Title: A Phase 1, Open-label, Single-dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of AMG 986 Administered Orally to Healthy Volunteers and Subjects With Severely Impaired Renal Function

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Confidentiality Notice

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Investigator's Agreement

I have read the attached protocol entitled A Phase 1, Open-label, Single-Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of AMG 986 Administered Orally to Healthy Volunteers and Subjects with Severely Impaired Renal Function, dated 28 September 2017, 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 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 1, Open-label, Single-Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of AMG 986 Administered Orally to Healthy Volunteers and Subjects with Severely Impaired Renal Function

Study Phase: 1

Indication: Heart Failure

Primary Objective:

- To evaluate the pharmacokinetics (PK) of AMG 986 following the administration of a single oral 200 mg dose to healthy volunteers and subjects with severely impaired renal function.

Secondary Objective:

- To evaluate the safety and tolerability of AMG 986 following single oral dose administration to subjects with severely impaired renal function relative to heathy matched control subjects.

Exploratory Objectives:

- To determine unbound concentrations of AMG 986 in plasma.
- To determine AMG 986 metabolite concentrations in plasma.

Hypothesis:

- Clinically significant changes in AMG 986 PK that would require dose adjustment are not expected in subjects with severe renal impairment when compared to subjects with normal renal function.

Primary Endpoints:

- AMG 986 PK parameters including area under the plasma concentration time curve from time 0 to the time of the last quantifiable sample (AUC_{0-t}) and maximum observed plasma concentration after dosing (C_{max}). Additional AMG 986 PK parameters may include but not limited to terminal phase half-life ($t_{1/2}$); time of maximum AMG 986 plasma concentration (t_{max}); and AUC from time 0 to infinity (AUC_{inf}).

Secondary Endpoint:

- Subject incidence of adverse events and clinically significant changes in vital signs, physical examinations, clinical laboratory tests and ECGs

Exploratory Endpoints:

- Plasma protein binding of AMG 986
- AMG 986 metabolite concentrations in plasma

Study Design:

This is a phase 1, multicenter, open-label, single-dose study conducted in subjects with severely impaired renal function as determined by the modification of diet in renal disease (MDRD) equation for estimated glomerular filtration rate (eGFR). Approximately 12 subjects will be assigned to the two treatment groups in the study. Approximately 6 subjects with severely impaired renal function (eGFR 15 to 29 ml/min/1.73 m^2) will be assigned to group 1; approximately 6 subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2) will be assigned to the control group 2. All subjects in each group will receive a single oral dose of 200 mg AMG 986.

An attempt will be made to match the control group of healthy males and females with normal renal function (group 2) to the group of subjects with severely impaired renal function (group 1) by age range, body weight range, gender (proportion of male and female subjects), and race. Enrollment of subjects in the control group will be initiated after all subjects in the renal impairment (RI) group have been enrolled. The mean age ± 5 years and mean body weight ± 10% of the subjects in the RI group will be used to help match the subjects in the control group. The priority for matching subject characteristics of the two groups will be: age range, body weight range, gender, then race.

Sample Size: The sample size, approximately 12 subjects in 2 groups of 6 subjects each, is based on practical and is consistent with the number of subjects enrolled in similar studies.

Summary of Subject Eligibility Criteria:

Males or females ≥ 18 and ≤ 65 years of age, with a BMI of ≥ 18 and ≤ 38 kg/m^2 at screening.

- Subjects enrolled in group 1 will have severe RI (eGFR 15 to 29 mL/min/1.73m^2). It will be anticipated that these subjects will not require hemodialysis or renal transplantation, and will have renal function appropriate to severe RI for the duration of the study.
- Subjects enrolled in group 2 will be subjects with normal renal function (eGFR ≥ 90 mL/min/1.73m^2).

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

Investigational Product

Amgen Investigational Product Dosage and Administration:

AMG 986 for oral administration will be provided as 25 mg tablets in 15-count bottles. All subjects will receive a single oral dose of 200 mg AMG 986.

Procedures:

Screening

After informed consent has been obtained, all screening procedures and tests to establish eligibility will be performed within 28 days prior to the administration of AMG 986. Subjects who meet the eligibility criteria after completion of all screening, day -1 and day 1 pre-dose procedures will be enrolled in the study. Screening procedures are summarized in the Schedule of Assessments. Day -1 assessments will be performed 1 day before investigational product administration. Subjects will be admitted to the research facility on day -1 for residency.

Treatment

On the morning of day 1, enrolled subjects will receive IP by oral administration as a single 200 mg dose on an empty stomach (no food or liquids, except water, for at least 8 hours prior to dose administration). Subjects will remain in a fasted state (no food or liquids, except water) for at least 2 hours after dose administration. Subjects will reside at the research facility until day 2 procedures have been completed, according to the Schedule of Assessments. Subjects will be discharged and will be provided with instructions to return to the research facility at specified time points to complete procedures through the end of the study (according to the Schedule of Assessments).

All adverse events, including serious adverse events, and use of concomitant medication will be collected for the duration of the study.

End of Study

Subjects will be followed through day 30. Subject participation is complete once end-of-study (EOS) procedures are performed.

All adverse events (including serious adverse events and deaths) and use of concomitant medication will be collected for the duration of the study up to and including the EOS visit. If

there is a clinically significant clinical or laboratory abnormality that requires monitoring, subjects will be followed until resolution of the abnormality or until it is considered stable.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 2).

Statistical Considerations:

PK parameters of total AMG 986 in plasma will be calculated using non-compartmental methods. Descriptive statistics will be provided for all endpoints and will include selected demographics, adverse events, vital signs, ECG, PK, and selected laboratory measurements. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. PK parameters and clinical lab data will be summarized at each time point when samples are collected. Additionally, 90% confidence intervals will be calculated for the mean group difference ie, the geometric mean ratio (GMR) after back-transforming. These 90% CIs will be tabulated and presented for all PK parameters compared. Assuming 20% for the intra-subject standard deviation for AMG 986 log–transformed PK parameters ($AUC_{0\text{-}t}$ and C_{max}) and assuming that it is the same in the 2 groups, the current sample size of 6 would provide a CI for the GMR of (0.81, 1.23). The number and percentage of subjects reporting any treatment-emergent adverse event will be tabulated by system organ, preferred term, and renal function group. With 12 subjects receiving AMG 986, there is a 46% chance of seeing an AE with a 5% incidence rate. Clinically significant changes in vital signs, ECGs, and clinical laboratory tests will be noted. For a full description of statistical analysis methods, please refer to Section 10.

Sponsor:

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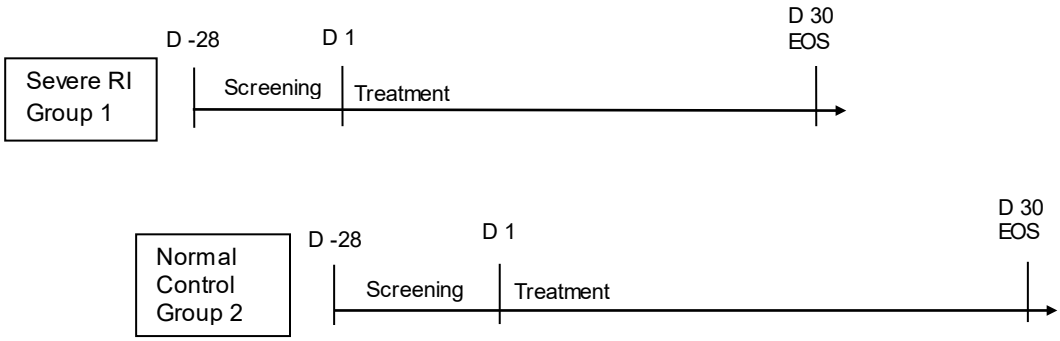
Study Design and Treatment Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
ADHERE	US Acute Decompensated Heart Failure National Registry
AE	adverse event
ALT	alanine aminotransferase
APJ	apelin receptor
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{0-t}	area under the concentration-time curve from time 0 to the time of the last quantifiable sample
BMI	body mass index
BP	blood pressure
C_{max}	maximum observed concentration
CRF	electronic case report form
CTCAE	common terminology criteria for adverse events
DILI	drug induced liver injury
ECG	Electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a study
End of Study	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
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
Enrollment	when the investigator decides that the subject has met all eligibility criteria
GCP	good clinical practice
GMR	geometric mean ratio
HBcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
hERG	human Ether-a-go-go-Related Gene
HepCab	hepatitis C antibody
HF	heart failure

Abbreviation or Term	Definition/Explanation
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
HR	heart rate
ICF	informed consent form
ICH	international conference on harmonization
IP	investigational product
IPIM	investigational product instruction manual
IUD	intrauterine device
IV	Intravenous
MDRD	modification of diet in renal disease
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
P-gp	P glycoprotein
PK	Pharmacokinetics
PR Interval	pr interval is measured from the beginning of the P wave to the beginning of the QRS complex in the hearts electrical cycle as measured by ECG
Primary Completion	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
QRS Interval	qrs interval is the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT interval	qt interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG
QTc interval	qt interval corrected for heart rate using accepted methodology
QTcF	qt interval corrected for heart rate using Fridericia's formula
RI	renal impairment
RR	respiratory rate
SAE	serious adverse event
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.

