for at least 2 hours post dose.

In Part C of the study, subjects will receive oral investigational product administered on an empty stomach (no food or liquids, except water, at least 2 hours prior to drug administration) and refrain from food and liquid (except water) intake for at least 2 hours post dose.

Table 7. Cohort Investigational Product Dose Administration

Study Part	Cohort Name	Dosing Route	No. Doses	AMG 986 Total Dose (mg)
Part A	Cohort 1 IV (Part A)	IV	Single	0.5 mg LD
Part A	Cohort 2 IV (Part A)	IV	Single	3 mg LD
Part A	Cohort 3 IV (Part A)	IV	Single	6 mg LD + 36 mg MD
Part A	Cohort 4 IV (Part A)	IV	Single	20 mg LD + 120 mg MD
Part A	Cohort 5 IV (Part A)	IV	Single	60 mg LD + 360 mg MD
Part A	Cohort 1 PO (Part A)	PO	Single	5
Part A	Cohort 2 PO (Part A)	PO	Single	30
Part A	Cohort 3 PO (Part A)	PO	Single	100
Part A	Cohort 4 PO (Part A)	PO	Single	200
Part A	Cohort 5 PO (Part A)	PO	Single	400
Part A	Cohort 6 PO (Part A)	PO	Single	650
Part B	Cohort 1 IV (Part B) [a]	IV	Multiple	6 mg LD + 38 mg MD
Part B	Cohort 2 IV (Part B) [b]	IV	Multiple	60 mg LD + 376 mg MD
Part B	Cohort 1 PO (Part B)	PO	Multiple	5
Part B	Cohort 2 PO (Part B)	PO	Multiple	30
Part B	Cohort 3 PO (Part B)	PO	Multiple	100
Part B	Cohort 4 PO (Part B)	PO	Multiple	200
Part B	Cohort 5 PO (Part B)	PO	Multiple	400
Part B	Cohort 6 PO (Part B)	PO	Multiple	650
Part C	Cohort- HFpEF (Part C)	PO	Multiple	10 mg QD (Days 1-7) 30 mg QD (Days 8-14) 100 mg QD (Days 15-21)
Part C	Cohort- HFrEF (Part C)	PO	Multiple	10 mg QD (Days 1-7) 30 mg QD (Days 8-14) 100 mg QD (Days 15-21)

a. Cohort 1 IV (Part B)
LD: 6 mg / 1 h
MD: 36 mg / 23h (Day 1)
MD: 38 mg / 24h (Days 2-4)
[total infusion = 96 h]

b. Cohort 2 IV (Part B)
LD: 60 mg / 1 h
MD: 360 mg / 23h (Day 1)
MD: 376 mg / 24h (Days 2-4)
[total infusion = 96 h]

Investigational product for oral administration will be prepared as tablets in strengths of 5 mg and 25 mg. The tablets will be swallowed whole (not chewed) with a total volume of 240 mL (8 fluid ounces) of water. A mouth check will be performed by the principal investigator or qualified designee to ensure all tablets have been properly ingested.

Investigational product for IV infusion will be prepared by an unblinded pharmacist in normal saline bags for loading and maintenance doses. Additional details on administration of IP can be obtained in the Investigational product instruction manual (IPIM).

The dosing schedule is illustrated in a study schema in the protocol synopsis.

6.2.1.2 Dose-cohort Study Escalation and Stopping Rules

The progression of dose cohorts will initially be sequential with some overlap within and across study Parts. Dose escalation will occur after the DLRM voting members have reviewed available safety data through at least 4 days post-dose for single dose cohorts and through at least 4 days post-dose for multiple dose cohorts. Following the dose escalation decision, the next cohort(s) will be open for enrolment. There will be at least 2 weeks between the end of a dosing cohort and the start of a subsequent cohort(s) as proposed in the study schema.

Based on emerging safety and tolerability data and upon assessment by the DLRM members, cohorts may be removed or additional cohorts may be added. Subject numbers within each cohort may also be increased or decreased based on the decision from the DLRM. Doses to be administered within each cohort may be higher or lower than the last. Dosing of any subject shall not exceed the highest planned IV and PO cohorts for Parts A and B. (Refer to Table 7).

The dosing schedule is described by a schema in the protocol synopsis.

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

6.2.1.3.1 Dose Level Review Meetings

The DLRM will be held to review data, monitor safety and make dose change decisions. The DLRM team members will consist of the principal investigator or designee, Amgen medical monitor, Amgen Global Safety officer or designees, Amgen clinical study research manager or designee and biostatistics representative or designee. Additional members may be added as needed (eg, PK scientist). The voting members include the principal investigator or designee, Amgen medical monitor and Amgen Global safety officer or designee. The DLRM meeting will be conducted in an unblinded manner and attendees will be approved to access treatment assignments for the cohorts reviewed following Amgen standard procedure.

In Part A of the study, AMG 986 safety and tolerability will be evaluated at a DLRM before advancing to the next dose cohort. In support of escalation to the next planned dose level, a review of AMG 986 exposure and dose predictions will be conducted using available PK data from all dose cohorts. At the conclusion of each IV cohort, predictions of exposure and dose will be reviewed using PK data from the most recent cohort. A review of AMG 986 safety and tolerability will adhere to these guidelines during each DLRM governing dose escalations in Part A beginning with the starting dose cohort (cohort 1 IV, 0.5 mg) through cohort 5 IV (60 mg LD + 360 mg MD), as shown in the study schema at the end of the protocol synopsis section.

In Part B of the study, AMG 986 safety and tolerability will be evaluated at a DLRM before advancing to the next dose cohort. In support of escalation to the next planned dose level, AMG 986 exposure and dose predictions will be updated using available PK data that will include observed PK exposure after single day dosing in Part A of the study. Predictions of AMG 986 exposure anticipated for cohort 2 IV will be reviewed using available PK data from cohort 1 IV (6 mg LD + 36 mg/ 23 hours MD on Day 1 and 38 mg/24 hours MD on Days 2-4).

In Part C of the study, safety and tolerability will be evaluated at a DLRM at the end of the dosing period for each cohort.

The DLRM members are responsible for dosing decisions, which may include escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), de-escalation to a lower dose, continuation, delay or termination of dosing, or repetition or expansion of a cohort. Dosing decisions will be made based on unanimous agreement between the Amgen medical monitor, Amgen Global safety officer or designee and principal investigator or designee participating in the unblinded DLRM.

All available study data including echocardiograms, demographics, IP administration, medical history, concomitant medications, adverse events, ECG's, vital signs, plasma PK and laboratory results will be reviewed. Pharmacokinetic data for past cohorts, if available, may be reviewed at the DLRM's. DLRM will not require that all queries be resolved or source verified.

Data will be reviewed unblinded (eg, treatment assignment will be revealed) since unblinding is deemed necessary for the review team to make dosing decisions. Study sites will report all AEs categorized as CTCAE v.4 Grade 2 or higher to the unblinded

medical monitor (eg, Amgen study clinical director or medically qualified designate) via email within 24 hours of event occurrence. Study sites will include all available clinical information regarding an event as part of this report and provide follow-up information as it becomes available. The medical monitor will be responsible to complete the unblinded review of the information within 24 hours of receipt in order to look for any emerging safety signal (from either a single AE or pattern of AEs).

6.2.1.3.2 Dose Level Determination

To avoid exposing multiple subjects at the same time to an untested treatment, this study will use a sentinel dosing design. Within each cohort, the first 2 subjects enrolled will be randomized such that 1 subject will receive AMG 986 and the other receives matching placebo. Provided there are no safety signals up to 24 hours after completion of dosing for the sentinel subject(s), the remaining subjects in the cohort will be dosed thereafter.

The dose escalation schedule may be modified based on emerging PK, PD and safety findings. Dose adjustments will be made on a treatment cohort basis (not on an individual basis). The review of available safety data and dosing change decisions will be documented and Amgen will issue a written notification of the dose change to the investigators.

Following the dose escalation decision, the next cohort(s) will be open for enrolment.

6.2.1.3.3 Dose Stopping Rules

IV or PO dosing will be stopped or modified by the DLRM if suspected adverse drug reactions and/or changes in safety data (including but not limited to vital sign, ECG or clinical laboratory results) are observed and these changes pose a significant health risk in the opinion of either the investigator or Amgen.

No antidote to AMG 986 exists. Standard medical therapies should be used to treat adverse signs or symptoms that do not promptly resolve with discontinuation of the IP.

Investigators must follow patients until the complete resolution of any clinically significant event, irrespective of an IP dosing change.

For subjects receiving IV investigational product the following scheme should be applied in the occurrence of a significant change in blood pressure, heart rate, other vital sign, ECG, laboratory result or any other significant adverse event considered by the

investigator to be clinically relevant and directly related to infusion of investigational product.

- A change from baseline systolic or diastolic blood pressure levels ≥15% or a change in heart rate ≥25% during infusion should be followed by a 50% reduction of infusion rate for at least 15 minutes.
- If 3 consecutive assessments of blood pressure, heart rate, or other vital signs taken 5 minutes apart are considered to be back to pre-dose levels, restoration of initial infusion rates should be attempted with close monitoring.
- If subsequent assessments show a persistent and significant change in the same vital signs or adverse event considered by the investigator to be related to investigational product, a decision by the investigator can be made to
    - Continue at the reduced rate of infusion.
    - Further reduce infusion rate or stop infusion rate entirely.
- If other clinically relevant adverse event considered by the investigator to be related to investigational product occurs, a decision by the investigator can be made to:
    - Reduce rate of infusion by 50%.
    - Stop infusion rate entirely.

In either case, subsequent assessments, as described above, should guide investigational product administration.

In the event that a change from initial dosing rate is necessary, the Amgen medical monitor should be informed as soon as possible.

For subjects receiving ascending multiple doses of oral IP in Part C of the study, the following scheme should be applied to the occurrence of a significant change in blood pressure, heart rate, other vital sign, ECG, laboratory result or any other significant adverse event considered by the investigator to be clinically relevant and directly related to the PO administration of IP.

- During the observation period after administration of the oral IP, a persistent (lasting more than 2 assessment time-points) adverse event, change in baseline systolic or diastolic blood pressure ≥ 15% or a change in heart rate ≥ 25% deemed clinically significant by the investigator should prompt a possible change for the next oral IP administration.
- The decision to completely withhold IP, to resume IP or to resume with a reduced dose will be made with agreement of Amgen, the investigator and the subject.
- The dose reduction after a clinically significant event should follow the guidelines below:
    - If the subject does not tolerate the 10 mg dose, IP should be completely withheld.

- If the subject does not tolerate the 30 mg dose, IP should be reduced to 15 mg for the next administration. Upon occurrence of a novel event of intolerance with 15 mg, dosage will be reverted to 10 mg in the next IP administration and maintained at 10 mg until the end of the 21-day dosage period.
- If the subject does not tolerate the 100 mg dose, IP should be reduced to 75 mg for the next administration. Upon occurrence of a novel event of intolerance with 75 mg, dosage will be reverted to 50 mg in the next IP administration and maintained at 50 mg until the end of the 21-day dosage period.
- Patients will be observed for at least 6 hours after the first administration of a new dose.

For more details on the administration of oral or intravenous investigational product, refer to the Investigational Product Instruction Manual.

The quantity, volume, start date/time, stop date/time, and the amount of IP used as applicable to prepare the dose on the individual subjects will be entered in each subject's Investigational Product Administration CRF prior to receipt of unblinded authorization. Upon receipt of written authorization from Amgen to unblind, the unblinded pharmacist will release the specified unblinded pharmacy records to site staff designated to enter the subject PLN into each subject's Investigational Product Administration CRF. The effects of overdose of AMG 986 are not known. All overdose occurrences must be documented and corresponding adverse events must be recorded on the appropriate CRF and in source documents.

The study may be terminated at any point in time at the discretion of the sponsor.

In addition, dosing will be stopped or modified as shown in Table 8.

Clinically or medically significant suspected adverse drug reactions and serious adverse events considered to be related to study procedures will be followed until resolved or considered stable.

Table 8. Cohort Dose Stopping Rules

Scenario	Action
Any occurrence of a single CTCAE v4 Grade 2 adverse drug reaction or higher in a cohort, or occurrence of an event (including but not limited to abnormalities in vital sign, ECG or clinical laboratory results) suspected of being caused by administration of IP.	Stop dosing index subjects and additional subjects and convene DLRM (if event occurs outside the regularly scheduled DLRM window) Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance. Treatment unblinding to support evaluation of safety[a] Upon unanimous decision by the DLRM members, one of the following decisions may be made: – Resume dosing of index subject (if applicable) – Stop enrollment of the cohort (if applicable) – Resume enrollment of the cohort as planned – Resume enrollment of the cohort at a lower dose – Expand the cohort at the same dose – Add a lower dose cohort to the study – Escalate to an intermediate dose (a dose lower than the next planned dose) – Escalate to the next planned dose

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Abbreviations: CTCAE = Common terminology Criteria for Adverse Events;
[a] Finding must be confirmed by repeat measurement, whenever possible

Table 8. Cohort Dose Stopping Rules

Scenario	Action
Any occurrence of a CTCAE v4 Grade 2 suspected adverse drug reaction in 2 or more subjects in the same cohort, or occurrence of two events (including but not limited to abnormalities in vital sign, ECG or clinical laboratory results) requiring reduction in the dose administered in the same cohort.	Stop dosing index subjects and additional subjects and convene DLRM (if event occurs outside the regularly scheduled DLRM window) Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance. Treatment unblinding to support evaluation of safety[a] Upon unanimous decision by the DLRM members, one of the following decisions may be made: – Resume dosing of index subject (if applicable) – Stop enrollment of the cohort (if applicable) – Resume enrollment of the cohort as planned – Resume enrollment of the cohort at a lower dose – Expand the cohort at the same dose – Add a lower dose cohort to the study – Escalate to an intermediate dose (a dose lower than the next planned dose) – Escalate to the next planned dose
Any occurrence of a CTCAE v4 Grade 3 or greater suspected adverse drug reaction or occurrence of an event (including but not limited to abnormalities in vital sign, ECG or clinical laboratory results) requiring complete withdrawal of IP administration in the same cohort.	Stop dosing index individual and additional subjects in the cohort and convene DLRM (if event occurs outside regularly scheduled DLRM window) Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance Treatment unblinding to support evaluation of safety [a] If an adverse event is determined by unanimous decision of the DLRM members to be related to investigational product and clinically or medically significant, no further doses should be administered at this dose and no dose escalation should proceed. Enrollment of the study may continue at a lower dose or a lower dose cohort may be added to the study

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Abbreviations: CTCAE = Common terminology Criteria for Adverse Events;
[a] Finding must be confirmed by repeat measurement, whenever possible

Table 8. Cohort Dose Stopping Rules

Scenario	Action
Any occurrence of a CTCAE v4 Grade 3 or greater suspected adverse drug reaction or occurrence of an event (including but not limited to abnormalities in vital sign, ECG or clinical laboratory results) requiring complete withdrawal of IP administration in the same cohort.(Continued)	Otherwise, upon unanimous decision of the DLRM members, one of the following decisions may be made: – Resume dosing of index subject(s) if applicable – Resume enrollment of the cohort as planned – Resume enrollment of the cohort at a lower dose – Expand the cohort at the same dose – Add a lower dose cohort to the study – Escalate to the next planned dose – Escalate to an intermediate dose (a dose lower than the next planned dose)
Confirmed QTc ≥ 500 msecs or prolonged to ≥ 60 msecs from baseline in 2 subjects in the cohort within the first 6 hours post dose	Dosing will be stopped for any subject that meets this criterion. Serum potassium, magnesium and calcium will be measured immediately and the patient will receive supplementation to correct any low values. The investigator should notify the Amgen medical monitor immediately. Electrocardiogram monitoring will continue hourly for at least 3 hours until the QTc interval decreases to < 480 msecs. If hourly ECG's demonstrate a rising QTc interval or QTc prolongation >515 msecs, the subject will continue to be monitored for at least 24 hours until the QTc decreases to < 480 msecs. A DLRM will be held to analyze all relevant safety and PK data (if available) and decide on the following options – Resume dosing of index subject(s) (if applicable) – Stop enrollment of the cohort – Complete enrollment of the cohort at the same dose level – Expand the cohort at the same dose level – Open a new cohort at a lower dose level – Escalate to an intermediate dose (a dose lower than the next planned dose) – Escalate to the next planned dose level

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Abbreviations: CTCAE = Common terminology Criteria for Adverse Events;
[a] Finding must be confirmed by repeat measurement, whenever possible

6.2.2 Non-Amgen Investigational Product

Not applicable for this study.

