Statistical Analysis Plan

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
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List of Abbreviations and Definition of Terms

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	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	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 (i.e. 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
HBcAg	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
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

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20150186 of product AMG 986 dated 28 September 2017. The scope of this plan includes the primary analysis that is planned and will be executed by the Amgen Global Bio-statistical Science department unless otherwise specified. The primary analysis will be considered as final analysis.

The clinical study report (CSR) will be written based on the results based on the primary analysis. Data collected and analyzed in Amgen-owned databases and systems will adhere to approved Data Element Standards and International Case Report Form (CRF) Standards established by Biomedical Data Stewardship Governance (BDSG).

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
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	• 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	
• To evaluate the safety and tolerability of AMG 986 following single oral dose administration to subjects with severely impaired renal function relative to healthy matched control subjects	• Subject incidence of adverse events and clinically significant changes in vital signs, physical examinations, clinical laboratory tests, and ECGs
Exploratory	
• To determine unbound concentrations of AMG 986 in plasma	• Plasma protein binding of AMG 986
• To determine AMG 986 metabolite concentrations in plasma	• AMG 986 metabolite concentrations in plasma

2.2 Clinical Hypotheses

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. Study Overview

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 the modification of diet in renal disease (MDRD) equation for estimated glomerular filtration rate (eGFR). Approximately 12 subjects will be assigned to the two groups in the study. 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 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.

3.2 Sample Size

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 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 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%.

4. Covariates and Subgroups

4.1 Planned Covariates

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.

4.2 Subgroups

No subgroup analyses are planned for this study.

5. Definitions

Age at Enrollment

Subject age at enrollment will be collected in years in the clinical database.

AUC

Area under the plasma AMG 986 concentration-time curve.

AUC_{0-24}

Area under the concentration-time curve from time 0 extrapolated to 24 hours.

AUC_{inf}

Area under the concentration-time curve from time 0 extrapolated to infinity.

Baseline

Baseline is defined as the last assessment taken prior to the first administration of AMG 986.

C_{max}

Maximum observed plasma AMG 986 concentration.

Baseline ECG recording

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).

Body Mass Index

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

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 (i.e. last subject last visit), following any additional parts in the study (e.g. long-term follow-up), as applicable.

End of Study for Individual subject

The end of study for individual subject is defined as the last day that protocol-specified procedures are conducted for an individual subject.

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.

End of Treatment

The end of treatment is defined as the last assessment for the protocol specified treatment phase of the study for an individual subject.

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. The Glomerular Filtration Rate (GFR) will be estimated as

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).

Investigational Product

Investigational product refers to AMG 986 in this study.

Primary Completion

The primary completion 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.

Study Day 1

The study day 1 is defined as the first day that protocol specified investigational product(s) /protocol-required therapies is/are administered to the subject.

Half-life ($t_{1/2}$)

The time required for the observed concentration of a drug to be reduced by one-half.

T_{max}

The time of maximum observed plasma AMG 986 concentration.

Treatment-Emergent Adverse Event

Events categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by the flag indicating if the adverse event started prior to the first dose on the Events CRF and up to and including 30 days after the end of investigational product or the End of Study date, whichever is earlier.

6. Analysis Sets

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

6.1 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.

6.2 Pharmacokinetic (PK) Analyses Set

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

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

No formal interim safety analysis is planned for this study (Refer to protocol section 10.3.1).

7.2 Primary Analysis

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

7.3 Final Analysis

The primary analysis will be the final analysis.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database. The database will be subject to edit checks outlined in the Clinical Data Management Plan (DMP). See details of this section in the DMP.

8.3 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. Details of the imputation algorithm are provided in Appendix A.

8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations in each group. The clinical study team will identify and document the criteria for important protocol deviations.

8.5 Outliers

All confirmed outlier data will be included in the analyses presented in this statistical analysis plan unless there is sufficient scientific justification to exclude them.

Pharmacokinetic (PK) concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard pharmacokinetic evaluation practice.