Abbreviation or Term	Definition/Explanation
Study Day 1	defined as the first day that protocol specified investigational product(s)/protocol-required therapies is/are administered to the subject
TBL	total bilirubin
TEMP	Temperature
t_{max}	time to max plasma concentration
ULN	upper limit of normal
V_{ss}	steady-state volume of distribution

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1. OBJECTIVES

1.1 Primary

To evaluate the pharmacokinetics (PK) of AMG 986 following the administration of a single oral 200 mg dose to healthy volunteers and subjects with severely impaired renal function.

1.2 Secondary

- To evaluate the safety and tolerability of AMG 986 following single oral dose administration to subjects with severely impaired renal function relative to heathy matched control subjects.

1.3 Exploratory

- To determine unbound concentrations of AMG 986 in plasma.
- To determine AMG 986 metabolite concentrations in plasma.

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 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.

2.1 Disease

Heart failure (HF) 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. 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). 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 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.

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.

Non-cardiac comorbidities including chronic kidney disease (CKD) are extremely common in HF patients. In a meta analysis of the published literature that included 57 studies that evaluated CKD in HF patients, the pooled prevalence of CKD was reported as 32% in all HF patients, 53% in acute HF patients, and 42% in chronic HF patients (Damman et al, 2014). In the same publication, the pooled rate of worsening

renal function was reported as 23% in all HF patients, 23% in acute HF patients, and 25% in chronic HF patients. In the US, the Acute Decompensated Heart Failure National Registry (ADHERE) Cohort showed that the prevalence of moderate (Stage III), severe without dialysis (Stage IV), and severe with dialysis (Stage V) renal dysfunction was 41.2%, 11.5%, and 6.6%, respectively for males, and 45.7%, 14.8%, and 7.3%, respectively for females (Heywood et al, 2007). In the same meta-analysis (Damman et al, 2014) the mortality rate was also estimated: at baseline, the pooled mortality rate was 16% in HF patients with CKD and 11% in HF patients without CKD, after a mean follow-up of 681 days. The pooled unadjusted odds ratio (OR) of all-cause mortality in HF patients with CKD vs HF patients without CKD was 2.34 (95% confidence interval [CI], 2.2-2.5). Furthermore, worsening renal failure during the course of disease was also correlated to mortality when compared with patients without worsening renal failure (pooled unadjusted OR = 1.81 [95% CI, 1.55-2.12]). The use of some HF therapies, such as ACE inhibitors and loop diuretics, can result in acute renal failure or acute worsening of pre-existing chronic kidney dysfunction. Acute worsening of cardiac output can also lead to decreases in renal function (Ezzat et al, 2015; Tariq and Aronow, 2015; McMurray et al, 2012; Schoolwerth et al, 2001). Therefore, the knowledge of the safety and pharmacokinetic behavior of AMG 986, being developed as a promising therapy for heart failure patients, in subjects with renal dysfunction is extremely relevant.

2.2 Amgen Investigational Product Background

AMG 986 is a small-molecule agonist that binds to the APJ receptor and activates $G_{\alpha i}$ and arrestin pathways.

Refer to the specific section of the IB for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

2.2.1 Pharmacology

Nonclinical Pharmacology

AMG 986 increased cardiac contraction and relaxation in isolated perfused rat hearts. This increase in load-independent contractility without change in calcium transients was also observed in adult rat cardiomyocytes. The contractile effects of AMG 986 appeared to be specific through APJ receptor, since the compound has no impact on phosphodiesterase inhibition. The cardiovascular effects of AMG 986 *in vivo* were studied in both rodent and canine models. In a rat model of systolic heart failure (induced by myocardial infarction), AMG 986 increased cardiac output, reduced systemic

vascular resistance, and improved ventriculo-arterial coupling. In that same model, AMG 986 had beneficial effects on cardiac function that were additive to those of the reference drug captopril. 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 two canine heart failure models (microembolism and tachypacing), AMG 986 improved left ventricular contractile function without negative impact on heart rate and/or myocardial oxygen consumption. Details of AMG 986 nonclinical pharmacology are summarized in the Investigators 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 (V_{ss}) were variable across species and mean estimates of elimination half-life ($t_{1/2,z}$) 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.

Human Pharmacokinetics

Preliminary PK analyses were conducted in 54 healthy subjects who had received AMG 986 by intravenous infusion or by oral tablet administration in Study 20150183. A total of 4 oral dose cohorts (24 subjects) and 5 intravenous (IV) dose cohorts (30 subjects) have been studied.

After single oral dose administration at 5 mg, 30 mg, 100 mg and 200 mg, mean estimates of terminal half-life ranged from 13.2 to 18.0 hours, absorption was rapid with median estimates of T_{max} that ranged from 1.0 to 2.0 hours and oral bioavailability ranged from 61% to 80% (Table 1).

Pharmacokinetic dose proportionality was not assessed formally; however, exposure to AMG 986 generally increased with increased oral AMG 986 doses.

The excretion of unchanged AMG 986 in urine was low in subjects who received AMG 986 by single IV infusion at 0.5 mg/1 hour or 3 mg/1 hour. In IV cohorts 1 and 2, approximately 4% of dose was excreted unchanged within 12 hours following IV dosing and minimal additional excretion of dose occurred between 12 and 48 hours after IV administration.

Table 1. Preliminary AMG 986 PK Estimates in Healthy Subjects After Single Oral Dose Administration and Exposure Margins (Study 20150183)

Dose (mg)	Obs/ Pred	F (%)	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	75	334 (22)	2460 (34)	422X	150X	293X	219X
30	Obs	61	1850 (33)	12600 (25)	76X	29X	53X	43X
100	Obs	64	5760 (24)	34100 (5)	24X	11X	17X	16X
200	Obs	80	12200 (34)	85600 (33)	12X	4X	8X	6X

[1] Ratio of mean observed C_{max} and AUC_{24h} exposure at NOAEL 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 C_{max} and AUC_{inf} exposures.

[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 C_{max} and AUC_{inf} exposures.

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; F= oral bioavailability; Obs = observed

2.2.3 Toxicology

Nonclinical Toxicology

The nonclinical toxicology package for AMG 986 includes repeat dose toxicology studies with both oral (28-day studies in rat and dog) and IV (14-day studies in rat and dog) dose routes, developmental and reproductive toxicology studies in rats and rabbits (oral dosing), as well as genetic toxicology, phototoxicity and safety pharmacology studies.

Repeat Dose Toxicology Studies:

In the 28-day oral toxicology studies, estimates of AUC_{24h} exposures in rats and dogs at the no-observed-(adverse)-effect-level (NO[A]EL) doses were 4-fold and 6-fold greater than the human exposure at 200 mg, respectively (Table 1). These margins from the toxicology studies support the planned oral dose of 200 mg.

In developmental and reproductive toxicology studies in rats and rabbits, oral administration of AMG 986 resulted in embryo-fetal toxicity 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, and decreases in embryo-fetal survival.

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 IV dog cardiovascular (CV) study, AMG 986 related CV effects were limited to small 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) after single oral doses up to 300 mg/kg. No effects on QT/QTc interval were observed in the anesthetized or conscious dog safety pharmacology studies and there were no changes in QTc interval in the 28-day oral or 14-day IV dog toxicology studies.

The IC50 value for inhibitory effect of AMG 986 on hERG current (IKr current) was estimated to be > 300 µM (157 µg/mL, unbound concentration), more than 3000-fold

higher than the human unbound concentration at the oral dose of 200 mg. Details of AMG 986 nonclinical package are summarized in the Investigators Brochure.