6.3 Non-Investigational Product

Not applicable for this study.

6.3.1 Non-Amgen Non-Investigational Product

Not applicable for this study.

6.4 Other Protocol-required Therapies

Not applicable for this study.

6.5 Hepatotoxicity Stopping and Rechallenge Rules

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

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

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

- TBL > 2x upper limit of normal (ULN) or INR > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:

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

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

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

For subjects who do not meet the criteria for permanent discontinuation of Amgen investigational product outlined above and have no underlying liver disease, and eligibility criteria requiring normal transaminases and TBL at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of Amgen investigational product and other protocol-required therapies:

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

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

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

Investigational product should be withheld pending investigation into alternative causes of DILI. If investigational product is withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI. Re-challenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.5.3).

6.5.3 Criteria for Re-challenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to re-challenge the subject should be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with re-challenge, then Amgen investigational product and other protocol-required therapies, as appropriate should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.5.1) should never be re-challenged.

6.6 Concomitant Therapy

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.11.

Concomitant therapies are to be collected from informed consent through EOS. Therapy name, indication, dose, unit, frequency, route, start date and stop date should be collected.

Acetaminophen (no more than 325 mg per dose and 2 g per day) for analgesia and hormone replacement therapy (eg, estrogen, thyroid hormone) will be allowed. Any herbal medicines, vitamins and supplements consumed by the subject within 30 days prior to receiving the first dose of AMG 986 and continuing use if considered, will be reviewed by the principal investigator and Amgen medical monitor. Written documentation of this review and Amgen acknowledgment are required for subject participation. Details of all concomitant medications will be recorded in the subject's source documents and on the CRF.

Subjects must not consume grapefruit or grapefruit products during the study or within 7 days of study Day 1.

6.7 Alcohol and Tobacco Restrictions

Subjects are not permitted to consume any alcohol while in residence and within 24 hours prior to a study visit (including screening).

During the study, the use of alcohol will be limited to no more than 1 drink per day (1 drink being the equivalent of 12 ounces of regular beer, 5 ounces of wine or 1.5 ounces of 80 proof distilled spirits).

Subjects are not permitted to use nicotine or tobacco containing products (including but not limited to: snuff, chewing tobacco, cigars, cigarettes, pipes, or nicotine patches) throughout the screening period and for the duration of the study.

There will be no restrictions regarding caffeine intake during the screening period or at any time during the study.

6.8 Other Treatment Procedures

Not applicable for this study.

6.9 Medical Devices

Not applicable for this study.

6.10 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s), device(s) or combination product (s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

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

6.11 Excluded Treatments, Medical Device use, and/or Procedures During Study Period

During the study period, use of strong CYP3A4 inhibitors is not allowed, including (not limited to): macrolide antibiotics (eg, clarithromycin, telithromycin), antifungals (eg, itraconazole, voriconazole), antivirals (eg, ritonavir, saquinavir, indinavir, nelfinavir), nefazodone.

During the study period, ingestion of grapefruit or grapefruit products and other foods that are known to inhibit CYP3A4 is not allowed.

During the study period, use of strong CYP3A4 inducers is not allowed, Including (not limited to): phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital. Subjects should not take St John's Wort.

During the study period, use of strong P-glycoprotein inhibitors is not allowed, including (not limited to): elacridar and valspodar.

During the study period, use of PDE5 inhibitors including but not limited to avanafil, sildenafil, tadalafil, vardenafil is not allowed.

During the study period, use of vasodilators that could in the opinion of the investigator potentially lead to a drop in blood pressure in combination with investigational product is not allowed.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

A complete schedule of assessments has been included in Section 7.1.

Refer to the applicable supplemental (eg, laboratory, imaging, ECG) manuals for detailed collection and handling procedures.

Table 9. Schedule of Assessments for Cohorts 1 & 2 IV Part A

Activity	Screening	Check-in	Treatment Period												
Study Day	**-28 to -2**	**-1**	**1**												
Study Time (Hours)			**Predose**	**0**	**0.25**	**0.5**	**1**	**1.25**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**
General & Safety Assessments															
Informed Consent	X														
Residency [A]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History	X														
Physical Examination	X	X													
Weight	X	X													
Height	X														
Vital Signs (BP [F], HR, RR, TEMP) [B]	X	X	X		X	X	X	X	X	X	X	X	X	X	X
ECG [C]	X		X			X	X		X	X		X	X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events [W]			X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments															
Chemistry, Hematology, & Urinalysis	X	X													
Troponin I	X		X												
FSH (postmenopausal females only) [D]	X														
HIV, HepCAb, HBsAg, HBcAb	X														
Drug, Alcohol, & Cotinine Screen	X	X													
Echocardiographic Assessments															
M-mode and 2-D									X				X		
M-mode, 2-D, Flow & Tissue Doppler			X												
Investigational Product Administration															
IP Administration (LD, 1 hr infusion)				X											
Pharmacokinetic Assessments															
AMG 986 Plasma PK Collection			X		X	X	X [G]	X	X	X	X	X	X	X	X
Cumulative Urine Collection for AMG 986 PK			X [H]												X [I]

Footnotes defined on page 71

Table 9. Schedule of Assessments for Cohorts 1 & 2 IV Part A

Activity	Follow Up Period					EOS
Study Day	**2**	**3**	**4**	**5**	**14**	**30**
Study Time (Hours)	**24**	**48**	**72**	**96**		
General & Safety Assessments						
Informed Consent						
Residency [A]	X	X				
Medical History						
Physical Examination	X	X		X		X
Weight						
Height						
Vital Signs (BP [F], HR, RR, TEMP) [B]	X	X	X	X	X	X
ECG [C]	X	X				X
Concomitant Medications	X	X	X	X	X	X
Adverse Events [W]	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X
Laboratory Assessments						
Chemistry, Hematology, & Urinalysis	X	X		X	X	X
Troponin I	X			X		
FSH (postmenopausal females only) [D]						
HIV, HepCAb, HBsAg, HBcAb						
Drug, Alcohol, & Cotinine Screen						X
Echocardiographic Assessments						
M-mode and 2-D						
M-mode, 2-D, Flow & Tissue Doppler	X					
Investigational Product Administration						
IP Administration (LD, 1 hr infusion)						
Pharmacokinetic Assessments						
AMG 986 Plasma PK Collection	X	X	X	X		
Cumulative Urine Collection for AMG 986 PK	X [J]	X [K]				

Footnotes defined on page 71

Table 10. Schedule of Assessments for Cohorts 3 to 5 IV Part A

Activity	Screening	Check-in	Treatment Period									
Study Day	**-28 to -2**	**-1**	**1**									
Study Time (Hours)			**Predose**	**0**	**0.25**	**0.5**	**1**	**1.25**	**1.5**	**2**	**6**	**12**
General & Safety Assessments												
Informed Consent	X											
Residency [A]		X	X	X	X	X	X	X	X	X	X	X
Medical History	X											
Physical Examination	X	X										
Weight	X	X										
Height	X											
Vital Signs (BP [F], HR, RR, TEMP) [B]	X	X	X		X	X	X	X	X	X	X	X
ECG [C]	X		X			X	X		X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events [W]			X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments												
Chemistry, Hematology, & Urinalysis	X	X										
Troponin I	X		X									
FSH (postmenopausal females only) [D]	X											
HIV, HepCAb, HBsAg, HBcAb	X											
Drug, Alcohol, & Cotinine Screen	X	X										
Echocardiographic Assessments												
M-mode and 2-D									X		X	
M-mode, 2-D, Flow & Tissue Doppler			X									
Investigational Product Administration												
IP Administration (LD, 1 hr infusion)				X								
IP Administration (MD, 23 hr infusion)							X					
Pharmacokinetic Assessments												
AMG 986 Plasma PK Collection			X		X	X	X [G]	X	X	X	X	X
Cumulative Urine Collection for AMG 986 PK			X [H]									X [I]

Footnotes defined on page 71

Table 10. Schedule of Assessments for Cohorts 3 to 5 IV Part A

Activity	Treatment Period									Follow-Up Period						EOS
Study Day	2									3	4	5	6	7	14	30
Study Time (Hours)	24	24.25	24.5	25	26	27	29	31	36	48	72	96	120	144		
General & Safety Assessments																
Informed Consent																
Residency [A]	X	X	X	X	X	X	X	X	X	X						
Medical History																
Physical Examination	X									X		X				X
Weight																
Height																
Vital Signs (BP [F], HR, RR, TEMP) [B]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[T]	X	X
ECG [C]	X		X	X	X		X		X	X	X					X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X[T]	X	X
Adverse Events [W]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[T]	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X[T]	X	X
Laboratory Assessments																
Chemistry, Hematology, & Urinalysis	X									X		X			X	X
Troponin I	X											X				
FSH (postmenopausal females only) [D]																
HIV, HepCAb, HBsAg, HBcAb																
Drug, Alcohol, & Cotinine Screen																X
Echocardiographic Assessments																
M-mode and 2-D							X				X		X[U]			
M-mode, 2-D, Flow & Tissue Doppler	X									X						
Investigational Product Administration																
IP Administration (LD, 1 hr infusion)																
IP Administration (MD, 23 hr infusion)																
Pharmacokinetic Assessments																
AMG 986 Plasma PK Collection	X [G]	X	X	X	X	X	X	X	X	X	X	X	X	X[T]		
Cumulative Urine Collection for AMG 986 PK	X [J]									X [K]						

Footnotes defined on page 71

Table 11. Schedule of Assessments for Cohorts 1-6 PO Part A

Activity	Screening	Check-in	Treatment Period										Follow Up Period					EOS
Study Day	**-28 to -2**	**-1**	**1**										**2**	**3**	**4**	**5**	**14**	**30**
Study Time (Hours)			**Predose**	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**96**		
General & Safety Assessments																		
Informed Consent	X																	
Residency [A]		X	X	X	X	X	X	X	X	X	X	X	X					
Medical History	X																	
Physical Examination	X	X											X			X		X
Weight	X	X																
Height	X																	
Vital Signs (BP [F], HR, RR, TEMP) [B]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG [C]	X		X		X	X	X		X	X		X	X	X				X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events [W]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																		
Chemistry, Hematology, & Urinalysis	X	X											X			X	X	X
Troponin I	X		X										X			X		
FSH (postmenopausal females only) [D]	X																	
Pregnancy	X	X																X
HIV, HepCAb, HBsAg, HBcAb	X																	
Drug, Alcohol, & Cotinine Screen	X	X																X
Echocardiographic Assessments																		
M-mode and 2-D							X			X		X						
M-mode, 2-D, Flow & Tissue Doppler			X										X					
Investigational Product Administration																		
IP Administration				X														
Pharmacokinetic Assessments																		
AMG 986 Plasma PK Collection			X		X	X	X	X	X	X	X	X	X	X	X	X		
Cumulative Urine Collection for AMG 986 PK			X [H]									X [I]	X [J]					

Footnotes defined on page 71

Table 12. Schedule of Assessments for IV Cohorts Part B

Activity	Screening	Check-in	Treatment Period												
Study Day	**-28 to -2**	**-1**	**1**										**2**	**3**	**4**
Study Time (Hours)			**Predose**	**0**	**0.25**	**0.5**	**1**	**1.25**	**1.5**	**2**	**6**	**12**	**24**	**48**	**72**
General & Safety Assessments															
Informed Consent	X														
Residency [A]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History	X														
Physical Examination	X	X											X		
Weight	X	X													
Height	X														
Vital Signs (BP [F], HR, RR, TEMP) [B]	X	X	X		X	X	X	X	X	X	X	X	X	X	X
ECG [C]	X		X			X	X		X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events [W]			X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments															
Chemistry, Hematology, & Urinalysis	X	X													
Troponin I	X		X										X		
Plasma Osmolality			X [E]										X	X	
Urine Osmolality			X [N]										X [S]	X [S]	
FSH (postmenopausal females only) [D]	X														
HIV, HepCAb, HBsAg, HBcAb	X														
Drug, Alcohol, & Cotinine Screen	X	X													
Echocardiographic Assessments															
M-mode and 2-D	X										X				X
M-mode, 2-D, Flow & Tissue Doppler			X										X	X	
Investigational Product Administration															
IP Administration (LD, 1 hr infusion)				X											
IP Administration (MD, 23 hr infusion [Day 1])							X								
IP Administration (MD, 24 hr infusion [Days 2-4])													X	X	X
Pharmacokinetic Assessments															
AMG 986 Plasma PK Collection			X		X	X	X [G]		X	X	X	X	X [G]	X [G]	X [G]
Cumulative Urine Collection for AMG 986 PK			X [M]												

Footnotes defined on page 71

Table 12. Schedule of Assessments for IV Cohorts Part B

Activity	**Follow-Up Period**														**EOS**
Study Day	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**6**	**7**	**8**	**10**	**14**	**30**
Study Time (Hours)	**96**	**96.25**	**96.5**	**97**	**98**	**99**	**101**	**103**	**108**	**120**	**144**	**168**	**216**		
General & Safety Assessments															
Informed Consent															
Residency [A]	X	X	X	X	X	X	X	X	X	X					
Medical History															
Physical Examination							X			X				X	X
Weight															
Height															
Vital Signs (BP [F], HR, RR, TEMP) [B]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG [C]	X		X	X	X		X		X	X	X				X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events [W]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments															
Chemistry, Hematology, & Urinalysis	X									X				X	X
Troponin I	X														
Plasma Osmolality	X														
Urine Osmolality	X [S]														
FSH (postmenopausal females only) [D]															
HIV, HepCAb, HBsAg, HBcAb															
Drug, Alcohol, & Cotinine Screen															X
Echocardiographic Assessments															
M-mode and 2-D					X			X				X			
M-mode, 2-D, Flow & Tissue Doppler	X									X					X
Investigational Product Administration															
IP Administration (LD, 1 hr infusion)															
IP Administration (MD, 23 hr infusion [Day 1])															
IP Administration (MD, 24 hr infusion [Days 2-4])															
Pharmacokinetic Assessments															
AMG 986 Plasma PK Collection	X [G]	X	X	X	X	X	X	X	X	X	X	X	X		
Cumulative Urine Collection for AMG 986 PK	X [M]														

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Table 13. Schedule of Assessments for PO Cohorts Part B

Activity	Screening	Check-in	Treatment Period													
Study Day	**-28 to -2**	**-1**	**1**										**2**	**3**	**4**	**5-6**
Study Time (Hours)			**Predose**	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24 [Q]**	**48 [Q]**	**72[Q]**	**73-143 [Q]**
General & Safety Assessments																
Informed Consent	X															
Residency [A]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History	X															
Physical Examination	X	X											X			
Weight	X	X														
Height	X															
Vital Signs (BP [F], HR, RR, TEMP) [B]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
ECG [C]	X		X		X	X	X		X	X		X	X			
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events [W]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																
Chemistry, Hematology, & Urinalysis	X	X											X			X [P]
Troponin I	X		X										X			X [R]
Plasma Osmolality			X [E]										X			
Urine Osmolality			X [N]										X [S]			
FSH (postmenopausal females only) [D]	X															
Pregnancy	X	X														
HIV, HepCAb, HBsAg, HBcAb	X															
Drug, Alcohol, & Cotinine Screen	X	X														
Echocardiographic Assessments																
M-mode and 2-D	X						X			X						
M-mode, 2-D, Flow & Tissue Doppler			X										X			
Investigational Product Administration																
IP Administration [L]				X									X	X	X	X
Pharmacokinetic Assessments																
AMG 986 Plasma PK Collection			X		X	X	X	X	X	X	X	X	X	X	X	
Cumulative Urine Collection for AMG 986 PK			X [M]													

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Table 13. Schedule of Assessments for PO Cohorts Part B

Activity	Treatment Period									Follow-Up Period						EOS
Study Day	7									8	9	10	11	14	21	30
Study Time (Hours)	144 [Q]	144.5	145	146	147	148	150	152	156	168	192	216	240			
General & Safety Assessments																
Informed Consent																
Residency [A]	X	X	X	X	X	X	X	X	X	X						
Medical History																
Physical Examination	X									X				X	X	X
Weight																
Height																
Vital Signs (BP [F], HR, RR, TEMP) [B]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG [C]	X	X	X	X		X	X		X	X	X			X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events [W]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																
Chemistry, Hematology, & Urinalysis	X									X				X	X	X
Troponin I										X		X				
Plasma Osmolality	X															
Urine Osmolality	X [S]															
Pregnancy [D]																X
FSH (postmenopausal females only) [D]																
HIV, HepCAb, HBsAg, HBcAb																
Drug, Alcohol, & Cotinine Screen														X	X	X
Echocardiographic Assessments																
M-mode and 2-D				X								X		X	X	
M-mode, 2-D, Flow & Tissue Doppler	X									X						X [O]
Investigational Product Administration																
IP Administration [L]	X															
Pharmacokinetic Assessments																
AMG 986 Plasma PK Collection	X	X	X	X	X	X	X	X	X	X	X	X	X			
Cumulative Urine Collection for AMG 986 PK										X [K]						

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[A] Subjects in study Parts A and B will remain in-house from Day -1 through the completion of all assessments designated in the SOA.
[B] Vital signs will be performed pre-dose for each day in residency and at time points in the SOA.
[C] ECGs will be performed on Day 1 pre-dose. Study eligibility QTc must be < 450 msec as mentioned in section 122. Consultation with the medical monitor is required prior to dosing if QTc > 450 msec on Day 1 pre-dose. At screening a single ECG will be performed. At baseline, ECGs will be performed on 3 occasions separated by at least 30 minutes all in triplicate for a total of 9 ECGs. At all other time points ECGs will be performed in a standardized method, in triplicate and approximately 30 seconds apart, prior to blood draws or other invasive procedures.
[D] Female subjects only.
[E] Should be collected for subjects who qualify for enrollment.
[F] BP measurements will be obtained in triplicate approximately 2 minutes apart in a semi-Fowler position at pre-dose and at time points corresponding to ECG monitoring.
[G] PK sample collection to occur just prior to the end of infusion.
[H] Urine sample obtained at pre-dose void collection (5mL to 10mL aliquot).
[I] Aliquot (5mL to 10mL) of cumulative urine collection (0h to 12h) taken for PK sample.
[J] Aliquot (5mL to 10mL) of cumulative urine collection (12h to 24h) taken for PK sample.
[K] Aliquot (5mL to 10mL) of cumulative urine collected over past 24h taken for PK.
[L] Once daily PO AMG 986/placebo administration for 7 consecutive days.
[M] Aliquot (5mL to 10mL) of 24h urine collection taken for PK sample.
[N] Cumulative collection of urine over past 24 h required for baseline assessment. Required for subjects who meet eligibility requirements for enrollment. Not a requirement to assess eligibility for enrollment.
[O] This assessment will be performed only if deemed necessary by the investigator upon review of the prior assessment.
[P] Chemistry, Hematology, & Urinalysis to be collected on Day 5.
[Q] Procedures to be completed prior to dosing: physical examination, vital signs, ECGs, laboratory assessments, echocardiographic assessments, pharmacokinetic assessments.
[R] Troponin I to be collected on Day 5.
[S] Cumulative collection of urine over past 24 h required for osmolality assessment
[T] To be collected for only Cohort 5 IV Part A
[U] To be collected for only Cohorts 4 and 5 IV Part A
[V] If dose is reduced, patients will be observed for at least 6 hours after the first administration of a new dose
[W] Adverse events possibly related to any study procedures/study activity are reported from signing of the ICF.

Table 14. Schedule of Assessments for Patient Cohort Part C

Activity	10 mg PO Treatment													
Study Day	**-28 to -2[k]**	**-1**	**1**						**2**	**3**	**4**	**5**	**6**	**7**
Study Time (Hours)			Predose	0	1	2	4	6	24[G]	48[G]	72[G]	96[G]	120[G]	144[G]
General & Safety Assessments														
Informed Consent[J]	X													
Medical History	X													
Physical Examination	X	X							X					
Weight	X	X												
Height	X													
Vital Signs (BP[E], HR, RR, TEMP)[A]	X	X	X		X	X		X	X	X	X	X	X	X
ECG[B]	X		X		X	X	X	X						
Concomitant Medications	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Adverse Events[I]			→	→	→	→	→	→	→	→	→	→	→	→
Serious Adverse Events	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Laboratory Assessments														
Chemistry, Hematology, & Urinalysis	X	X							X					
Troponin I	X		X						X		X			
NT-proBNP	X													
FSH (postmenopausal females only)[C]	X													
Pregnancy[C]	X	X												
HIV, HepCAb, HBsAg, HBcAb	X													
Drug, Alcohol, & Cotinine Screen	X	X												
Echocardiographic Assessments														
M-mode, 2-D, Flow & Tissue Doppler	X		X					X			X			
Investigational Product Administration[E]														
IP Administration PO (10 mg, Days 1-7)				X					X	X	X	X	X	X
Pharmacokinetic/Biomarker Assessments														
AMG 986 Plasma PK Collection			X		X	X	X	X	X					
Plasma and Serum Biomarker Collection			X											
Cell Pellet Collection			X											

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Table 14. Schedule of Assessments for Patient Cohort Part C

Activity	30 mg PO									
Study Day	**8**				**9**	**10**	**11**	**12**	**13**	**14**
Study Time (Hours)	168[G] (Predose)	170	172	174	192[G]	216[G]	240[G]	264[G]	288[G]	312[G]
General & Safety Assessments										
Informed Consent										
Medical History										
Physical Examination										
Weight										
Height										
Vital Signs (BP[E], HR, RR, TEMP)[A]	X		X		X	X	X	X	X	X
ECG[B]		X		X						
Concomitant Medications	→	→	→	→	→	→	→	→	→	→
Adverse Events[I]	→	→	→	→	→	→	→	→	→	→
Serious Adverse Events	→	→	→	→	→	→	→	→	→	→
Laboratory Assessments										
Chemistry, Hematology, & Urinalysis	X				X					
Troponin I	X									X
NT-proBNP										
FSH (postmenopausal females only)[C]										
Pregnancy[C]										
HIV, HepCAb, HBsAg, HBcAb										
Drug, Alcohol, & Cotinine Screen										
Echocardiographic Assessments										
M-mode, 2-D, Flow & Tissue Doppler	X			X			X			
Investigational Product Administration										
IP Administration PO (30 mg, Days 8-14)[E]	X				X	X	X	X	X	X
Pharmacokinetic/Biomarker Assessments										
AMG 986 Plasma PK Collection	X	X	X	X	X					
Plasma and Serum Biomarker Collection	X									
Cell Pellet Collection										

Footnotes defined on page 75

Table 14. Schedule of Assessments for Patient Cohort Part C

Activity	100 mg											EOS
Study Day	**15 Predose**					**16**	**17**	**18**	**19**	**20**	**21**	**30**
Study Time (Hours)	336[G]	337	338	340	342	360[G]	384[G]	408[G]	432[G]	456[G]	480 [G]	
General & Safety Assessments												
Informed Consent												
Medical History												
Physical Examination	X										X	X
Weight												
Height												
Vital Signs (BP[E] HR, RR, TEMP)[A]	X	X		X		X	X	X	X	X	X	X
ECG[B]	X	X	X		X							X
Concomitant Medications												
Adverse Events[I]												
Serious Adverse Events												
Laboratory Assessments												
Chemistry, Hematology, & Urinalysis	X					X					X	X
Troponin I												X
NT-proBNP												
FSH (postmenopausal females only)[C]												
Pregnancy[C]												X
HIV, HepCAb, HBsAg, HBcAb												
Drug, Alcohol, & Cotinine Screen												
Echocardiographic Assessments												
M-mode, 2-D, Flow & Tissue Doppler	X				X			X			X	X
Investigational Product Administration												
IP Administration PO (100 mg, Days 15-21)[E]	X					X	X	X	X	X	X	
Pharmacokinetic/Biomarker Assessments												
AMG 986 Plasma PK Collection	X	X	X	X	X	X					X	
Plasma and Serum Biomarker Collection	X										X	
Cell Pellet Collection												

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[A.] Vital signs will be performed pre-dose for each day and at time points in the SOA.
[B.] ECGs will be performed on Day 1 pre-dose and may be repeated. . At screening a single ECG will be performed. At baseline, a single ECG will be performed. . At all other time points single ECGs will be performed in a standardized method, and prior to blood draws or other invasive procedures.
[C.] Female subjects only.
[D.] BP measurements will be obtained in a semi-Fowler position at pre-dose and at time points listed in the SOA.
[E.] Once daily PO AMG 986/placebo administration for 7 consecutive days.
[F.] This assessment will be performed only if deemed necessary by the investigator upon review of the prior assessment.
[G.] Procedures to be completed prior to dosing: physical examination, vital signs, ECGs, laboratory assessments, echocardiographic assessments, pharmacokinetic assessments.
[H.] If dose is reduced, patients will be observed for at least 6 hours after the first administration of a new dose
[I.] Adverse events possibly related to any study procedures/study activity are reported from signing of the ICF.
[J.] At the discretion of the PI and with safety considerations paramount, subjects may undergo study procedures on an inpatient basis.
[k.] Screening and Day -1 activities may be performed on the same day.

7.2 General Study Procedures

Before any study-related screening or baseline procedure can be completed, a subject must sign and date the IRB-approved ICF. After informed consent has been obtained, all screening procedures and tests establishing eligibility will be performed. Screening procedures are summarized in the Schedule of Assessments (Section 7.1).

During the study, every effort should be made to perform study procedures as indicated in the Schedule of Assessments (Section 7.1). Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the investigator's discretion.

Throughout the study, the permitted time windows for scheduled assessments will be as follows:

Table 15. Study Visit Windows

Study Part	Cohort Name	Visit Window	PK Plasma Collection Window	PK Urine Collection Window
Part A	Cohorts 1-2 IV (Part A)	Days 14 & 30: ± 1 day	Days 1-2: ± 10 minutes Days 3-5: ± 1 hour	Day 1: ± 1 hour Days 2-5: ± 2 hours
	Cohorts 3-5 IV (Part A)	Days 14 & 30: ± 1 day	Days 1-2: ± 10 minutes Days 3-6: ± 1 hour	Day 1: ± 1 hour Days 2-6: ± 2 hours
	Cohorts 1-4 PO (Part A)	Days 14 & 30: ± 1 day	Day 1: ± 10 minutes Days 2-5: ± 1 hour	Day 1: ± 1 hour Days 2-5: ± 2 hours
	Cohorts 5-6 PO (Part A)	Days 14 & 30: ± 1 day	Day 1: ± 10 minutes Days 2-5: ± 1 hour	Day 1: ± 1 hour Days 2-5: ± 2 hours
Part B	Cohorts 1-2 IV (Part B)	Days 14 & 30: ± 1 day	Days 1-5: ± 10 minutes Days 6-8: ± 1 hour	Day 5: ± 2 hours
	Cohorts 1-4 PO (Part B)	Days 11, 14, & 21: ± 1 day	Day 1: ± 10 minutes Day 7: ± 10 minutes Days 2-6: ± 1 hour Days 8-10: ± 1 hour	Day 8: ± 2 hours
	Cohorts 5-6 PO (Part B)	Days 11, 14, & 21: ± 1 day	Day 1: ± 10 minutes Day 7: ± 10 minutes Days 2-6: ± 1 hour Days 8-10: ± 1 hour	Day 8: ± 2 hours

Table 15. Study Visit Windows

Study Part	Cohort Name	Visit Window	PK Plasma Collection Window	PK Urine Collection Window
Part C	HFrEF and HFpEF	Not Applicable	Days 1: ± 10 minutes Days 2-4: ± 1 hour Day 5: ± 10 minutes Days 6-8: ± 1 hour Day 9: ± 10 minutes Days 10-16: ± 1 hour Days 17-21: ± 1 hour	Not collected

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Meal Restrictions:

The clinical site will provide standardized meals to the subjects during the in-house residency period.