2.3 Risk Assessment

AMG 986 has an identified risk of embryo-fetal toxicity. 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 refrain from sperm donation 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, expected acute risks associated with AMG 986 are of a cardiovascular nature, such as hypotension, although other effects, such as tachycardia or even hypertension cannot be excluded.

Overall, the nonclinical (toxicology and safety pharmacology) package suggests a safe profile at the doses planned in 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-day studies) or IV (14-day studies) dose administration. The AUC exposure margins based on NO(A)EL doses from the rat and dog toxicology studies support the planned clinical dose range. Additionally, no AMG 986-related effects in the safety pharmacology studies were identified, and data indicate that QTc interval prolongation risk is low.

Developmental and reproductive toxicology studies identified a risk for embryo-fetal toxicity as described above.

As of 14 March 2017, 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 9 fully implemented cohorts of 8 healthy subjects each. The subjects reviewed included those who received single oral doses of AMG 986 up to 200 mg, oral doses of 5 mg of AMG 986 for 7 consecutive days, as well as IV doses of AMG 986 over 24 hours

(loading doses up to 20 mg over 1 hour followed by maintenance doses up to 120 mg over 23 hours) and placebo. There was a total of 54 subjects who received AMG 986 and 18 subjects who received placebo. Of these 72 subjects, 71 completed the investigational product. 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 72 subjects, no serious adverse events, 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. Twelve subjects (16.7%) were reported to have treatment emergent adverse events during double-blind treatment. The most common event was headache, which occurred in 5 subjects (6.9%). The event of headache was reported as a common terminology criteria for adverse events (CTCAE) severity grade 1 in 4 of the subjects, and CTCAE grade 2 in 1 subject. Most of the adverse events were CTCAE grade 1 events. There were 4 CTCAE grade 2 events, and none of the events occurred in more than 1 subject. No events were CTCAE grade ≥3 events.

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 meaningful individual subject changes in vital signs (including blood pressure) were identified within or across any of the 9 cohorts. There was no notable variation in the vital signs with the increasing doses of AMG 986 throughout the study. Additionally, no laboratory (including troponin I) or ECG abnormalities were detected.

In summary, the clinical experience accumulated with AMG 986 suggests that the administration of AMG 986 was well tolerated.

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

2.4 Rationale

This study will evaluate the safety, tolerability, and PK of AMG 986 in male and/or female subjects with severely impaired renal function relative to heathy matched control subjects. All subjects will receive IP in a fasted state as a single 200 mg dose by the oral route. Healthy subjects with normal renal function will serve as a control group to

subjects with severely impaired renal function. The dose selected for this study is based on model predictions of human exposure from preclinical studies and the First-In-Human study in healthy subjects, the safety and tolerability profile for the selected dose in healthy human subjects and the potential clinical doses to be investigated in patients with heart failure who may also have renal impairment.

While clinical doses have not been selected for study in a pivotal trial of AMG 986 in patients with heart failure, a single dose of 200 mg was selected for this study. Selection of the 200 mg oral dose level for evaluation was based on the following: (1) observed AMG 986 PK results in healthy subjects (2) acceptable safety and tolerability of a single oral dose up to 400 mg in study 20150183 (3) acceptable safety and tolerability of multiple daily oral dose of 200 mg. 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.

Evaluation of AMG 986 PK in subjects with renal impairment at the planned dose will allow the conclusions of this study to be applied to subsequent studies where a dose as high as 200 mg could be tested.

2.5 Clinical Hypothesis

Clinically significant changes in AMG 986 PK that would require dose adjustment are not expected in subjects with severe renal impairment when compared to subjects with normal renal function.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 1, multicenter, open-label, single-dose study conducted in subjects with severely impaired renal function as determined by estimated glomerular filtration rate (eGFR). The eGFR is estimated using the 4-Parameter Modification of Diet in Renal Disease (MDRD) equation (Levey et al, 2009). Approximately 12 subjects will be assigned to 1 of 2 treatment groups. Approximately 6 subjects with severely impaired renal function (eGFR 15 to 29 ml/min/1.73 m^2) will be assigned to group 1; approximately 6 subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2) will be assigned to the control group 2. All subjects will be assigned to receive a single oral dose of 200 mg AMG 986.

An attempt will be made to match the control group of healthy males and females with normal renal function (group 2) to the group of subjects with severely impaired renal

function (group 1) by age range, body weight range, gender (proportion of male and female subjects), and race. The mean age ± 5 years and mean body weight ± 10% of the subjects in the severely renal impaired group will be used to help match the subjects in the control group. The priority for matching subject characteristics of the two groups will be: age range, body weight range, gender, then race.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

This study will be conducted at approximately 3 clinical research facilities in the United States. Sites that do not enroll subjects within 1 month of site initiation may be closed.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as "subjects". Approximately 12 subjects in 2 groups of 6 subjects each will be enrolled in the study. The sample size justification for subjects enrolled in this study is provided in Section 10.2.

3.4 Replacement of Subjects

Enrolled subjects who do not receive AMG 986 or do not receive the full dose of AMG 986 may be replaced. Subjects who drop out of the study for reasons other than adverse events or serious adverse events after receiving investigational product may be replaced at the discretion of Amgen in consultation with the investigator or their designee.

All data from any replaced subjects will be captured and kept in the clinical trial database and identified as such.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

Subject participation will last up to approximately 58 days, including a 28-day screening period prior to administration of AMG 986 and an on-study period lasting up to 30 days.

3.5.2 End of Study

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when the last subject has completed assessments for pharmacokinetics.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The end of study date is defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.

4. SUBJECT ELIGIBILITY

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

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

4.1 Inclusion Criteria

101. Male or female subjects, who are ≥ 18 and ≤ 65 years of age at the time of screening

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

103. Women must be of non-reproductive potential
    - Postmenopausal defined as:
        - Age of ≥ 55 years with no menses for at least 12 months; OR
        - Age of < 55 years with no menses for at least 12 months AND with a follicle-stimulating hormone level > 40 IU/L) or according to the definition of "postmenopausal range" for the laboratory involved; OR
    - History of hysterectomy; OR
    - History of bilateral oophorectomy.

104. Women must have negative results for both the screening (serum) and day -1 (serum or urine) pregnancy tests

105. Men must agree to practice an acceptable method of effective birth control while on study through 11 weeks after receiving the dose of study drug. Acceptable methods of effective birth control include sexual abstinence; vasectomy and testing shows there is 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 IUD (women).

106. Men must be willing to abstain from sperm donation while on study through 11 weeks after receiving the dose of study drug

107. Body mass index (BMI) ≥ 18 and ≤ 38 kg/m^2 at screening.

108. Laboratory test values (clinical chemistry and hematology) within normal limits for subjects with normal renal function or consistent with the underlying condition for subjects with renal impairment, or clinically acceptable to the investigator for both normal renal function and subjects with renal impairment.

109. Physical examination and 12-lead electrocardiograms (ECGs) are clinically acceptable to the investigator.

110. Non-hypertensive subjects or subjects with treated, stable hypertension as defined by blood pressure not exceeding 170/100 mm Hg as an average during screening and day -1; for subjects with renal impairment, no change in dosage and medication for ≥ 4 weeks prior to screening, and expected to remain on this dose and medication for the entire duration of the study

111. Willing to maintain current general diet and physical activity regimen

112. Renal function in 1 of the following 2 categories at the time of screening for:

- Group 1: Severe RI (eGFR 15 to 29 ml/min/1.73 m^2) and not anticipated to require hemodialysis or renal transplantation, and anticipated to have renal function appropriate to severe RI for the duration of the study
- Group 2: Normal renal function (eGFR ≥ 90 ml/min/1.73m^2)

4.2 Exclusion Criteria

Exclusion Criteria for All Subjects:

201. Subjects whose second MDRD eGFR result on day -1 is not within 15% of the first eGFR result performed during the screening period. Healthy volunteers who have normal renal function, but show a difference greater than 15% in eGFR based on MDRD during the screening period, will be included in the trial at the discretion of the investigator and the sponsor after a 24-hour creatinine clearance has been performed that meets eligibility criteria.

202. Subjects who are the recipient of a renal transplant and/or are on immunosupressants.

203. Subjects with a history of hospitalization for heart disease or angina within 4 months of screening.

204. Current or prior malignancy within 5 years of enrollment 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.

205. Positive for human immunodeficiency virus (HIV antibodies), hepatitis B surface antigen (HBsAg) or hepatitis C virus antibodies (HepCAb) at screening

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

207. Subject likely to not be available to complete all protocol-required study visits or procedures (including the research facility residency period), and/or to comply with all required study procedures to the best of the subject and investigator's knowledge.

208. 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.

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

210. Women who are lactating/breastfeeding or who plan to breastfeed while on study through 11 weeks after receiving the dose of study drug.

211. Men with partners who are pregnant or planning to become pregnant while the subject is on study through 11 weeks after receiving the dose of study drug.

212. QTc Interval:

- Group 1 (Severe Renal Impairment): QTc > 470 msec or history/evidence of long QT syndrome.
- Group 2 (Normal Renal Function): QTc > 450 msec or history/evidence of long QT syndrome.

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

214. Blood donation ≥ 500 mL within 60 days of day 1.

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

216. 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.

217. Unwilling or unable to abstain from alcohol consumption from 24 hours prior to admission to the research facility (day -1) and throughout the duration of the study.

218. Known history of drug or alcohol abuse within last 12 months.

219. Subjects with a positive drug and alcohol screen at screening or day -1

220. 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 dose of investigational product (AMG 986).

221. Concurrent use of any medications (over-the-counter or prescription) within 14 days or 5 half-lives (whichever is longer) prior to dose of AMG 986, except acetaminophen (up to 2 g per day) for analgesia, hormone replacement therapy (eg, estrogen, thyroid), and medications used to treat CKD and other chronic comorbidities in subjects with severe renal impairment. Continued use if applicable, will be reviewed by the Principal Investigator and the Amgen Medical Monitor. Written documentation of this review and Amgen acknowledgment is required for subject participation.

222. Concurrent or prior use of strong CYP3A4 inhibitors within 14 days or 5 half-lives (whichever is longer) of study day 1, including (not limited to): macrolide antibiotics (eg, clarithromycin, telithromycin), antifungals (eg, itraconazole, voriconazole), antivirals (eg, ritonavir, saquinavir, indinavir, nelfinavir), nefazodone.

223. 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.

224. Concurrent or prior use of strong CYP3A4 inducers within 30 days or 5 half-lives (whichever is longer) of study day 1, Including (not limited to): phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital. Subjects should also not take St. John's Wort.

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

226. Concurrent or prior use of Phosphodiesterase 5 (PDE5) inhibitors within 28 days of study day 1, including (not limited to) avanafil, sildenafil, tadalafil, vardenafil.

227. Concurrent use or prior use of vasodilators within 28 days of study day 1, that could in the opinion of the investigator potentially lead to a drop in blood pressure in combination with investigational product (AMG 986).

228. Current use or prior use of all herbal medicines, vitamins, and supplements consumed by the subject within the 30 days prior to receiving the first dose of AMG 986.

229. 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.

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 and/or legally acceptable representatives must personally sign and date the informed consent form before commencement of study-specific activities/procedures. A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria.

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

Each subject who enters into the screening period for the study (defined as the point at which the subject signs the Informed Consent Form (ICF)) receives a unique subject identification number before any study 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. Subjects who fail screening may be rescreened once at the discretion of the investigator and with approval in consultation with Amgen.

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.

[redacted]

5.1 Treatment Assignment

This is a phase 1, open-label, non-randomized study conducted in subjects with severely impaired renal function as determined by the modification of diet in renal disease (MDRD) equation for estimated glomerular filtration rate (eGFR). Subjects who meet eligibility requirements (Section 4) will be assigned into one of 2 treatment groups: severe RI (eGFR 15 to 29 mL/min/1.73 m^2) or normal renal function (eGFR ≥ 90 mL/min/1.73 m^2 or above).

Subjects with severely impaired renal function (eGFR 15 to 29 ml/min/1.73 m^2) will be assigned to group 1. Subjects with normal renal function will be assigned to the control group 2. Enrollment of subjects in the control group will be initiated after all subjects in the RI group have been enrolled.

An attempt will be made to match the control group of healthy males and females with normal renal function (group 2) to the group of subjects with severely impaired renal function (group 1) by age range, body weight range, gender (proportion of male and female subjects), and race. The mean age ± 5 years and mean body weight ± 10% of the subjects in the severely renal impaired group will be used to help match the subjects

in the control group. The priority for matching subject characteristics of the two groups will be: age range, body weight range, gender, then race. After review of the characteristics of the subjects enrolled in the RI group, Amgen will decide on the acceptability of eligible subjects in the control group to match the RI group, and be enrolled in the study.

All subjects in each group will receive a single oral dose of 200 mg AMG 986 on day 1. Subjects will be assigned an identification number in the order in which they were qualified.

6. TREATMENT PROCEDURES

6.1 Classification of Product(s)

The Amgen Investigational Product (except if required by local regulation) used in this study include: AMG 986. The dose of AMG 986 that is planned is a single 200 mg dose administered orally.

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.

6.2 Investigational Product

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

A physician must be available at the time of administration of Investigational Product (AMG 986).

6.2.1 Amgen Investigational Product: AMG 986

AMG 986 for oral administration will be manufactured and packaged by Amgen, Inc. and distributed using Amgen clinical investigational product distribution procedures.

AMG 986 for oral administration will be provided to the site as 25 mg tablets available in 15-count bottles.

6.2.1.1 Dosage, Administration, and Schedule

Subjects will be admitted to the study clinic on day -1 and will remain resident until completion of all study procedures 24 hours after dosing until day 2.

On day 1, enrolled subjects will receive IP (200 mg AMG 986) by oral administration on an empty stomach (no food or liquids, except water, for at least 8 hours prior to dose administration) on study day 1. Subjects will remain in a fasted state (no food or liquids,

except water) for at least 2 hours after dose administration. Fasting instructions will apply to both treatment groups. Following completion of all study procedures on day 2 (see Schedule of Assessments), subjects will be discharged from the clinic with instructions to return to the research facility at specified time points for collection of blood samples for PK assessments and completion of safety assessments through the end of the study.

Emesis and diarrhea will be documented in the subject source and on the Event CRF, with time and severity of the event noted. Any subject who experiences emesis within 4 hours of dosing may be excluded from the pharmacokinetic analysis. Any subject who experiences diarrhea within 24 hours of dosing may be excluded from the pharmacokinetic analysis.

The effects of overdose of this product are not known.

6.3 Criteria for Additional Safety Assessment due to Potential Hepatotoxicity

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:

- *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

- TBIL > 2x upper limit of normal (ULN) or INR > 1.5

AND

- No other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or elevated TBIL values include, but are not limited to:
  - Hepatobilliary 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 including herbal and dietary supplements, plants, and mushrooms,

- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
- Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

6.4 Concomitant Therapy

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.7. Subjects with impaired renal function may continue to use established therapies necessary for the treatment of renal disease (and conditions secondary to renal disease).

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 (up to 2 g per day) for analgesia and hormone replacement therapy (eg, estrogen, thyroid) will be allowed. All herbal medicines, vitamins, and supplements consumed by the subject within the 30 days prior to receiving the first dose of AMG 986, and continuing use if applicable, will be reviewed by the Principal Investigator and the Amgen Medical Monitor. Written documentation of this review and Amgen acknowledgment is 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.

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.7.

6.5 Alcohol and Tobacco Restrictions

Subjects will be required to abstain from alcohol consumption throughout the course of the study. Alcohol consumption is prohibited 24 hours prior to admission to the research facility (day -1) and throughout the duration of the study.

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.

6.6 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.

6.7 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, rifapentine, phenobarbital. Subjects should not take St. John's Wort.

During the study period, use of strong P-gycoprotein 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.