Subjects are required to refrain from food and drinks (except water) 8 hours prior to each laboratory measurement.

Exercise Restrictions:

Subjects are required to refrain from strenuous exercise during screening, during in-house residency period and 48 hours prior to each outpatient visit.

7.2.1 Screening

After informed consent is obtained, screening procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Section 7.1).

For Rescreen Subjects: A new informed consent form must be signed unless it has been < 30 days since the previous ICF signature was obtained.

Repeat Assessments: Screening assessments (eg, vital signs, ECGs, laboratory assessments, cotinine and urine drug screen) may be repeated during screening. The decision regarding whether a subject has failed screening after repeat assessment will be decided on a case-by-case basis at the discretion of the Principal Investigator. The decision to re-screen a subject will be made on a case-by-case basis at the discretion of the Amgen Medical Monitor in consultation with the Principal Investigator.

7.2.2 Baseline / Day -1

Baseline is defined as assessments completed on Day -1 or Day 1 pre-dose, when the procedure is performed on Day 1 pre-dose. Subjects will be admitted to the research

facility on the day before IP administration (Day-1). The baseline / Day -1 procedures are to be completed at time points designated in the Schedule of Assessments (Section 7.1).

7.2.3 Treatment

Treatment begins when the first dose of protocol-required therapies is administered to a subject. The treatment procedures are to be completed during the Treatment Visits at time points designated in the Schedule of Assessments (Section 7.1).

If any subject stops treatment (eg, due to an adverse event), the subject will be asked to continue to complete protocol-required visits for safety monitoring as determined by the Principal Investigator in consultation with the Amgen Medical Monitor and Amgen Global Safety Officer.

When multiple post dose procedures are required to be conducted at the same nominal time point, the following order of precedence will be used: (1) vital signs, (2) ECGs, (3) PK sample collection, (4) Echocardiogram.

7.2.4 Safety Follow-up Visit(s)/End of Study Visit

Subjects will return to the clinic for follow-up visits in accordance to the Schedule of Assessments (Section 7.1) and be followed through the completion of the EOS procedures on Day 30. If an EOS test result demonstrates a clinically significant clinical or laboratory abnormality, the subject will be followed until resolution of the abnormality or until it is considered clinically stable by the investigator.

7.2.5 Long-term Follow-up

Not applicable for this study.

7.2.6 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and association to AMG 986.

7.2.7 Medical History

The investigator or designee will collect a complete medical history from birth to enrollment at screening and other times shown in Section 7.1. Any unresolved medical history will be graded according to Common Terminology Criteria for Adverse Events CTCAE version 4.0 (Appendix A) unless specified otherwise. Medical history will include information on the subject's concurrent medical conditions. All findings will be recorded on the relevant CRF.

7.2.8 Physical Examination

The investigator or qualified designee will perform a physical examination at the time points indicated in Section 7.1. Pre-dose abnormal findings will be reported on the medical history CRF. Any adverse change from the Baseline physical examination (Screening and Day -1 physical examination) will be documented on the Event CRF.

7.2.9 Physical Measurements

Height measurement (in cm and without shoes) and weight measurement (in kg and without shoes) will be obtained. Body mass index (BMI) will be calculated using height and weight measurements taken at screening and using the following formula:

$$\text{BMI (kg/m}^2\text{)} = \text{weight (kg)}/[\text{height (cm/100)}]^2$$

7.2.10 Vital Signs

Safety vital signs will be recorded by the investigator or designee at time points specified in Section 7.1.

The following measurements must be performed: systolic/diastolic BP, HR, respiratory rate, and temperature.

Blood pressure will be measured in the following manner:

- Subjects should be lying in a semi-Fowler position quietly and comfortably for at least 5 minutes. The upper arm should be bare without constrictive clothing and supported at heart level.
- An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. Neither the subject nor the observer (measurer) should talk during measurement.

In Parts A and B, BP measurements will be performed in a standardized method in triplicate approximately 2 minutes apart. Triplicate measurements of BP will be obtained at pre-dose and at time points corresponding to ECG monitoring. At time points in which ECG monitoring is not performed, single measures of BP will be obtained as part of the safety vital signs monitoring. In Part C, single BP measurements will be performed in a standardized method at pre-dose and at time points corresponding to ECG monitoring. At time points in which ECG monitoring is not performed, single measures of BP will be obtained as well. PK sample collection should occur after blood pressure measurements and ECG monitoring are completed.

Respiratory rate will be assessed by a full minute count. Abnormal measurements maybe repeated at the investigator's discretion. All data collected will be entered on the CRF.

The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF.

Record all measurements on the vital signs CRF. Abnormal measurements may be repeated at the discretion of the investigator and must be reported on the corresponding CRF page. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples.

7.2.11 Serum Follicle-stimulating Hormone Test (Females Only)

Additional serum will be collected for an FSH test for females at screening. Females must be of non-reproductive potential (ie, postmenopausal – age of ≥ 55 years with no spontaneous menses for at least 12 months, or age of < 55 years with no menses for at least 12 months AND with postmenopausal gonadotropin levels (follicle-stimulating hormone levels > 40 IU/Lor according to the definition of “postmenopausal range” for the laboratory involved) OR history of hysterectomy; OR history of bilateral oophorectomy OR history of bilateral salpingectomy).

Results must be consistent with postmenopausal status per local laboratory ranges for inclusion in this study. Postmenopausal status will be recorded on the medical history CRF.

7.2.12 Drug, Alcohol and Cotinine Screening

Drug, alcohol, and cotinine assessments are to be completed at screening, Day -1, and other times as listed in the Schedule of Assessments including amphetamines, barbiturates benzodiazepines, cocaine, ethanol, opiates, and tetrahydrocannabinol.

Subjects with a positive cotinine or drug test at screening may be retested once at the discretion of the investigator. Subjects with a positive test for cotinine at screening will be asked to refrain from being around second-hand smoke for 24 hours prior to Day -1. Subjects who test positive at Day -1 for drug, alcohol or cotinine will not qualify for investigational product administration and will be withdrawn from study participation.

7.2.13 Electrocardiogram

Electrocardiograms (henceforth referred to as electrocardiogram or ECG) will be performed using standard electrocardiogram machine at the times shown in the Schedule of Assessments (Section 7.1).

In Parts A and B, electrocardiograms will be collected as follows:

With the exception of the Screening ECG, which will be performed as a single electrocardiogram, all ECGs should be performed in a standardized method, in triplicate, and approximately 30 seconds apart, prior to blood draws or other invasive procedures.

At screening a single ECG will be performed. At baseline (on day 1 pre-dose) ECGs will be performed on 3 occasions separated by at least 30 minutes all in triplicate for a total of 9 ECGs (3 sets of triplicate). At all other time points, ECGs will be performed in a standardized method, in triplicate, and approximately 30 seconds apart, prior to blood draws or other invasive procedures.

Subject must be in a semi-Fowler position in a rested and calm state for at least 5 minutes before the electrocardiogram is obtained.

If the subject is unable to be in the semi-Fowler position, the subject should be in the most recumbent position possible. The electrocardiogram will be performed prior to any blood draws. The interval and frequency of electrocardiogram assessments may be modified based on emerging PK, and/or PD, and/or safety data but the number of ECG measurements should not exceed what is planned in the specific cohort.

The electrocardiogram must include the following measurements: RR, QRS, QT, QTc, and PR intervals.

The Principal Investigator or designated site physician will review all electrocardiograms. Once signed, the original electrocardiogram tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original electrocardiogram will be made available to Amgen.

In Part C, electrocardiograms will be collected as follows:

At screening a single ECG will be performed. At baseline (on day 1 pre-dose) a single ECG will be performed on 1 occasion for a total of 1 ECG. At all other time points, ECGs will be performed in a standardized method, prior to blood draws or other invasive procedures.

Subject must be in a semi-Fowler position in a rested and calm state for at least 5 minutes before the electrocardiogram is obtained.

If the subject is unable to be in the semi-Fowler position, the subject should be in the most recumbent position possible. The electrocardiogram will be performed prior to any blood draws. The interval and frequency of electrocardiogram assessments may be

modified based on emerging PK, and/or PD, and/or safety data but the number of ECG measurements should not exceed what is planned in the specific cohort.

The electrocardiogram must include the following measurements: HR, QRS, QT, QTc, and PR intervals.

The Principal Investigator or designated site physician will review all electrocardiograms. Once signed, the original electrocardiogram tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original electrocardiogram will be made available to Amgen.

7.2.14 Echocardiograms

Echocardiograms will be completed at the time points detailed in the Schedule of Assessments in Section 7.1. Where possible, staff involved in the treatment and evaluation of the study subject should not view study echocardiograms (with the exception of the screening echocardiogram which should be reviewed by site staff to confirm subject eligibility). Further, the sonographer should abstain from commenting on any observations in the echocardiograms that may be potentially unblinding. The echocardiograms will be sent to the core imaging vendor for analysis. Please refer to the echocardiography instruction manual for detailed information on acquiring, storing, and transmitting the echocardiograms.

7.2.15 Clinical Chemistry

Blood samples for clinical chemistry will be collected at the time points specified in the Schedule of Assessments (Section 7.1). Baseline assessments will be taken on Day-1.

All laboratory tests must be reviewed and signed by the principal investigator or qualified designee. Additional safety laboratory assessments may be performed for subject safety.

The tests listed in

Table 16 will be conducted and analyzed by standard laboratory procedures.

Table 16. List of Analytes

Chemistry	Hematology	Urinalysis
Alanine Aminotransferase (ALT / SGPT) Albumin Alkaline Phosphatase (ALP) Aspartate Aminotransferase (AST / SGOT) Bicarbonate (HCO3) or Carbon Dioxide (CO2) Direct Bilirubin Total Bilirubin (TBIL) Blood Urea Nitrogen (BUN) or Urea Calcium Chloride Troponin I NT-proBNP Creatinine Total Creatine Kinase Glucose Lipid Profile Total Cholesterol HDL LDL Triglycerides Magnesium Phosphorus or Phosphate Plasma Osmolality Potassium Total Protein Sodium Uric acid	Mean Corpuscular Hemoglobin Concentration Mean Corpuscular Hemoglobin Mean Corpuscular Volume Hematocrit Hemoglobin Platelets Red Blood Cells White Blood Cells White Blood Cell Differential Basophils Eosinophils Lymphocytes Monocytes Total Neutrophils (OR segmented neutrophils and band cells)	Bilirubin Blood Glucose Ketones Microscopic Exam (performed at the discretion of the PI or qualified designee) White blood cells Red blood cells Epithelial Cells Casts Bacteria Crystals pH Protein Specific Gravity Urobilinogen Urine Collection 24 hour urine collection Urine Volume Urine Osmolality FSH Pregnancy

*Hepatitis B surface antigen, Hepatitis C antibody, PCR for Hepatitis C RNA (if Hepatitis C antibody is positive), and HIV assessments are recommended.
*The estimated blood volume required for this study is approximately 222 mL.

Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion.

7.2.16 Hematology

Blood samples for hematology tests will be collected at the time points as specified in Section 7.1. All laboratory tests must be reviewed and signed by the principal

investigator or qualified designee. Additional safety laboratory assessments may be performed for subject safety.

Table 16 will be conducted using standard laboratory procedures.

Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion.

7.2.17 Urinalysis

Urine samples will be collected at Screening and as specified in Section 7.1. All laboratory tests must be reviewed and signed by the Principal Investigator or qualified designee. Additional safety laboratory assessments may be performed for subject safety. The tests listed in

Table 16 will be conducted using standard laboratory procedures.

Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion.

7.2.18 Estimated Glomerular Filtration Rate

For determining eligibility, estimated glomerular filtration rate (eGFR) will be calculated by the estimated Modification of Diet in Renal Disease (MDRD) formula based on serum creatinine, age, sex and race values at time points indicated in the Schedule of Assessments (Section 7.1).

7.2.19 Hepatitis B Surface Antigen and Core Antibody, Hepatitis C Antibody and HIV Status

Hepatitis B surface antigen and core antibody, Hepatitis C antibody, and human immunodeficiency virus (HIV) titers will be assessed at screening only and must be confirmed negative to be eligible for this study.

7.2.20 Concomitant Medications and Adverse Event Reporting

Subjects will be assessed for concomitant medication(s) usage during each out-patient visit. Any concomitant medication use reported throughout the study will be recorded in the source documents and the CRF.

Subjects will be assessed for adverse events/serious adverse events at least daily during resident periods and during each outpatient visit. Determination of the severity of all adverse event(s) will be consistent with Common Terminology Criteria for Adverse Events (CTCAE) V4 (Appendix A) unless specified otherwise. Adverse events will be captured in the source documents and on the CRF when reported or observed.

7.3 Antibody Testing Procedures

Not applicable for this study.

7.4 Biomarker Development

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

Amgen may attempt to develop blood tests designed to identify subjects most likely to respond positively or negatively to AMG 986.

Blood Samples

Where authorized by the IRB/IEC-approved informed consent, blood samples are to be collected for biomarker development at the time points detailed in the Schedule of Assessments in Section 7.1

7.5 Pharmacogenetic Studies

In Part C patient cohorts, if the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of HF and/or to identify subjects who may have positive or negative response to AMG 986. No additional samples will be collected for this part of the study. For subjects who consent to these analyses, DNA may be extracted from samples already collected.

Cell pellets will be collected at pre-dosing from subjects who consent to pharmacogenetics testing.

7.6 Optional Sub-studies

Not applicable for this study.