Medications excluded in the eligibility criteria (Section 4.2) are excluded for the duration of the study. Any exceptions (eg, medication given for the treatment of an adverse event) should be first discussed with Amgen.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 2. Schedule of Assessments

Activity	Screening		Treatment Period																	EOS
Study Day	-28 to -2	-1	1								2	3	4	5	6	8	11	15	22	30
Time (in hours)[1]			Pre	0	1	2	4	6	8	12	24	48	72	96	120					
Informed consent	X																			
Residency[2]		X	X	X	X	X	X	X	X	X	X									
Medical History	X	X																		
Body Weight	X	X																		X
Height	X																			
eGFR	X	X																		
Physical examination	X	X																		X
Vital signs (BP, HR, RR, Temp)	X[3]	X[3]	X		X	X	X	X			X	X	X	X	X					X
12-Lead ECG[4]	X		X		X	X	X	X			X	X	X	X	X					X
Adverse events[5]				X	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	X
Serious Adverse Events[6]	X	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→	X
Concomitant Medications Recording	X	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→	X
IP Administration				X																
Clinical Chemistry and Hematology	X	X									X			X						X
Troponin I	X		X								X			X						
Serum FSH (female only)[7]	X																			
Serum/urine pregnancy	X	X																		X
HIV, HepCAb, HBsAg, HBcAb	X																			
Drug, Alcohol, & Cotinine Screen[8]	X	X																		
AMG 986 Plasma PK Collection			X		X	X	X	X	X	X	X	X	X	X	X					

Footnotes defined on following page

[1] Time in hours relative to the time of administration of study drug on day 1
[2] Residency – Subjects will remain in-house from day -1 through the completion of all assessments on day 2, as designated in the Schedule of Assessments.
[3] Vital Signs – At screening and day -1, blood pressure will be measured on 2 occasions separated by at least 5 minutes, and an average of the blood pressures will be taken to confirm eligibility.
[4] ECGs – At screening a single ECG will be performed. At pre-dose (day 1), 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 triplicates). At all other time points, ECGs will be performed in a standardized method, in triplicate, and approximately 30 seconds apart.
[5] AEs – All adverse events observed by the investigator or reported by the subject that occurs after the dose of AMG 986 through EOS.
[6] SAEs – All serious adverse events observed by the investigator or reported by the subject that occur after the informed consent through 30 days after the last dose of AMG 986 or EOS, whichever is later.
[7] Only if required to ensure menopause in a female subject
[8] An alcohol breath test may also be used at day -1 should the saliva drug screen not include alcohol as an analyte

7.2 General Study Procedures

A signed and dated IRB-approved ICF must be obtained before any study-specific procedures are performed. Screening procedures will be performed within 28 days prior to AMG 986 administration.

During the study, every effort should be made to perform study procedures as indicated in the Schedule of Assessments. 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.

In the event that multiple procedures are required to be conducted at the same time, the following order of precedence will be used to ensure that certain safety assessments are not disturbed by blood draws: (1) ECG recording; (2) vital sign assessment; (3) PK blood sampling; (4) clinical laboratory tests; and (5) physical examination and physical measurements. Pharmacokinetic samples will be collected as close to the nominal time point as possible.

Acceptable deviation windows (including PKs) are as follows:

- ± 10 minutes on days 1-2
- ± 1 hour on days 3-6

Any missed visits, tests not done, and examinations not conducted must be reported as such on the CRFs.

Laboratory samples will be analyzed as follows:

- Hematology, chemistry, troponin I, serum FSH (if required), serum/urine pregnancy test, serology (HBsAg, HBcAb, and HepCAb), HIV, urine/serum drug/alcohol/cotinine testing will be analyzed at local laboratories
- Pharmacokinetic samples will be sent to Amgen for analysis

Refer to the provided Amgen manual for detailed collection, processing, and shipping procedures.

Meal Restrictions

Subjects will be required to fast at least 8 hours prior to IP administration (no food or liquid, except water) and refrain from food and liquid (except water) intake for at least 2 hours after IP administration on study day 1. Subjects are required to refrain from food and drinks (except water) 8 hours prior to each blood sample collection for clinical laboratory assessment.

During in-house residency period, subjects will receive standardized meals provided by the clinical site.

Subjects should maintain their current diet regimen throughout the study. This information will be verified at each visit, and recorded in the subjects' source documents. Consumption of grapefruit, grapefruit juice, and grapefruit-containing products is prohibited and must be avoided throughout the study.

Exercise Restrictions

Subjects should maintain their current exercise regimen. Subjects will be required to refrain from strenuous exercise 48 hours prior to each visit, and during the in-house residency. This information will be verified at each visit, and recorded in the subject source document.

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.

7.2.1 Screening

The following procedures are to be completed during the screening period at time points designated in the Schedule of Assessments.

- Confirmation that the Informed Consent Form has been signed
- Medical/Surgical History
- Physical Examination
- Height and Weight
- eGFR
- Vital signs (eg, blood pressure, heart rate, respiratory rate, oral temperature)
- 12-lead ECG
- Serious Adverse Event assessment/reporting
- Documentation of concomitant medications
- Laboratory Assessments: clinical chemistry, hematology, troponin I, serum/urine pregnancy test or serum FSH (if required to ensure menopause in a female subject), drug, alcohol and cotinine screening
- HIV, Hepatitis B, and Hepatitis C testing

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, and urine or serum 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 Day -1

The following procedures are to be completed during day -1 designated in the Schedule of Assessments.

- Medical History
- Physical examination
- Body Weight
- eGFR
- Vital Signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Serious Adverse Event assessment/reporting
- Documentation of concomitant medications
- Laboratory Assessments: clinical chemistry, hematology, serum/urine pregnancy test, drug, alcohol, and cotinine screening.
- In-house residency per Schedule of Assessments

7.2.3 Treatment

Treatment begins when the first dose of protocol-required therapies is administered to a subject.

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments. The dose of AMG 986 is to be administered upon completion of all predose procedures on the day of dosing (day 1); subjects will receive a single 200 mg oral dose of AMG 986.

<u>Predose on Day 1:</u>

- Vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- 12-lead ECG
- Serious adverse event assessment/reporting
- Documentation of concomitant medications
- Troponin I
- AMG 986 PK sampling as per Schedule of Assessments
- In-house residency per Schedule of Assessments

Dosing at Day 1 (hour 0)

- IP administration
- Adverse event assessment/reporting
- Serious adverse event assessment/reporting
- Documentation of concomitant medications
- In-house residency per Schedule of Assessments

Postdose at Specified Timepoints on Day 1 through Day 22:

- Vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- 12-lead ECG (day 1 to day 6)
- AMG 986 PK sampling as per Schedule of Assessments (day 1 to day 6)
- Laboratory Assessments: clinical chemistry and hematology
- Troponin I (day 1 and day 6)
- Serious Adverse Event assessment/reporting
- Adverse Event assessment/reporting
- Documentation of concomitant medications
- In-house residency per Schedule of Assessments

If the 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.

7.2.4 End of Study Visit

Subjects will return to the clinic for follow-up visits in accordance to the Schedule of Assessments and be followed through the completion of the End of Study (EOS) procedures on study 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.

The following procedures are to be completed during the End of study visit as designated in the Schedule of Assessments:

- Body weight
- Physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, oral temperature)
- 12-lead ECG
- Laboratory Assessments: clinical chemistry, hematology, serum/urine pregnancy test

- Serious Adverse Event assessment/reporting
- Adverse Event assessment/reporting
- Documentation of concomitant medications

7.2.5 Demographics

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

7.2.6 Subject Residency

Eligible subjects will be checked into the clinical site on day -1 and will be discharged after all assessments and procedures are completed at the end of day 2.

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 the Schedule of Assessments. 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 complete physical examination (excluding breast, genital, and rectal examination) at the time points indicated in the Schedule of Assessments. 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:

BMI (kg/m^2) = weight (kg)/[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 the Schedule of Assessments.

The following measurements must be performed: systolic/diastolic blood pressure (BP), heart rate (HR), respiratory rate, and oral 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. If the subject is unable to be in the Fowler position, the subject should be in the most recumbent position possible. The upper arm should be bare without constrictive clothing and supported at heart level. For group 1 ensure to use arm on non-dominant or non-access side. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF.
- 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.
- At screening and day -1, blood pressure will be measured on 2 occasions separated by at least 5 minutes, and an average of the blood pressures will be taken to confirm eligibility.

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 are collected.

7.2.11 Pregnancy Test (Females Only)

A serum pregnancy test will be performed on all female subjects at screening. A serum or urine pregnancy test will be collected on all female subjects at day -1 and EOS as specified in the Schedule of Assessments. The screening (serum) and day -1 (serum or urine) pregnancy test must be confirmed negative for the subject to be eligible for this study.

Females who become pregnant during the study will be followed for safety until end of study. A Pregnancy Notification Worksheet (Appendix C) will be completed for subjects with a positive test result at any point after providing informed consent.

7.2.12 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 – defined as: age of ≥ 55 years with no menses for at least 12 months; OR age of < 55 years with no menses

for at least 12 months AND with a follicle-stimulating hormone level > 40 IU/L or according to the definition of "postmenopausal range" for the laboratory involved; OR history of hysterectomy; OR history of bilateral oophorectomy).

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.

7.2.13 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. Drug screening includes 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 drugs, alcohol, or cotinine will not qualify for AMG 986 administration and will be withdrawn from study participation.

An alcohol breath test may also be used at day -1 should the saliva drug screen not include alcohol as an analyte. Due to limitations with saliva test, certain parameters may not be assessed on day -1 (eg, barbiturates).

7.2.14 Electrocardiogram (ECG)

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

ECGs 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 predose (day 1), 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 must include the following measurements: PR, RR, QRS, and QTc intervals.

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

7.2.15 Clinical Chemistry

Blood samples for clinical chemistry will be collected at the time points specified in the Schedule of Assessments.

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

The tests listed in Table 3 will be conducted and analyzed by standard laboratory procedures.

Table 3. List of Analytes

Local Laboratory Chemistry	Local Laboratory Hematology	Other
Sodium Potassium Calcium Chloride Bicarbonate (HCO_3) or Carbon Dioxide (CO_2) Total protein Albumin Glucose Blood urea nitrogen (BUN) or Urea Creatinine Total creatine kinase Total bilirubin Direct bilirubin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Troponin I Lipid Profile • Total Cholesterol • HDL • LDL • Triglycerides Magnesium Phosphorous or Phosphate	Hemoglobin Hematocrit Mean corpuscular volume Platelets Red Blood Cells White blood cell Differential • Total neutrophils (OR segmented neutrophils and band cells) • Eosinophils • Basophils • Lymphocytes • Monocytes	Local Laboratory: Hepatitis B surface antigen Hepatitis B core antibody Hepatitis C antibody HIV Serum FSH Serum or Urine Pregnancy Drug, Alcohol, and Cotinine Screening (Serum, Urine, Saliva, or Breath test (alcohol screen only))

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

The tests listed in Table 3 will be conducted and analyzed by 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 Plasma AMG 986 Concentrations

Blood samples for PK assessments will be collected at the time points as specified in the Schedule of Assessments.

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.

eGFR in mL/min per 1.73 m2 = 175 x SerumCr-1.154 x age-0.203 x 1.212 (if patient is black) x 0.742 (if female)

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 assess 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 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 during each 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 document and on the CRF when reported or observed.

7.3 Approximate Phlebotomy Volume

Subjects enrolled in this study will agree to provide whole blood for safety, and PK assessments during their participation in this study as noted in Table 4 below:

Table 4. Approximate Blood Volume Collection

Test	Volume per Collection, mL	Number of Collections	Total Volume, mL
Clinical Chemistry	5	5	25
Troponin I	5	4	20
Clinical Hematology	5	5	25
Serum pregnancy test (females only)	5	1	5
HIV/Hepatitis B, C Panel	15	1	15
Serum FSH (females only)	5	1	5
AMG 986 PK plasma concentration	5	12	60
TOTAL (All Groups)			155

7.4 Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the aspects of AMG 986 (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 AMG 986 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 AMG 986, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events. Subjects who have discontinued AMG 986 and/or protocol required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow-up that is agreed to by the subject.

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, medical device(s), 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 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)
- disease flare

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

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).

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 Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after dose of investigational product through the Safety Follow-Up Visit/End of Study Visit 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 investigational product (AMG 986), and/or any study-mandated activity/procedure(s), and
- Action taken

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) version 4. 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). 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? Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

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.

9.2.1.2 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 dose of Investigational product (AMG 986) or the Safety Follow-Up Visit/End of Study Visit, whichever is later are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event CRF.

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

The investigator must assess whether the serious adverse event is possibly related to the investigational product (AMG 986). 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? 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. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the 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.

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

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

9.2.1.3 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.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking Amgen Investigational Product (AMG 986) 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 dose of Amgen Investigational Product (AMG 986).

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 breastfeeds while taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur through 11 weeks after the dose of protocol-required therapies (AMG 986).

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.

Men whose partners become pregnant while the subject is on study through 11 weeks after receiving the dose of study drug must practice sexual abstinence or use a condom for 11 weeks after receiving the dose of study drug, and will be followed for safety until the end-of-study visit.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoints

- AMG 986 PK parameters including area under the plasma concentration time curve from time 0 to the time of the last quantifiable sample (AUC_{0-t}) and maximum observed plasma concentration after dosing (C_{max}). Additional AMG 986 PK parameters may include but not limited to terminal phase half-life ($t_{1/2}$); time of maximum AMG 986 plasma concentration (t_{max}); and AUC from time 0 to infinity (AUC_{inf}).

10.1.1.2 Secondary Endpoint

- Subject incidence of adverse events and clinically significant changes in vital signs, physical examinations, clinical laboratory tests, and ECGs

10.1.1.3 Exploratory Endpoints

- Plasma protein binding of AMG 986
- AMG 986 metabolite concentrations in plasma

10.1.2 Analysis Sets

For all analyses, subjects will be analyzed according to the group they were assigned.

10.1.2.1 Safety Analysis Set

The safety analysis set will consist of all study subjects who receive at least one dose of AMG 986. Subjects withdrawing prior to AMG 986 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.

10.1.3 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.

Group 1 will be the group formed with subjects with severely impaired renal function. Group 2, the group formed with subjects with normal renal function, will be considered the control group. An effort will be made to match the subjects in group 2, the normal renal function group to the subjects in group 1, by age range, body weight, gender, and race. The mean age ± 5 years and mean body weight ± 10% of the subjects in the severely renal impaired group will be used to help match the subjects in the control group. No subgroup analyses are planned.

10.1.4 Handling of Missing and Incomplete Data

Incomplete data in the Primary Endpoints will be excluded from analysis. The number and frequency of missing values will be reported in the final study report.

Imputation for missing or incomplete dates will be performed, if required. If imputed dates are used, they will be identified as such in the final study report.

PK concentrations below the lower limit of quantification will be set to zero.

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 AMG 986 PK and safety plus tolerability, following a single oral administration of a 200-mg dose by descriptive summaries based on the observed data. The sample size of this study is based on practical considerations and is consistent with the number of subjects enrolled in similar studies. Approximately 12 subjects (6 subjects with severe RI and 6 subjects with normal renal function) will be enrolled for the study. Assuming 20% for the intra-subject standard deviation for AMG986 log-transformed PK parameters (AUC0-t and Cmax) and assuming that it is the same in the 2 groups, the current sample size of 6 would provide a Confidence Interval for the Geometric Mean Ratio of the parameters of (0.81, 1.23). For safety considerations, with a total of 12 subjects receiving AMG 986, there is a 46% chance of detecting an adverse event with a true incidence of 5% and a 72% chance of detecting a more common adverse event with a true incidence rate of 10%.

10.3 Planned Analyses

10.3.1 Data Review Team Meeting

A data review team meeting is not planned.

10.3.2 Primary Analysis

The primary analysis will occur after the database locks following the last subject's last visit.

10.3.3 Final Analysis

The primary analysis will be the final analysis.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

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

10.4.2 Primary Endpoints

10.4.2.1 Pharmacokinetic Analysis

The PK parameters for each subject will be estimated using non-compartmental methods. All plasma concentrations below the limit of quantification of the assay will be considered as zero for all analyses unless explicitly noted otherwise.

Summary statistics will be provided for each renal function group for AMG 986 PK parameters. These parameters will include $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, t_{max}, $t_{1/2}$ as appropriate. Binding of AMG 986 to plasma proteins will be determined to calculate select unbound PK parameters, if appropriate, and summary statistics will be provided. Graphs of AMG 986 plasma concentration-time profiles for individual subjects and for means for each function group may be provided. The mean difference for the 2 groups will be back transformed to produce the geometric mean ratio. Lower and upper limits of the 90% confidence interval for these ratios of the PK parameters will also be reported.

10.4.3 Secondary Endpoints

10.4.3.1 Safety Endpoints

10.4.3.1.1 Adverse Events

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, and significant treatment emergent adverse events will also be provided if observed.

10.4.3.1.2 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 group. Depending on the size and scope of changes, summaries of changes from baseline over time may be provided.

10.4.3.1.3 Electrocardiogram

All on-study ECG data will be reviewed 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. 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).

10.4.3.1.4 Clinical Laboratory

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

10.4.4 Exploratory Endpoints

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

10.4.4.1 Plasma Protein Binding of AMG 986

Pharmacokinetic parameters of unbound AMG 986, such as AUC, t_{max}, and C_{max}, will be assessed and summarized, if appropriate.