7.7 Sample Storage and Destruction

Any blood sample (eg, biomarker, PK, pharmacogenetics) collected according to the Schedule of Assessments (Section 7.1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of

unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing (not pharmacogenetics testing) on remaining samples (ie, residual and back-up) to investigate and better characterize aspects of the AMG 986 (eg, mechanism of action/target, metabolites) and to be applied in assay development. Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of these 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 prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving 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 options for continuation of the Schedule of Assessments (Section 7.1) and collection of data, including endpoints and adverse events. The Investigator must document the change to the Schedule of Assessments (Section 7.1) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

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

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

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

8.3 Reasons for Removal From Washout, Run-in, Invasive Procedures, Treatment, or Study

8.3.1 Reasons for Removal From Treatment

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

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, pregnancy)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)

8.3.2 Reasons for Removal from Study

Reasons for removal of a subject from the study are:

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease-related Events

Not applicable for this study.

9.1.2 Adverse Events

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

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

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

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

9.1.3 Serious Adverse Events

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

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

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

Information for a serious adverse event is collected from signing of the ICF through 30 days post last dose of AMG 986 or placebo.

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

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease-related Events

Not applicable for this study.

9.2.2 Adverse Events

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

Adverse events possibly related to any study procedures/study-activity are reported from signing of the ICF. All other adverse events are reported from the time of randomization (first dose of investigational product). The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from signing of the ICF or from the time of randomization (after the first dose of IP) through the End of Study are reported using the Event CRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity [and/or toxicity per protocol],
- Assessment of relatedness to IP (AMG 986 or placebo),
- Assessments of relatedness to any study-mandated activity/procedure and
- Action taken

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE). The grading scale used in this study is described in Appendix A.

The investigator must assess whether the adverse event is possibly related to the investigational product (AMG 986 or placebo). This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product (AMG 986 or placebo)?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity [eg, administration of investigational product, protocol-required therapies, use of medical device(s) and/or procedure (including any screening procedure(s)]. This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by a study activity [eg, administration of investigational product, protocol-required therapies, use of medical device(s)], and/or procedure”?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject’s baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be

recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

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

The investigator will report all AEs categorized as CTCAE v.4 Grade 2 or higher to the Medical Monitor (eg, Amgen Study Clinical Director or medically qualified designate) via email within 24 hours of event occurrence. The investigator will include all available clinical information regarding an event as part of this reporting procedure and provide follow-up information as it becomes available. The Amgen Medical Monitor will be responsible to complete the unblinded review of the information within 24 hours of receipt in order to look for any emerging safety signal (from either a single AE or pattern of AEs).

9.2.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last day of the dosing interval of investigational product or end of study, whichever is later, are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Serious Adverse Event Report Form (SAER). The SAER Form may also be utilized to report serious adverse events after the end of study (refer to Section 9.2.2.3).

See Appendix B for a sample of the Serious Adverse Event Report (SAER) Form.

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

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

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

See Appendix B for a sample of the Serious Adverse Event Report Form.

The investigator must assess whether the **serious** adverse event is possibly related to the investigational product (AMG 986 or placebo). This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product (AMG 986 or placebo)? Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

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

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

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

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

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

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs in

compliance with all reporting requirements according to local regulations and good clinical practice.

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

9.2.2.4 Reporting a Safety Endpoint as a Study Endpoint

Not applicable for this study.

9.2.2.5 Serious Adverse Events That are not to be Reported by the Sponsors to Regulatory Agencies in an Expedited Manner

Not applicable for this study.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking IP (AMG 986 or placebo) report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur through 11 weeks after the last dose of IP (AMG 986 or placebo).

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant. If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (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 a Serious Adverse Event.

If a female subject breastfeeds while taking IP (AMG 986 or placebo) report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur through 11 weeks after the last dose IP (AMG 986 or placebo).

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoints

- Subject incidence of treatment-emergent adverse events
- Subject incidence of clinically significant changes in physical examinations, vital signs, laboratory safety tests, and electrocardiograms (ECGs)

10.1.1.2 Secondary Endpoints

- AMG 986 PK parameters including, but not limited to, maximum observed concentration (C_{max}), the time of maximum observed concentration (t_{max}), area under the concentration-time curve (AUC), and oral bioavailability
- Changes over time from baseline in echocardiographic parameters of left ventricular systolic and diastolic functions (left ventricular ejection fraction, fraction shortening, stroke volume, wall thickening, end-systolic and end-diastolic volumes and indexes, septal and lateral e', E/A ratio, E/e' ratio, E wave deceleration time, left atrial volume index in healthy subjects, and for Part C, additionally, global strain, and ventriculo-arterial coupling in heart failure patients.

10.1.1.3 Exploratory Endpoints

- AMG 986 excretion in urine
- Characterization of potential metabolites of AMG 986 in plasma and urine (if appropriate)
- Change from baseline in free water clearance in the urine after multiple daily doses of AMG 986 (Parts B)
- Change from baseline in fasting glucose and fasting lipid profiles after AMG 986 administration
- Change from baseline of heart failure prognostic markers, eg, NT-pro-BNP, Troponin, Galectin-3, soluble ST-2, and GDF-15 (Part C)
- Change from baseline of endothelial functional markers eg, endothelin-1 and angiotensin II, apelin, ADMA and SDMA (Parts B and C)
- Change from baseline for QTc and relationship to AMG 986 exposure

10.1.2 Analysis Sets

For all analyses, subjects will be analyzed according to the dose and treatment they received, not the dose and treatment to which they were randomized.

10.1.2.1 Safety Analysis Set

The safety set will consist of all study subjects who receive at least one dose of AMG 986 or placebo. Subjects withdrawing prior to AMG 986 or placebo administration due to adverse events related to study procedure will not be included in the safety analysis set but those adverse events will be included in the adverse events listing for all enrolled subjects.

10.1.2.2 Pharmacokinetic (PK) Analysis Set

The PK analysis set will consist of all subjects for whom at least one PK parameter or endpoint can be reliably estimated.

10.1.2.3 Pharmacodynamics (PD) Analysis Set

The PD analysis set will consist of all subjects for whom at least one PD parameter, including echocardiographic parameters, can be reliably estimated.

10.1.3 Covariates and Subgroups

Baseline values may be used as a covariate in analyses. For any variable, unless otherwise defined, baseline is defined as the last assessment taken prior to the first administration of AMG 986 or Placebo.

No subgroup analyses are planned. Within each cohort for Parts A and B, subjects will be randomized so that 6 subjects receive AMG 986 and 2 subjects receive placebo. Within each cohort for Part C, 15 subjects will receive AMG 986 and 5 subjects will receive placebo. Data from placebo-treated healthy subjects in each of Parts A and B will be pooled across the Part's cohorts for analysis. Data for placebo-treated subjects in Part C will not be pooled together.

10.2 Sample Size Considerations

This is a Phase 1 study and no formal statistical hypothesis testing will be performed. The study is designed to characterize the safety, tolerability, and PK/PD following single and multiple administration of AMG 986 by descriptive summaries based on the observed data. The sample size for all Parts A, B, and C of this study is based on practical considerations and is consistent with the number of subjects enrolled in similar studies. Approximately 152 healthy subjects (8 subjects per cohort in 11 cohorts for Part A and 8 cohorts in Part B) are expected to be enrolled. Part C will enroll an additional

40 patient subjects. For safety considerations, with up to 144 subjects receiving AMG 986 (114 healthy and 30 patients), there is a 99.94% chance of detecting an adverse event with a true incidence rate of 5% or greater and a 99.99 % chance of detecting a more common adverse event with a true incidence rate of 10%. A rare event with a true incidence rate of 1% will have a chance of 76.48% to being detected with the current total sample size receiving AMG986. For Part A, with 66 subjects receiving AMG 986, there is a 96.6% chance to detect an AE with a 5% incidence rate and for Part B, with 48 subjects receiving AMG 986, a 91.5% chance to detect and AE with the same 5% incidence. For Part C, with 30 subjects receiving AMG 986, there is a 78.5% chance of observing an AE with a 5% incidence rate and 95.7% chance of observing a more common AE with a 10% incidence rate.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Amgen staff and their designees involved in the study will not be blinded, but will be given treatment assignments only when there is a need to use the information for analysis discussion and internal decision-making, in particular, when concerning safety issues. Access to treatment assignments and other restricted data are described in Amgen standard documents. Unblinded individuals will ensure the keeping of the blind. Unblinding and potentially unblinding information should not be distributed to the investigators or subjects prior to a study cohort being formally unblinded. An exception is the unblinding of the Principal Investigator or designee who, as a member of the DLRM, will have access to the unblinding DLRM outputs.

10.4 Planned Analyses

10.4.1 Interim Analysis

Not applicable for this study.

10.4.2 Data Monitoring Committee (DMC), Data Review Team (DRT) or Dose Level Review Team (DLRT)

A Dose Level Review Team (DLRT) will be used to oversee progress of the study and make recommendations relating to early closure/extension or alteration of the study based on ongoing monitoring of the study data (ICH GCP 5.5.2). The DLRT members will consist of the principal investigator or designee, Amgen Medical Monitor, Amgen Global Safety Officer or designee, Amgen Clinical Research Study Manager or designee, and a Biostatistics representative or designee. Additional members may be added as needed (eg, PK scientist). The key objectives of the DLRT are to review data,

monitor study's safety, and make dose change decisions. DLRMs will be conducted in an unblinded manner. Amgen standard procedures will be followed to unblind the DLRM attendees specifically the Principal Investigator or designee.

10.4.3 Primary Analysis

The primary analysis will occur after the database lock following last subject last visit.

10.4.4 Final Analysis

The primary analysis will be the final analysis.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Descriptive statistics will be provided for selected demographics, adverse events, vital signs, ECG, PK, selected laboratory measurements, and selected echocardiographic measures. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages.

Placebo-treated subjects in Part A and separately, subjects in Part B will be combined to form composite placebo groups for each Part. Separate summaries and analyses will be performed for Cohorts in Parts A and B of the study. Placebo-treated subjects in Part C will be separated per cohort (HFrEF versus HFpEF). Graphical summaries of the data may also be presented. When data are summarized by time, the values recorded against the scheduled time points listed in the protocol will be used. When assessing minimum/maximum increases or decreases over the study, all assessments, including unscheduled assessments will be used. Unless stated otherwise in the statistical analysis plan, the data analysis will be conducted using subjects in the safety analysis set. For statistical analyses comparing change from baseline, only subjects with both baseline and at least one post-baseline assessment will be included.

Results from the intravenous and from the oral portion of the study will be reviewed separately and together as well in some cases as appropriate.

10.5.2 Primary Endpoints

10.5.2.1 Safety Endpoints

10.5.2.1.1 Adverse Events

All subjects who receive a dose of AMG 986 or placebo will be included in the safety analyses. Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term according to the medical dictionary for

regulatory activities (MedDRA) terminology. Tables of events, fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment emergent adverse events will also be provided if observed.

10.5.2.1.2 Vital Signs

Subject-level data for vital signs including blood pressure, heart rate, respiratory rate, and body temperature will be presented and reviewed for each subject. The analyses of vital signs will include summary statistics over time (for each protocol scheduled study visit) by cohort by Part. Depending on the size and scope of changes, summaries of changes from baseline over time may be provided.

10.5.2.1.3 Electrocardiogram

All on-study ECG data will be listed and may be plotted. Summaries over time and/or changes from baseline over time will be provided for all ECG parameters (eg, RR, PR, QRS, QTc). 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. For Parts A and B, baseline ECG recording is defined as the mean of the 3 sets of triplicate ECG results at Day 1 pre-dose (a total of 9 assessments). The ECG measurements from Part C of this clinical study will not be performed as triplicates but as single assessments per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

10.5.2.1.4 Clinical Laboratory

Analyses of laboratory values will include summary statistics over time (for each protocol scheduled visit) by cohort. Additional summaries may include descriptive statistics of changes from baseline over time.

10.5.3 Secondary Endpoints

10.5.3.1 Pharmacokinetics Analysis (PK)

Plasma samples will be analyzed for AMG 986 concentrations using a validated assay. Individual concentration-time plots for AMG 986 will be presented for each subject as well as mean concentration-time plots for each cohort. Pharmacokinetic parameters

including but not limited to AUC, C_{max}, and t_{max} will be estimated using non-compartmental methods. Actual dosing and sampling times will be used for calculation of PK parameters.

Summary statistics will be generated for each PK parameter for each dose cohort for each Part of the study. A population PK analysis may also be performed to obtain additional PK parameters for each Part of the study.

Bioavailability may also be calculated and summarized if data collected is deemed adequate.

10.5.3.2 Echocardiographic Measures

Echocardiographic parameters of left ventricular systolic function (left ventricular ejection fraction, stroke volume, wall thickening and end-systolic volume index) and left ventricular diastolic function (E/e' ratio, E-wave deceleration time, and left atrial volume index) in healthy subjects participating in all Parts of the study will be measured and analyzed for changes from baseline. In Part C, additional echocardiographic measures such as ventriculo-arterial coupling and global strain patterns in heart failure patients will be evaluated. Changes from baseline for these parameters will be summarized by cohort and treatment group and by schedule assessment for all Parts of the study. Statistical modeling of a potential dose-response relationship may be pursued for a few key echocardiographic parameters in Part C as appropriate.

10.5.4 Exploratory Endpoints

The statistical analyses in this section are considered exploratory in nature and will be performed only when deemed appropriate.

10.5.4.1 AMG 986 in Urine

Urine samples will be collected and AMG 986 in urine will be analyzed so that fractions of dose eliminated unchanged in urine may be determined. Subject-level data and cohort summary statistics will be presented as appropriate.

10.5.4.2 AMG 986 Metabolites

If data allows, metabolites of AMG 986 will be identified in plasma as well as urine samples and their relative expression will be estimated from individual or pooled samples. Subject-level data and cohort summary statistics will be presented as appropriate.

10.5.4.3 Free-water Clearance in Urine

If data allows, free-water clearance in urine in response to administration of AMG 986 will be measured and their relative amounts estimated from individual or pooled samples. Subject-level data and cohort summary statistics will be presented as appropriate.

10.5.4.4 Fasting Glucose and Fasting Lipid Levels

If data allows, glucose tolerance and lipid levels for fasting subjects after dosing with AMG 986 will be measured and summarized as changes from baseline over time.

10.5.4.5 AMG 986 Impact on Heart Failure Prognostics

If data allow, heart failure prognostic markers, eg, NT-pro-BNP, Troponin, Galectin-3, soluble ST2 and GDF-15 will be measured in patients in Part C after dosing with AMG 986 and summarized as changes from baseline over time.