10.4.4.2 AMG 986 Metabolites

AMG 986 Metabolite concentrations in plasma will be measured and summarized, if data allows and team deems appropriate.

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 form 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

Amgen may amend the protocol at any time. After Amgen amends the protocol, the Investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment. The IRB must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IRB and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

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 Clinical Trial Agreement. 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 prestudy 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 (SEC) to obvious data errors in the clinical trial database. SECs will be documented in the CRF Standard Instructions 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 with different visit, [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, 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 may facilitate 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 International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

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

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

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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:

https://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 6.3 require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate 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 9.2.1.2.

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 6.3 or who experience AST or ALT elevations > 3 x ULN or 2-fold increase above baseline values for subjects with evaluated values before drug 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. The following are to be considered depending on the clinical situation:
  - Complete blood count (CBC) with differential to assess for eosinophilia
  - Serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis

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

AMGEN Study # 20150186 AMG 986	**Electronic Serious Adverse Event Contingency Report Form** <u>For Restricted Use</u>

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

AMGEN SAFETY US FAX#: 888 814 8653

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day____ Month_____ Year_____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day___ Month___ Year___

Serious Adverse Event <u>diagnosis</u> or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started (Day Month Year)	Date Ended (Day Month Year)	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the Event may have been caused by IP (AMG 986) or an Amgen device used to administer the IP? AMG 986 No✓	AMG 986 Yes✓	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No					
				☐Yes ☐No					
				☐Yes ☐No					

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

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

Date Admitted (Day Month Year)	Date Discharged (Day Month Year)

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

IP/Amgen Device:		Date of Initial Dose (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	Lot # and Serial #
AMG 986	☒ *open label*							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

FORM-056006 *Version 7.0 Effective Date: 1 February 2016*

Page 1 of 3

AMGEN Study # 20150186 AMG 986	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

	Site Number	Subject ID Number	

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

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

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

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

Date (Day Month Year)	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

AMGEN Study # 20150186 AMG 986	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

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

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

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20150186

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm / dd / yyyy_____

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

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

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

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

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: March 27, 2011 Page 1 of 1

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20150186

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Protocol Amendment 1

Protocol Title: A Phase 1, Open-label, Single-dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of AMG 986 Administered Orally to Healthy Volunteers and Subjects With Severely Impaired Renal Function

Amgen Protocol Number AMG 986 20150186

Protocol Date: 28 September 2017

Rationale:

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

- Incorporate changes required based on emerging pharmacokinetic data from the AMG 986 First in Human study (20150183):
  - 400 mg single dose to be reduced to 200 mg single dose throughout the protocol amendment
  - Dose rationale section updated based on dose change
- Key Sponsor Contacts updated based on changes in staff
- Nonclinical pharmacology section updated to align with recent Investigator Brochure update.
- In addition, inconsistency between schedule of assessment footnote and body of protocol was corrected, and typographical errors were corrected throughout protocol.

Description of Changes:

Header (throughout entire protocol)

Added bolded items and deleted strikethrough text:

Product: AMG 986

Protocol Number: 20150186

Date: ~~15 August 2017~~ **28 September 2017**

Protocol Title Page, Key Sponsor Contact(s) and Date

Added bolded items and deleted strikethrough text:

Key Sponsor Contact(s):	[redacted] MD, MSc Medical Sciences Medical Director Phone: [redacted] Email: [redacted] [redacted] PhD Clinical Pharmacologist Phone: [redacted] Email: [redacted] [redacted] Study Manager Phone: [redacted] Email: [redacted]
Date:	15 August 2017
Amendment 1 Date:	**28 September 2017**

Investigator's Agreement

Added bolded items and deleted strikethrough text:

Investigator's Agreement

I have read the attached protocol entitled A Phase 1, Open-label, Single-Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of AMG 986 Administered Orally to Healthy Volunteers and Subjects with Severely Impaired Renal Function, dated ~~15 August 2017~~ **28 September 2017**, and agree to abide by all provisions set forth therein.

Protocol Synopsis: Primary Objective, and Procedures

Added bolded items and deleted strikethrough text:

Primary Objective:

- To evaluate the pharmacokinetics (PK) of AMG 986 following the administration of a single oral ~~400~~ **200** mg dose to healthy volunteers and subjects with severely impaired renal function.

Treatment

On the morning of day 1, enrolled subjects will receive IP by oral administration as a single ~~400~~ **200** mg dose on an empty stomach (no food or liquids, except water, for at least 8 hours prior to dose administration). Subjects will remain in a fasted state (no food or liquids, except water) for at least 2 hours after dose administration. Subjects will reside at the research facility until day 2 procedures have been completed, according to the Schedule of Assessments. Subjects will be discharged and will be provided with instructions to return to the research facility at specified time points to complete procedures through the end of the study (according to the Schedule of Assessments).

Section 1.1, 1st sentence

Added bolded items and deleted strikethrough text:

To evaluate the pharmacokinetics (PK) of AMG 986 following the administration of a single oral ~~400~~ **200** mg dose to healthy volunteers and subjects with severely impaired renal function.

Section 2.2.1, 1st paragraph

Added bolded items and deleted strikethrough text:

Nonclinical Pharmacology

AMG 986 increased cardiac contraction and relaxation in isolated perfused rat hearts. ~~AMG 986 augmented the~~ **This increase in** load-independent contractility without change in calcium transients **was also observed** in adult rat cardiomyocytes. The ~~inotropic~~ **contractile** effects of AMG 986 ~~are~~ **appeared to be** specific through APJ receptor, since the compound has no impact on phosphodiesterase inhibition. **The cardiovascular effects of AMG 986 in vivo were studied in both rodent and canine models. In a rat model of systolic heart failure (induced by myocardial infarction), AMG 986 increased cardiac output, reduced systemic vascular resistance, and improved ventriculo-arterial coupling. In that same model, AMG 986 had**

beneficial effects on cardiac function that were additive to those of the reference drug captopril. 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 two canine heart failure models (microembolism and tachypacing), AMG 986 improved left ventricular contractile function without negative impact on heart rate and/or myocardial oxygen consumption. ~~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 Investigators Brochure.

Section 2.2.2, Table 1

Added bolded items and deleted strikethrough text:

Dose (mg)	Obs/ Pred	F (%)	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	75	334 (22)	2460 (34)	422X	150X	293X	219X
30	Obs	61	1850 (33)	12600 (25)	76X	29X	53X	43X
100	Obs	64	5760 (24)	34100 (5)	24X	11X	17X	16X
200	Obs	80	12200 (34)	85600 (33)	12X	4X	8X	6X
~~400~~	~~[3]Pred~~	~~NA~~	~~24300~~	~~167000~~	~~6X~~	~~2X~~	~~4X~~	~~3X~~
~~650~~	~~[3]Pred~~	~~NA~~	~~39400~~	~~272000~~	~~3.6X~~	~~1.4X~~	~~2.5X~~	~~2.0X~~

[1] Ratio of mean observed C_{max} and AUC_{24h} exposure at NOAEL 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~~ **exposures**.

[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~~ **exposures**.

~~[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; F= oral bioavailability; Obs=observed; ~~Pred=predicted~~

Section 2.2.3, 2nd paragraph

Added bolded items and deleted strikethrough text:

In the 28-day oral toxicology studies, estimates of AUC24h exposures in rats and dogs at the no-observed-(adverse)-effect-level (NO[A]EL) doses were ~~2~~ **4**-fold and ~~3~~ **6**-fold greater than the ~~predicted~~ human exposure at ~~400~~ **200** mg, respectively (Table 1). These margins from the toxicology studies support the planned oral dose of ~~400~~ **200** mg.

Section 2.2.3, 2nd and 6th paragraph

Added bolded items and deleted strikethrough text:

The IC50 value for inhibitory effect of AMG 986 on hERG current (IKr current) was estimated to be > 300 µM (157 µg/mL, unbound concentration), ~~approximately 1600X~~ **more than 3000-fold** higher than the ~~predicted~~ human ~~maximum~~ unbound concentration~~s~~ at the ~~highest planned~~ oral dose of ~~400~~ **200** mg. Details of AMG 986 nonclinical package are summarized in the Investigators Brochure.