10.5.4.6 AMG 986 Impact on Endothelial Function

If data allow, endothelial functional markers, eg, endothelin-1, angiotensin II, apelin, ADMA and SDMA will be measured in Parts B and C after dosing with AMG 986 and summarized as changes from baseline over time.

10.5.4.7 AMG 986 Exposure vs. QT/QTc Changes

If data allow, the relationship between AMG 986 exposure and QT/QTc interval changes will be inspected graphically and model-based PK/PD analyses may be conducted to examine the relationship further.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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

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

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record. The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable 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 informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

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

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

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

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the demographics page, in addition to the unique subject identification number, include the age at the time of enrollment.
- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in strict confidence by the investigator, except as described below.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB 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 named such individuals to have access to his/her study related records, including personal information.

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the Investigator's participation in the study according to the study contract. The investigator is to notify the IRB 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 investigational product 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 investigational product(s), and by what mechanism, after termination of the study and before it is available commercially.

12.2 Study Documentation and Archive

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

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

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

Elements to include:

- Subject files containing completed CRF, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation, and all correspondence to and from the IRB and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.

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

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

12.3 Study Monitoring and Data Collection

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

The Clinical Monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study related records needed to verify the entries on the CRFs.

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

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

Data capture for this study is planned to be electronic:

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

Amgen (or designee) will perform self-evident corrections (SECs) to obvious data errors in the clinical trial database. SECs will be documented in the Standard Self Evident Corrections document and the CRF Specific Instructions, both of these will be available through the EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date but different visits eg, week 4 and early termination) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Section 7.1), the investigator can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

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

12.6 Publication Policy

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

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

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

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

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

13. REFERENCES

AMG 986 Investigator's Brochure (always refer to the most current edition). Thousand Oaks, CA: Amgen Inc.

International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2013. http://www.icmje.org/

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Krum H, Teerlink JR. Medical therapy for chronic heart failure. *Lancet.* 2011;378: 713-721.

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The CTCAE version 4.0 is available at the following location:

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

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.5 require the following:

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

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

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.5 or who experience AST or ALT elevations > 3 x ULN are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve
- Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.
- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count (CBC) with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Obtain serum acetaminophen (paracetamol) levels

  - Obtain a more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Obtain viral serologies
  - Obtain CPK, haptoglobin, LDH, and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

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

Appendix B. Sample Serious Adverse Event Report Form

AMGEN AMG 986 20150183	Clinical Trial Serious Adverse Event Report – Phase 1–4 *Notify Amgen Within 24 Hours of knowledge of the event*	☐New ☐Follow-up

US: +805 814 6553

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Date of Birth Day Month Year	Sex ☐F ☐M	Race

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	Date Ended Day Month Year	Onset only if event occurred before the date of IP	Ever Serious (See codes below)	Relationship: Is there a reasonable possibility that the event may have been caused by AMG 986? If yes, see section 10		Relationship: Is there a reasonable possibility that the event may have been caused by an Ongoing Serious?			Outcome of Event: 01 Resolved 02 Resolving 03 Not resolved 04 Fatal	Criteria Only Patient is Mated 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 significant medical hazard

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized? ☐No ☐Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product: 01 Still being Administered 02 Permanently discontinued 03 Withheld
AMG 986 (Blinded)						

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

AMGEN AMG 986 20150183	Clinical Trial Serious Adverse Event Report – Phase 1–4 *Notify Amgen Within 24 Hours of knowledge of the event*	☐New ☐Follow-up

	Site Number	Subject ID Number	

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

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

Date Day Month Year	Test: Unit:										

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

Date Day Month Year	Additional Tests	Results	Units

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	Title	Date

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

US: +000 000 0000

1. Case Administrative Information

Protocol/Study Number: 20150183

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

2. Contact Information

Investigator Name _____ Site # _____

Phone (____) _____ Fax (____) _____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm ▼ / dd ▼ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm ▼ /dd ▼ /yyyy ____

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

If yes, provide product (or study drug) stop date: mm ▼ /dd ▼ /yyyy ____

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

5. Pregnancy Information

Pregnant female's LMP mm ▼ / dd ▼ / yyyy ____ ☐ Unknown

Estimated date of delivery mm ▼ / dd ▼ / yyyy ____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm ▼ / dd ▼ / yyyy ____

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

If yes, provide date of delivery: mm ▼ / dd ▼ / yyyy ____

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX# US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20150183

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

2. Contact Information

Investigator Name _____ Site # _____

Phone (____) _____ Fax (____) _____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm____/ dd____/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

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

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Protocol Amendment 8

Title: A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 986 in Healthy Subjects and Heart Failure Patients

Amgen Protocol Number (AMG 986) 20150183
IND Number 129185
Eudra-CT 2017-002940-34

Amendment Date: 27 July 2018

Rationale:

- Aligned information in the protocol with the AMG 986 Investigator's Brochure Edition 3.0, including revising the nonclinical pharmacology package, updating the nonclinical toxicology package to reflect chronic studies of up to 6- and 9-months duration in rats and dogs, respectively, updating the clinical experience, and clarifying language in the Risk Assessment
- Inconsistencies and typographical errors were corrected throughout the protocol

Description of Changes:

Header (throughout entire protocol)

Replace:

14 Mar 2018

With:

27 July 2018

Title Page, Key Sponsor Contact(s):

Replace:

[redacted] M.D., M.Sc

Medical Director

Telephone: [redacted]

Email: [redacted]

With:

[redacted], **M.D.**

Executive Medical Director, Translational Medicine

Telephone: [redacted]

Email: [redacted]

Title Page, amendment #

Added:

Amendment 8: **27 July 2018**

Investigator's Agreement

Added bolded items and deleted strikethrough text:

I have read the attached protocol entitled: A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 986 in Healthy Subjects and Heart Failure Patients dated **27** ~~14~~**July**~~Mar~~ 2018, and agree to abide by all provisions set forth therein.

Protocol Synopsis, Study Design: Part C

Added bolded items and deleted strikethrough text:

Part C

A total of up to 40 subjects, 20 with HFrEF and 20 with HFpEF, will be randomized to receive AMG 986 or placebo in a 3:1 ratio ~~at sites located in the United States, Canada, Australia, New Zealand, Sweden, Germany, France, Poland, Slovakia, Czech Republic, Bulgaria, Belgium, Singapore and The Netherlands,~~ (15 treated and 5 placebo).

Section 2, Background and Rationale

Added bolded items and deleted strikethroughs:

AMG 986 is a novel apelin receptor (APJ) small molecule agonist that binds and activates APJ receptor to improve cardiac function by increasing **left ventricular contractile function and cardiac reserve without a significant impact on heart rate** ~~cardiac contraction and relaxation, by improving cardiac reserve, and by decreasing systemic vascular resistance without a significant impact on heart rate and myocardial oxygen consumption.~~ AMG 986 is being developed as a potential treatment for heart failure.

Section 2.1, Disease

Added bolded items and deleted strikethroughs:

Heart failure (HF) **refers to a clinical condition in which the cardiac output is insufficient to meet the metabolic needs of body organs and is marked by cardiac systolic and/or diastolic dysfunction. Heart failure with predominantly systolic dysfunction, which is identifiable as decreased contraction, is more aptly described as heart failure with reduced ejection fraction (HFrEF). Alternatively, heart failure with a predominantly diastolic component, identifiable by decreased relaxation, is referred to as heart failure with preserved ejection fraction (HFpEF). Common to both types of heart failure is uncoupling of left ventricular and arterial interaction. In an attempt to preserve cardiac output, a series of compensatory changes occur over time, which include increased sympathetic tone and peripheral vasoconstriction, as well as activation of the renin-angiotensin-aldosterone system as key features.**

~~is a clinical syndrome marked by impaired cardiac function and is the final pathway for a diversity of diseases that afflict the heart. With a 1-year rate of cardiovascular mortality or HF hospitalizations of 30% to 40% in patients recently hospitalized for HF, symptomatic HF is associated with a worse prognosis than the majority of cancers.~~

Heart failure~~It~~ is a common and debilitating disease, affecting almost 6 million Americans, or more than 2% of the United States population (McMurray and Pfeffer, 2005; Roger et al, 2012). However, cumulative evidence from epidemiologic studies shows that there has been only modest improvement in the prognosis of HF over the past 40 years despite numerous clinical advances (Khand et al, 2000). **With a 1-year rate of cardiovascular mortality or HF hospitalizations of 30% to 40% in patients recently hospitalized for HF, symptomatic HF is associated with a worse prognosis than the majority of cancers.** ~~The pathophysiologic mechanisms for the progressive nature of HF are complex and include neurohormonal activation in addition to deranged cardiovascular hemodynamics. Injury may occur following acute damage to heart muscle, such as with myocardial infarction, infection, or inflammatory processes, or may have a more gradual onset as in the case with infiltrative diseases, hemodynamic pressure or volume overloading, or hereditary cardiomyopathy. HF~~

Heart failure is a progressive disorder with a natural history punctuated by frequent recurrent hospitalizations and ultimately death. Long-term goals of HF therapy are to implement chronic interventions that decrease death and hospital readmission (Jessup et al, 2009; McMurray et al, 2012), both of which occur frequently (Lloyd-Jones et al, 2010). More recently, efforts have been made in developing therapies that improve cardiac reserve, symptoms of HF and functional capacity.

AMG 986 was developed to explore the therapeutic potential associated with the APJ pathway. AMG 986 is a long-acting small-molecule agonist that binds to the APJ receptor and activates $G_{\alpha i}$ and beta-arrestin with sub-nM potency.

AMG 986 may have therapeutic potential for both HFrEF ~~**heart failure with reduced ejection fraction**~~ **and** ~~**as well as**~~ **HFpEF** ~~heart failure with preserved ejection fraction~~**.**

~~Another target for treatment of HF is to improve myocardial contraction and relaxation. HF is a condition most commonly marked by cardiac systolic dysfunction but increasingly noted to have a diastolic dysfunction component. Systolic dysfunction predominates in the condition of heart failure with reduced ejection fraction (HFrEF), whereas diastolic dysfunction predominates in the condition of heart failure with~~

~~preserved ejection fraction (HFpEF). Over time, in an attempt to preserve cardiac output, a series of compensatory changes can occur in both conditions, characterized by increased sympathetic tone and peripheral vasoconstriction, as well as the activation of various neurohormonal pathways. Accordingly, improvement of cardiac contraction and relaxation would appear to be a rational therapeutic approach to the treatment of HF (Hasenfuss and Teerlink, 2011). Attempts to improve cardiac contractility using adrenergic receptor agonists (ie, dobutamine) or phosphodiesterase inhibitors (ie, milrinone) have been met with little success, however. These mechanisms have significant safety liabilities attributable to increased oxygen consumption, intracellular calcium, and arrhythmias (Cuffe et al, 2002; Felker et al, 2003). AMG 986 is being developed to address the unmet needs not only in heart failure with a systolic component but with a diastolic component as well, without the aforementioned safety liabilities.~~

Section 2.2.1, Pharmacology, Nonclinical Pharmacology

Added bolded items and deleted strikethroughs:

The cardiovascular effects of AMG 986 *in vivo* were studied in both rodent and canine models. In the ZSF1 rat, (a model reproducing diastolic heart failure), AMG 986 increased cardiac contractile reserve, ejection fraction and stroke volume. Improvements in ventriculo-arterial coupling were also observed in ZSF1 rats. In a canine heart failure model (tachypacing), AMG 986 improved left ventricular contractile function without affecting heart rate. ~~AMG 986 increased cardiac contraction and relaxation in isolated perfused rat hearts. AMG 986 augmented the load-independent contractility without change in calcium transients in adult rat cardiomyocytes. The inotropic effects of AMG 986 are specific through APJ receptor since the compound has no impact on phosphodiesterase inhibition. In rats with systolic heart failure, AMG 986 increased cardiac output, reduced systemic vascular resistance and improved ventricular arterial resistance. Administration of AMG 986 in obese ZSF1 rats with metabolic dysfunction and preserved ejection fraction increased stroke volume, ventricular arterial coupling and cardiac reserve. In canine models of heart failure from ischemic and dilated cardiomyopathies, AMG 986 improved left ventricular contractile function and increased coronary flow without significant impact on heart rate and myocardial oxygen consumption. In the canine model of ischemic heart failure, AMG 986 exhibited a statistically significant increase of 10% in ejection fraction relative to vehicle at plasma concentrations of 0.210 µM (0.110 µg/mL) and greater. Additionally,~~

~~AMG 986 exhibited additive effects when added to the standard of care drug captopril in a rat model of systolic heart failure.~~ These nonclinical findings support the hypothesis that AMG 986 would be beneficial in addressing the underlying pathophysiology of heart failure in patients with either reduced or preserved ejection fraction. Details of AMG 986 nonclinical pharmacology are summarized in the **AMG 986** Investigator's Brochure.

Section 2.2.2, Pharmacokinetics, Predictions of Human Pharmacokinetics

Added bolded items and deleted strikethroughs:

Human PK model predictions were used to support selections of IV and oral doses, as described in ~~Section 2.6~~ **Section 2.7** of the protocol. ~~Details of AMG 986 human PK predictions are summarized in the AMG 986 Investigator's Brochure.~~

Section 2.2.3, Toxicology, Nonclinical Toxicology

Added bolded items and deleted strikethroughs:

The nonclinical toxicology package for AMG 986 included repeat dose toxicology studies with both oral (**up to 6-months in duration in rats and 9-months in duration in dogs**~~28 day studies in rat and dog~~) and IV (14-day studies in rat and dog) dose routes and genetic toxicology, phototoxicity and safety pharmacology studies.

Repeat Dose Toxicology Studies:

The no-observed-adverse effect-levels (NOAEL) in all of the repeat dose oral and IV toxicology studies in rat and dog were the highest doses evaluated. For the 28-day oral studies, the no-observed-effect-levels (NOEL) in rats was 1000 mg/kg/day (limit dose) and the NOAEL in dogs (based on clinical signs of emesis) was 300 mg/kg/day. Estimates of AUC_{24h} exposures in rats at the NOEL dose and dogs at the NOAEL dose were 150-fold and 219-fold greater than observed human exposure at the 5 mg oral dose and **2.2**~~1.4~~-fold and **3.2**~~2.0~~-fold greater than the **observed** ~~predicted~~ human exposure at 650 mg, respectively (Table 3). The margins from the toxicology studies support administration of the oral dose up to 650 mg planned for the current study.

In developmental and reproductive toxicology studies in rats and rabbits, oral administration of AMG 986 resulted in embryo-fetal toxicity **and malformations** ~~at all doses tested~~. In rats, AMG 986-related fetal tail abnormalities and skeletal dysmorphogenesis were observed. In rabbits there were abortions, lower maternal body weights/ body weight gains~~,~~ **associated with** ~~and~~ decreases in embryo-fetal survival, **and external, visceral and skeletal malformations.**

AMG 986 was negative in both in vitro and in vivo genetic toxicology studies and in an in vitro phototoxicity assay.

Section 2.2.3, Toxicology, Safety Pharmacology

Added bolded items and deleted strikethroughs:

The NOEL for effects on neurobehavioral and respiratory function in rats was 1000 mg/kg (single oral dose). In an anesthetized beagle dog cardiovascular (CV) study, with IV dose administration in a cumulative dose escalation design, AMG 986-related CV effects were limited to small dose-independent increases (~10%) in the rate of left ventricular pressure rise in early systole (dP/dtmax) and similar increases (~10%) in mean blood pressure at plasma concentrations greater than 1.34 µg/mL.

~~These observations were consistent with the pharmacology of AMG 986 (positive inotropy).~~

The IC_{50} value for inhibitory effect of AMG 986 on hERG current (I_{Kr} current; potassium channel in human ventricles primarily responsible for repolarization) was estimated to be > 300 µM (157 µg/mL, unbound concentration), approximately 1000X higher than the predicted human maximum unbound concentrations at an oral dose of 650 mg and approximately 5000X higher than the highest planned IV infusion dose (60 mg loading dose + 360 mg/24 hours maintenance dose).

Details of AMG 986 nonclinical toxicology are summarized in the **AMG 986** Investigator's Brochure.

Section 2.3, Clinical Experience

(Added section 2.3 subsequently updated numbering of the section)

The AMG 986 clinical program thus far consists of 5 studies (4 ongoing, 1 completed). In addition to ongoing Study 20150183, there are three phase 1, open-label, single-dose studies of AMG 986, including, Study 20150186 (renal impairment), Study 20150187 (healthy Japanese subjects), and Study 20170553 (tablet vs capsule formulation). Enrollment and dosing have been completed for all 3 of these studies. Study 20150185 is a completed, phase 1, open-label study to evaluate the effect of food and concomitant itraconazole administration on the pharmacokinetics of AMG 986 in heathy subjects.

Overall, up to the 01 June 2018 cutoff date, data from these 5 studies indicate that AMG 986 has an acceptable safety and tolerability profile at all doses tested in

healthy subjects, in subjects with heart failure who have been evaluated thus far, in healthy Japanese subjects, and in subjects with renal impairment. No serious or fatal adverse events have been reported, most reported adverse events in these studies were CTCAE grade 1, and no trends or specific safety concerns have been identified based on the types and frequency of adverse events that have occurred.

Refer to the AMG 986 Investigator's Brochure for details on AMG 986 clinical experience.

Section 2.4.1, Risk Assessment

Added bolded items and deleted strikethroughs:

AMG 986 has an identified risk of embryo-fetal toxicity~~.~~ **and malformations. In developmental and reproductive toxicology studies in rats and rabbits, oral administration of AMG 986 resulted in abortions, embryo-fetal toxicity and external, visceral and skeletal malformations.** ~~AMG 986 caused embryo-fetal toxicity in nonclinical developmental and reproductive toxicology studies in 2 different species. Oral administration of AMG 986 resulted in abortions in rabbits and fetal skeletal and tail abnormalities in rats.~~ Women of childbearing potential are not eligible to participate in this study, and male subjects must agree to practice an acceptable method of effective birth control and not donate sperm while on study and through 11 weeks after receiving the last dose of AMG 986. These inclusion/exclusion criteria will ~~prevent pregnancy and~~ mitigate the risk of embryo-fetal toxicity.

AMG 986 has a potential risk of causing changes in blood pressure. ~~AMG 986 is expected to positively stimulate the endogenous apelin-dependent pathways, which include vasodilation. Therefore, possible expected acute risks associated with AMG 986 administration are of cardiovascular nature, such as hypotension.~~ **Studies have shown that the principal effect of the apelin/APJ system is to counterbalance the renin-angiotension-aldosterone system, and apelin affects vascular tone and blood pressure.**

AMG 986-related cardiovascular changes in the nonclinical program were limited to modest and reversible decreases in mean blood pressure at the highest IV dose in the rat and small dose-independent increases in mean blood pressure in the anesthesized dog. Subjects will be closely monitored for changes in cardiovascular parameters, such as blood pressure, heart rate, and ECG measurements, and for signs and symptoms suggesting adverse events.

The nonclinical (toxicology and safety pharmacology) package suggests a safe profile for the initiation of clinical trials with AMG 986. Genetic toxicology and photosafety evaluations indicated that AMG 986 is not genotoxic or phototoxic. No AMG 986-related toxicity was identified in the rat or dog toxicology studies that were conducted with oral (~~28 days studies~~**6- and 9-months duration in rats and dogs, respectively**) or IV (14-day studies) dose administration. The AUC-based exposure margins based on NO(A)EL doses from the rat and dog toxicology studies support the planned oral and IV infusion clinical dose ranges. Additionally, no AMG 986-related effects in the safety pharmacology studies were identified, including data indicating that QTc interval prolongation risk is low.

As of **01 June 2018**~~14 March 20~~17, safety and tolerability data on clinical exposure to AMG 986 from FIH study 20150183 ~~(a randomized, placebo-controlled, double-blind, single day ascending dose and multiple daily ascending dose study)~~ were available and reviewed for **1**9 fully implemented cohorts of 8 **to 9** healthy subjects each. The subjects reviewed included those who received single oral doses of AMG 986 up to **650**~~200~~ mg, oral doses ~~of 5 mg~~ of AMG 986 **up to 650 mg** for 7 consecutive days, IV-infused doses of AMG 986 ~~over~~ **up to** 24 hours (loading doses up to ~~2~~60 mg over 1 hour followed by maintenance doses up to **360** ~~120~~ mg over 23 hours**), IV-infused doses of AMG 986 over 4 days (loading dose up to 60 mg over 1 hour followed by maintenance doses up to 360 mg over 23 hours and subsequent maintenance doses** ~~and~~ **up to 376 mg over 24 hours for 3 additional days**), and placebo.

There was a total of ~~54~~**116** subjects who received AMG 986 and ~~18~~**38** subjects who received placebo. Of these ~~72~~**154** subjects, ~~15~~**171** completed the investigational product**, and 3 subjects withdrew after receiving investigational product due to subject request and not related to an adverse event.** ~~One subject withdrew from the study after receiving IP. This discontinuation of study was due to subject request and not related to an adverse event.~~

For these **15**~~472~~ subjects **there were**~~,~~ no serious adverse events **and**~~,~~ no adverse events with fatal outcome~~, and no discontinuation of IP due to adverse events were reported~~. There were no adverse events from the cardiac disorders system organ class. **Twenty-three** ~~Twelve~~ subjects (**14.9**~~16.7~~%) were reported to have treatment emergent adverse events during double-blind treatment. The most common event was headache, which occurred in ~~5~~**8** subjects (**5.2**~~6.9~~%). The event of headache was reported as a common terminology criteria for adverse events (CTCAE) severity grade 1 in 4**7** of the

subjects, and CTCAE grade 2 in 1 subject. The majority of the adverse events were CTCAE grade 1 events. There were **7**~~4~~ CTCAE grade 2 events **(the only grade 2 event that occurred in more than 1 subject was toothache),** and no~~ne~~ **grade 3** ~~of the~~ events**.** ~~occurred in more than 1 subject. No events were CTCAE grade ≥3 events.~~ **One CTCAE grade 4 event was reported; this event (blood creatine phosphokinase increased as high as 9927 U/L) occurred in a [redacted]-year-old [redacted] subject in the 650 mg PO multiple dose cohort on study day 5, was nonserious, resulted in no action/change to the investigational product administration, was not associated with clinical symptoms (eg, myalgia) or worsening renal function tests, occurred concurrently with a CTCAE grade 2 event of aspartate aminotransferase increased and a grade 1 event of alanine aminotransferase increased, did not require any treatment, and was reported as resolved on study day 29 (22 days after the last dose of investigational product).**

Overall, the prevalence of adverse events was comparable across all the cohorts and did not show higher incidence with increasing doses. The adverse event terms represented a variety of system organ classes and did not suggest a trend or indicate a specific safety concern.

After each dose cohort completed and before any dose escalation, an aggregate evaluation of adverse events, vital signs, ECG and laboratory parameters was performed in unblinded DLRMs. No **clinically** meaningful individual subject changes in vital signs (including blood pressure) were identified within or across any of the 19 cohorts. There ~~was~~ **were** no notable variation**s** in vital signs with increasing doses of AMG 986 throughout the study. Additionally, no **trends in** laboratory ~~(including troponin 1) or~~ ECG abnormalities (eg- QTc interval) were detected.

Additionally, data from 12 heart failure subjects enrolled in study 20150183 were available and reviewed. Eight subjects received oral doses of AMG 986 for 21 days (consisting of consecutive doses of 10, 30, and 100 mg for 7 days each) and 4 subjects received placebo. Four of the 12 subjects (33.3%) reported treatment-emergent adverse events during the double-blind treatment. No serious or fatal adverse events were reported. There was no discontinuation of investigational product due to an adverse event. All the events were CTCAE grade 1 events.

Refer to the AMG 986 Investigator's Brochure for further details on AMG 986 clinical experience.

Section 2.4.3, Overall Benefit/Risk Assessment

Added bolded items and deleted strikethroughs:

The nonclinical (toxicology and safety pharmacology) package suggests a safe profile for the initiation of clinical trials with AMG 986. The AUC-based exposure margins based on NO(A)EL doses from the rat and dog toxicology studies support the planned dose ranges. To date, the clinical experience accumulated with AMG 986 provides evidence that the administration of AMG 986 has an acceptable safety profile **in all** ~~up to~~ doses tested.

Section 2.7, Rationale

Added bolded items and deleted strikethroughs:

The proposed loading dose infusion is supported by the planned use of AMG 986 in acute clinical settings and its anticipated rapid onset of pharmacological response. Selection of a 1 hour loading dose infusion will allow rapid titration to therapeutic concentration levels. Establishment of therapeutic concentrations early in the treatment course would also take advantage of the rapid rate of pharmacological response anticipated for AMG 986. ~~Preliminary evidence in an isolated rat heart model demonstrated rapid increases in the rate of left ventricular pressure rise in early systole shortly after the start of AMG 986 infusion. In addition, s~~**S**ystemic apelin administration was shown within minutes to cause reductions in peripheral vascular resistance accompanied by increases in cardiac output in healthy subjects (Japp et al, 2010).

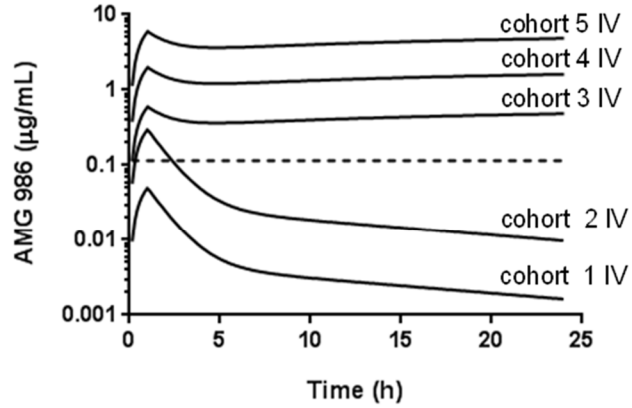
Section 2.7, IV Cohorts 1 to 5:

Added bolded items and deleted strikethroughs:

A clinical starting IV dose of 0.5 mg infused over 1 hour is not expected to elicit pharmacological activity based on observations in normal healthy dogs (Study 118965). In healthy subjects, an IV dose of 0.5 mg infused over 1 hour is predicted to achieve a maximum plasma concentration of 0.0501 μg/mL (Table 1), approximately one-half the nonclinical target plasma concentration of 0.1**35**~~10~~ μg/mL (0.2**58**~~10~~ μ/M) associated with a 10% increase in both ejection fraction and fractional shortening in the dog heart failure model. Model predictions of human maximal exposures for the next IV cohort dose of 3 mg infused over 1 hour is anticipated to approximate the target concentration associated with cardiovascular function improvement in the dog model (Figure 1).

Section 2.7, Rationale, Figure 1

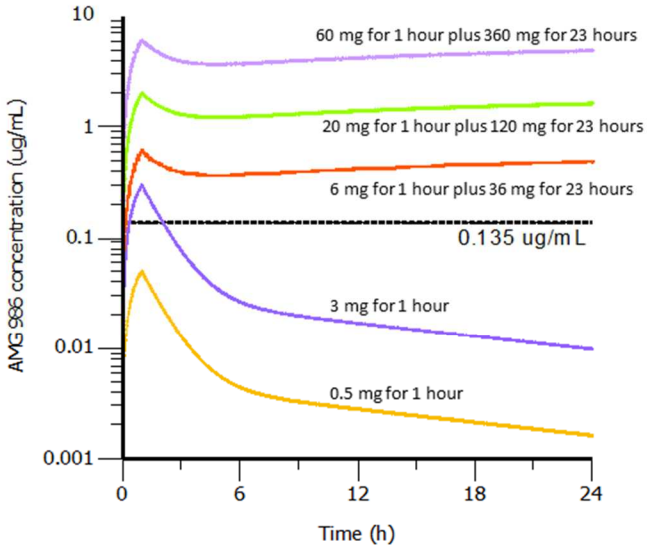
Replaced:



Group	Intravenous Infusion Dose
cohort 1 IV	0.5 mg for 1 hour
cohort 2 IV	3 mg for 1 hour
cohort 3 IV	6 mg for 1 hour plus 36 mg for 23 hours
cohort 4 IV	20 mg for 1 hour plus 120 mg for 23 hours
cohort 5 IV	60 mg for 1 hour plus 360 mg for 23 hours

AMG 986 PK profiles (solid lines) and concentration target at 0.110 µg/mL associated with 10% increase in ejection fraction in a heart failure dog model (dashed line)

With:

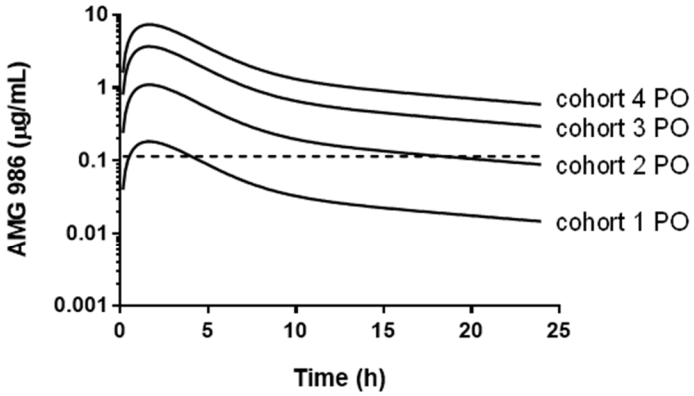


Group	Intravenous Infusion Dose
cohort 1 IV	0.5 mg for 1 hour
cohort 2 IV	3 mg for 1 hour
cohort 3 IV	6 mg for 1 hour plus 36 mg for 23 hours
cohort 4 IV	20 mg for 1 hour plus 120 mg for 23 hours
cohort 5 IV	60 mg for 1 hour plus 360 mg for 23 hours

AMG 986 PK profiles (solid lines) and concentration target at 0.135 µg/mL associated with 10% increase in ejection fraction and fractional shortening in the dog heart failure model (reference line)

Section 2.7, Rationale, Figure 2

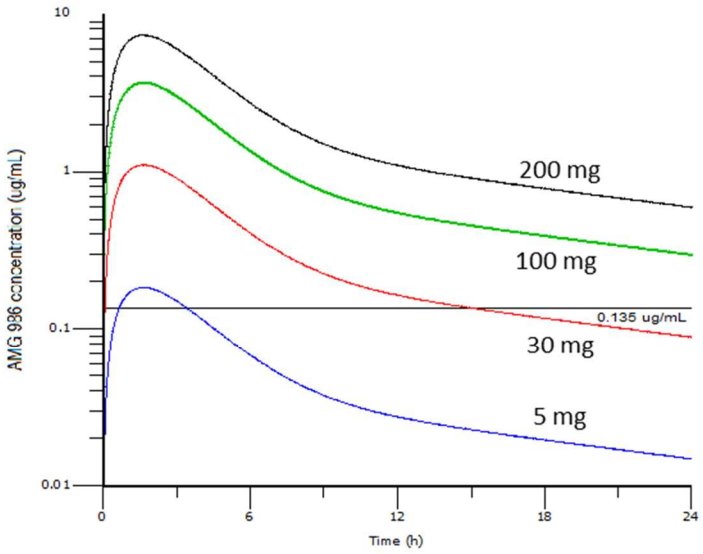
Replaced:



Group	Oral Dose
cohort 1 PO	5 mg
cohort 2 PO	30 mg
cohort 3 PO	100 mg
cohort 4 PO	200 mg

AMG 986 PK profiles (solid lines) and concentration target at 0.110 µg/mL associated with 10% increase in ejection fraction in a heart failure dog model (dashed line)

With:



Group	Oral Dose
cohort 1 PO	5 mg
cohort 2 PO	30 mg
cohort 3 PO	100 mg
cohort 4 PO	200 mg

AMG 986 PK profiles (solid lines) and concentration target at 0.135 µg/mL associated with 10% increase in ejection fraction and fractional shortening in the dog heart failure model (reference line)

Section 2.7, Oral Cohorts 5 and 6

Added bolded items and deleted strikethroughs:

After confirmation of safety and tolerability of oral AMG 986 at doses that range from 5 to 200 mg in Parts A and B, further escalations in dose are planned. The proposed single oral dose regimen extended for Part A will be 400 and 650 mg. Selection of the extended range of oral doses was based on the following: (1) acceptable safety and

tolerability of oral does up to 200 mg, (2) observed AMG 986 PK results and (3) exposure margins projected for AUC exposures up to 650 mg relative to exposures observed at NOEL and NOAEL doses in GLP toxicology studies. Although dose proportionality was not formally evaluated in the FIH study, increases in AUC and C_{max} exposures appeared to be linear and proportional to dose over the 5 to 200 mg oral dose range tested. Assuming dose proportional increases in AMG 986 exposure at 650 mg, estimates of AUC24h exposures in rats at the NOEL dose and dogs at the NOAEL dose were approximately 1.4 fold and 2.0 fold greater than the predicted human exposure at 650 mg, respectively ~~(Table 3)~~. **Estimates of AUC_{24h} exposures in rats at the NOEL dose and dogs at the NOAEL dose were 2.2-fold and 3.2-fold greater than the observed human exposure at the 650 mg oral dose, respectively (Table 3).**

Section 2.7, Rationale, Table 3 Heading

Added bolded items and deleted strikethroughs:

Table 3. Preliminary Observed ~~and Predicted~~ AMG 986 PK Estimates in Healthy Subjects after Single Oral Dose Administration and Exposure Margins

Section 3.2, Number of Sites

Added bolded items and deleted strikethroughs:

This study will be conducted in 15 or more sites in the **United States, Europe, Canada and Asia** ~~New Zealand, Australia, Sweden, Germany, France, Poland, Czech Republic, Bulgaria, Singapore and The Netherlands~~. Additional sites and/or countries could be added as necessary to complete enrollment.

Section 3.4, Replacement of Subjects

Added bolded items and deleted strikethroughs:

Subjects who are withdrawn or removed from treatment or the study prior to receiving AMG 986 will be replaced at the discretion of the Amgen Medical Monitor and Principal Investigator ~~by notifying the unblinded study pharmacist~~**. Subjects who are withdrawn or removed from treatment or the study may be replaced. This decision will be made by the Amgen Medical Monitor in consultation with the Principal Investigator and the Amgen Global Safety Officer.**

The new subject will receive the identical treatment as the replaced subject, but will be assigned a replacement randomization number associated with this new record. ~~The unblinded study pharmacist will retain the randomization list.~~

~~Subjects who are withdrawn or removed from treatment or the study may be replaced. This decision will be made by the Amgen Medical Monitor in consultation with the Principal Investigator and the Amgen Global Safety Officer.~~

Section 5.2 Site Personnel Access to Individual Treatment Assignments

Added bolded items and deleted strikethroughs:

Treatment assignments will be unblinded after **final** ~~database~~ lock. ~~After initial database lock and~~ **Upon** receipt of written authorization from Amgen to unblind, the unblinded pharmacist will release the specified unblinded pharmacy records to site staff designated to enter the subject **Package Lot Number (PLN)** ~~treatment~~ into each subject's ~~Unblinded~~ Investigational Product Administration ~~Case Report Form~~ ~~(~~CRF~~)~~.

Section 6.2.1.3.3, Dose Stopping Rules

Added bolded items and deleted strikethroughs

The quantity, volume, start date/time, stop date/time, and the amount of IP used as applicable to prepare the dose on the individual subjects will be **entered in each subject's Investigational Product Administration CRF prior to receipt of unblinded authorization. Upon receipt of written authorization from Amgen to unblind, the unblinded pharmacist will release the specified unblinded pharmacy records to site staff designated to enter the subject PLN into each subject's Investigational Product Administration CRF.** ~~blinded prior to initial database lock. Following initial database lock, upon written authorization from Amgen, the unblinded package lot number(s) will be recorded on each subject's unblinded IP administration CRF.~~

Section 13, References

Deleted:

~~Cuffe MS, Califf RM, Adams KF Jr, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA. 2002;287:1541-1547.~~

~~Felker GM, Benza RL, Chandler AB, et al. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. J Am Coll Cardiol. 2003;41:997-1003.~~

~~Hasenfuss G, Teerlink JR. Cardiac inotropes: current agents and future directions. Eur Heart J. 2011;32:1838-1845~~

Protocol Amendment 7

Title: A Phase I, Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 986 in Healthy Subjects and Heart Failure Patients

Amgen Protocol Number (AMG 986) 20150183
IND Number 129185
Eudra-CT 2017‑002940‑34

Protocol Date: 14 March 2018

Rationale:

The following updates were made to the protocol, dated 31 October 2017:

- Eligibility criterion for QTc threshold was extended from 450 msec to 500 msec.

  The rationale for this change is based on;

  Non clinical findings

  - Studies on the human ether-a-go-go related gene (hERG) current experiments showing no inhibition
  - 28 day oral dog toxicology studies showing no changes in QTc interval
  - 14 day IV dog toxicology findings showing no changes in QTc interval
  - Telemetry dog study showing no change in QTc interval

  Clinical findings in healthy volunteers administered AMG 986 as oral tablets or intravenous infusion

  - No evidence in Parts A and B of the study involving healthy volunteers that suggests AMG 986 affects the QTc interval
  - Consistency of findings, particularly across MAD cohorts in Part B where sustained concentration of drug was achieved
- Inconsistency and typographical errors were corrected throughout protocol.

Protocol Amendment 6

Title: A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 986 in Healthy Subjects and Heart Failure Patients

Amgen Protocol Number (AMG 986) 20150183
IND Number 129185
Eudra-CT 2017‑002940‑34

Protocol Date: 31 October 2017

Rationale:

The following updates were made to the protocol, dated 15 May 2017:

- Incorporate sections and sub-sections that clearly outline Risk/Benefit Assessment
- Key Sponsor Contacts updated based on changes in staff
- Provide further clarity on unblinding procedures
- Inconsistency, typographical errors were corrected throughout protocol.

Amendment 5

Protocol Title: A Phase I, Randomized, Double-blind, Placebo Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 986 in Healthy Subjects and Heart Failure Patients

Amgen Protocol Number AMG 986 20150183

IND Number 129185

Amendment Date: 15 May 2017

Rationale:

The following changes were made to the protocol 20150183, dated 15 May 2017:

- Updating safety/toxicology and risk assessment information based on recently available pre-clinical embryo-fetal toxicology studies and safety information from earlier and completed portions of the study
- Updating predicted pharmacokinetic data with actual observed data from earlier and completed portions of the study
- Testing higher oral dose formulation ranges of single and multiple doses of 400 mg and 650 mg in healthy volunteers to provide a better understanding of safety and tolerability of AMG 986
- Changing the duration of IP administration in Part C from 4 days per dose level (total of 12 days) to 7 days per dose level (total of 21 days) to provide an opportunity for insights on dose level on safety, tolerability, pharmacokinetics and pharmacodynamics
- Broadening the eligibility age for subjects in part C from 70 years of age to 85 years to better reflect the target populationLowering the NTproBNP eligibility criterion for HFrEF subjects from ≥ 600 pg/ml to ≥ 250 pg/ml to permit patients with less severe heart failure to participate
- Clarifying the need for a negative pre-enrollment pregnancy test for any female study participants
- Distinguishing the blood pressure and renal function thresholds for enrolment of healthy volunteer subjects from those with heart failure
- Aligning the starting dose in part C with doses used in Parts A and B of the study to enable more meaningful comparisons between patients and healthy volunteer subjects
- Increasing the BMI upper limit from 32 to 35 kg/m^2 to reflect the generally higher body weight of actual patients with HF compared to healthy volunteers.
- Broadening the geographic spread of study sites participating primarily in Part C of the study from just the United States to also include Canada, Australia, New

Amendment 4

Protocol Title: A Phase I, Randomized, Double-blind, Placebo Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 986 in Healthy Subjects and Heart Failure Patients

Amgen Protocol Number AMG 986 20150183

Amendment Date: 31 January 2017

Rationale:

This protocol amendment is being made to include the study of AMG 986 in patients with heart failure with either preserved or reduced ejection fraction. The primary objective of this amendment is to determine the safety, tolerability, pharmacokinetics and possibly pharmacodynamic impact of AMG 986 in patients with heart failure.

Specific changes are being made to

1. Define the objectives and endpoints that would be applicable to investigation of patient subjects in the study
2. Define the eligibility criteria for patients with heart failure that would qualify to participate in the study
3. Define the starting dose, dose escalation, dose reduction and dose stopping rules that would be applied to patient subjects.
4. Outline the schedule of assessments for patient subjects

Zealand, Sweden, Germany, France, Poland, Slovakia, Czech Republic, Bulgaria, Belgium, and The Netherlands.

- Administrative, grammatical and typographical corrections to enhance clarity of the protocol.

Amendment 3

Protocol Title: A Phase I, Randomized, Double-blind, Placebo Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 986 in Healthy Subjects

Amgen Protocol Number AMG 986 20150183

Amendment Date: 06 December 2016

Rationale:

This protocol amendment is being made in light of emerging data from the study. Specific changes are being made to:

1. Change Part B PO dosing duration to 7 days from 14 days. The rationale for this is to reduce exposure to healthy volunteers as longer duration of treatment is unlikely to provide substantively important exposure or safety information.
2. Allow earlier transition from ascending single day IV doses in Part A to ascending multiple daily IV doses in Part B starting with Cohort 1 IV (6 mg LD + 36 mg MD on Day 1 followed by 38 mg MD for Days 2-4). This will be done after confirmation of AMG 986 safety and tolerability in IV Cohort 4 (20 mg LD + 120 mg MD) of Part A. The rationale for this is supported by the anticipated exposure, safety and tolerability of AMG 986 in IV Cohort 4 of Part A at 20 mg (LD) + 120 mg (MD).
3. Allow earlier transition to the PO cohorts of Part B starting with Cohort 1 PO (5 mg QD for 7 days) upon a DLRM decision to proceed for the 30 mg PO single dose cohort in Part A. The rationale for this is supported by the observed exposure, safety and tolerability of AMG 986 in PO Cohort 2 Part A (30 mg PO single dose).
4. Perform additional PK and echocardiographic assessments at later time points after dosing in Part B. The rationale for this is supported by observed exposure to date and reanalyzed predicted exposure.

Minor administrative, typographical and grammatical changes were made.

Amendment 2

Protocol Title: A Phase I, Randomized, Double-blind, Placebo Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 986 in Healthy Subjects

Amgen Protocol Number AMG 986 20150183

Amendment Date: 27 October 2016

Rationale:

The primary objective of this protocol amendment is to:

1. Clarify the intravenous dosing requirements for a loading dose and a maintenance dose.
2. Update the restrictions for nicotine and caffeine use on the study.
3. Remove cumulative PK urine collection outside of residency.

Minor administrative, typographical, and grammatical changes were made.

Amendment 1

Protocol Title: A Phase I, Randomized, Double-blind, Placebo Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 986 in Healthy Subjects

Amgen Protocol Number AMG 986 20150183

Amendment Date: 08 July 2016

Rationale:

The primary objective of this protocol amendment is to enhance safety assessments of subjects during the study:

1. Include an unblinded medical monitor to review adverse events in real-time
2. Add the collection of laboratory assessments at 24 hours and discharge
3. Add the assessment of troponin levels at baseline prior to dosing, Days 2 and 5
4. Add the requirement to evaluate AMG 986 exposure and dose predictions using available human PK data and include in the review of dose cohorts by DLRM members.
5. Add a physical exam at 24 hours

Minor administrative, typographical, and grammatical changes were made.