Section 2.3, 8th paragraph

Deleted strikethrough text:

~~Investigation of a single oral dose of 400 mg, in a cohort of healthy volunteers in 20150183, has been reviewed at the time of this protocol authoring. A blinded subject level evaluation of adverse events and vital signs found no meaningful individual subject safety concerns within the cohort.~~

Section 2.4, 1st,2nd, and 3rd paragraph

Deleted strikethrough text and added bolded items:

This study will evaluate the safety, tolerability, and PK of AMG 986 in male and/or female subjects with severely impaired renal function relative to heathy matched control subjects. All subjects will receive IP in a fasted state as a single ~~400~~ **200** mg dose by the oral route. Healthy subjects with normal renal function will serve as a control group to subjects with severely impaired renal function. The dose selected for this study is based on model predictions of human exposure from preclinical studies and the First-In-Human study in healthy subjects, the safety and tolerability profile for the selected dose in healthy human subjects and the potential clinical doses to be investigated in patients with heart failure who may also have renal impairment.

While clinical doses have not been selected for study in a pivotal trial of AMG 986 in patients with heart failure, a single dose of ~~400~~ **200** mg was selected for this study. Selection of the ~~400~~ **200** mg oral dose level for evaluation was based on the following: (1) observed AMG 986 PK results in healthy subjects (2) acceptable safety and tolerability of a single oral dose up to 400 mg in study 20150183 (3) acceptable safety and tolerability of multiple daily oral dose of 200 mg. ~~(4) exposure margins projected for AUC values at an even higher 650 mg dose relative to exposures observed at NOEL and NOAEL doses in GLP toxicology studies and (5) the observed exposure of intravenous single and multiple doses of 60 mg over one hour loading followed by 360 mg maintenance dose over 23 hours being similar to the 400 mg oral dose in study 20150183 with acceptable safety and tolerability.~~ Although dose proportionality was not formally evaluated in the FIH study, increases in AUC and Cmax 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 400 mg, estimates of AUC24h exposures in rats at the NOAEL dose and dogs at the NOAEL dose were 2-fold and 3-fold of the predicted human exposure at 400 mg, respectively (Table 1).~~

Evaluation of AMG 986 PK in subjects with renal impairment at the planned dose will allow the conclusions of this study to be applied to subsequent studies where a dose as high as ~~400~~ **200** mg could be tested.

Section 3.1, 1st paragraph

Deleted strikethrough text and added bolded items:

This is a phase 1, multicenter, open-label, single-dose study conducted in subjects with severely impaired renal function as determined by estimated glomerular filtration rate (eGFR). The eGFR is estimated using the 4-Parameter Modification of Diet in Renal Disease (MDRD) equation (Levey et al, 2009). Approximately 12 subjects will be assigned to 1 of 2 treatment groups. Approximately 6 subjects with severely impaired renal function (eGFR 15 to 29 ml/min/1.73 m2) will be assigned to group 1; approximately 6 subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 m2) will be assigned to the control group 2. All subjects will be assigned to receive a single oral dose of ~~400~~ **200** mg AMG 986.

Section 5.1, 4th Paragraph

Deleted strikethrough text and added bolded items:

All subjects in each group will receive a single oral dose of ~~400~~ **200** mg AMG 986 on day 1. Subjects will be assigned an identification number in the order in which they were qualified.

Section 6.1, 1st Paragraph

Deleted strikethrough text and added bolded items:

The Amgen Investigational Product (except if required by local regulation) used in this study include: AMG 986. The dose of AMG 986 that is planned is a single ~~400~~ **200** mg dose administered orally.

Section 6.2.1.1, 2nd Paragraph

Deleted strikethrough text and added bolded items:

On day 1, enrolled subjects will receive IP (~~400~~ **200** mg AMG 986) by oral administration on an empty stomach (no food or liquids, except water, for at least 8 hours prior to dose administration) on study day 1. Subjects will remain in a fasted state (no food or liquids, except water) for at least 2 hours after dose administration. Fasting instructions will apply to both treatment groups. Following completion of all study procedures on day 2

(see Schedule of Assessments), subjects will be discharged from the clinic with instructions to return to the research facility at specified time points for collection of blood samples for PK assessments and completion of safety assessments through the end of the study.

Emesis and diarrhea will be documented in the subject source and on the Event CRF, with time and severity of the event noted. Any subject who experiences emesis within 4 hours of dosing may be excluded from the pharmacokinetic analysis. Any subject who experiences diarrhea within 24 hours of dosing may be excluded from the pharmacokinetic analysis.

Section 7.1, Table 2 Schedule of Assessments and footnotes

Deleted strikethrough text and added bolded items:

Activity	Screening		Treatment Period																	EOS
Study Day	-28 to -2	-1	1								2	3	4	5	6	8	11	15	22	30
Time (in hours)[1]			Pre	0	1	2	4	6	8	12	24	48	72	96	120					
Informed consent	X																			
Residency[2]		X	X	X	X	X	X	X	X	X	X									
Medical History	X	X																		
Body Weight	X	X																		X
Height	X																			
eGFR	X	X																		
Physical examination	X	X																		X
Vital signs (BP, HR, RR, Temp)	X[3]	X[3]	X		X	X	X	X			X	X	X	X	X					X
12-Lead ECG[4]	X		X		X	X	X	X			X	X	X	X	X					X
Adverse events[5]				X	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X
Serious Adverse Events[6]	X	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X
Concomitant Medications Recording	X	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X
IP Administration				X																
Clinical Chemistry and Hematology	X	X									X			X						X
Troponin I	X		X								X			X						
Serum FSH (female only)[7]	X																			
Serum/urine pregnancy[8]	X	X																		X
HIV, HepCAb, HBsAg, HBcAb	X																			
Drug, Alcohol, & Cotinine Screen[9 8]	X	X																		
AMG 986 Plasma PK Collection			X		X	X	X	X	X	X	X	X	X	X	X					

Footnotes defined on following page

1 Time in hours relative to the time of administration of study drug on day 1
2 Residency – Subjects will remain in-house from day -1 through the completion of all assessments on day 2, as designated in the Schedule of Assessments.
3 Vital Signs – At screening and day -1, blood pressure will be measured on 2 occasions separated by at least 5 minutes, and an average of the blood pressures will be taken to confirm eligibility.
4 ECGs – At screening a single ECG will be performed. At pre-dose (day 1), 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 triplicates). At all other time points, ECGs will be performed in a standardized method, in triplicate, and approximately 30 seconds apart.
5 AEs – All adverse events observed by the investigator or reported by the subject that occurs after the dose of AMG 986 through EOS.
6 SAEs – All serious adverse events observed by the investigator or reported by the subject that occur after the informed consent through 30 days after the last dose of AMG 986 or EOS, whichever is later.
7 Only if required to ensure menopause in a female subject
~~8 Does not apply to females with history of hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or post-menopausal, unless required by the clinic site.~~
8 An alcohol breath test may also be used at day -1 should the saliva drug screen not include alcohol as an analyte

Section 7.2.3, 2nd Paragraph

Deleted strikethrough text and added bolded items:

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments. The dose of AMG 986 is to be administered upon completion of all predose procedures on the day of dosing (day 1); subjects will receive a single ~~400~~ **200** mg oral dose of AMG 986.

Section 10.1.1.1, 1st Bullet

AMG 986 PK parameters including area under the plasma concentration time curve from time 0 to the time of the last quantifiable sample (AUC0-t) and maximum observed plasma concentration after dosing (Cmax). ~~Additonal~~ **Additional** AMG 986 PK parameters may include but not limited to terminal phase half life (t1/2); time of maximum AMG 986 plasma concentration (tmax); and AUC from time 0 to infinity (AUCinf).

Section 10.2, 1st Paragraph

Deleted strikethrough text and added bolded items:

This is a Phase 1 study and no formal statistical hypothesis testing will be performed. The study is designed to characterize AMG 986 PK and safety plus tolerability, following a single oral administration of a ~~400~~ **200**-mg dose by descriptive summaries based on the observed data. The sample size of this study is based on practical considerations and is consistent with the number of subjects enrolled in similar studies. Approximately 12 subjects (6 subjects with severe RI and 6 subjects with normal renal function) will be enrolled for the study. Assuming 20% for the intra-subject standard deviation for AMG986 log-transformed PK parameters (AUC0-t and Cmax) and assuming that it is the same in the 2 groups, the current sample size of 6 would provide a Confidence Interval for the Geometric Mean Ratio of the parameters of (0.81, 1.23). For safety considerations, with a total of 12 subjects receiving AMG 986, there is a 46% chance of detecting an adverse event with a true incidence of 5% and a 72% chance of detecting a more common adverse event with a true incidence rate of 10%.