8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. If required data transformations or alternative non-parametric methods of analyses will be utilized.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.3 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

Descriptive statistics will be provided for selected demographics, adverse events, vital signs, ECG, PK, and 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. Graphical summaries of the data may also be presented. When data are summarized by time, the values recorded against the scheduled time points listed in the protocol will be used. When assessing minimum/maximum increases or decreases over the study, all assessments, including unscheduled assessments will be used. All data analysis will be conducted using subjects in the safety analysis set except for pharmacokinetic analysis, which will be conducted using PK analysis set. For statistical analyses comparing change from baseline, only subjects with both baseline and at least one post-baseline assessment will be included. The primary analysis will occur after the database lock following last subject last visit.

9.2 Subject Accountability

The number and percent of subjects who were enrolled, received investigational product, completed study, discontinued the study (including reasons for discontinuing) will be

summarized by group. Key study dates for the first subject enrolled and last subject's end of study will be presented. A subject listing and summary noting inclusion in each analysis subset will be reviewed for all subjects enrolled. A subject listing noting reason for discontinuing the study and a list of subjects screened but not enrolled (screen failures) will be reviewed.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol. Eligibility deviations that are defined as IPDs will be summarized in both the IPD and Eligibility Deviation table and IPD and Eligibility Deviation listings.

9.4 Demographic and Baseline Characteristics

Summary statistics of the demographic and baseline characteristics will be tabulated using the Safety Analysis Set for both the study groups. The demographic characteristics include age, sex (male versus female), race and ethnicity. The baseline characteristics will be vital signs (blood pressure, heart rate, respiratory rate, and oral temperature), physical examinations (height, weight, BMI), ECG parameters, and selected laboratory parameters.

9.5 Efficacy Analyses

No efficacy analysis is applicable for this study.

9.6 Safety Analyses

9.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 will be used to code all events categorized as adverse events (AE) to a system organ class and a preferred term. The CTCAE version 4.0 will be used to grade severity of adverse events unless specified otherwise. Treatment-emergent adverse events are events with an onset after the administration of the first dose of investigational product.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, and fatal adverse events.

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in alphabetical order.

Subject incidence of events of interest (standardized MedDRA queries and/or Amgen customized queries) will also be summarized according to their categories and preferred term. Summaries of treatment-emergent and serious adverse events will be tabulated by system organ class, preferred term, and grade.

9.6.2 Laboratory Test Results

Analyses of laboratory values will include summary statistics over time (for each protocol scheduled visit) for selected laboratory analytes in Table 3 of the protocol by group. Additional summaries may include descriptive statistics of changes from baseline over time, change from baseline to the post dose maximum, time to post-dose maximum, change from baseline to the post-dose minimum and the time to the post-dose minimum. Shift tables based on CTCAE grading may be provided for select analytes.

9.6.3 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.

9.6.4 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 (e.g., 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).

9.6.5 Exposure to Concomitant Medication

All medication will be coded using the WHO drug dictionary. All prior and concomitant medications will be presented and reviewed.

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic Endpoints

The PK parameters for each subject will be estimated using non-compartmental methods and will be performed by the Clinical Pharmacology, Modeling & Simulation group (CPMS). Actual dosing and sampling times will be used for calculation of PK

parameters. 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.
Graphs of AMG 986 plasma concentration-time profiles for individual subjects and for means for each function group may be provided.
Geometric means and 90% CI for the ratio of the geometric means (group 1/ group 2) will be estimated using ANOVA model. The model will use the log-transformed PK parameters as the dependent variable (or response) and renal function group as independent variable. 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.

9.7.2 Analyses of Exploratory Endpoints

The statistical analyses in this section are considered exploratory in nature and will be performed only when deemed appropriate.
If data allows, plasma protein binding of AMG 986 will be determined and summarized.
If data allows, AMG 986 metabolite concentration in plasma will be measured and summarized.

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

Not applicable.

12. Prioritization of Analyses

Tables to precede listings.

13. Data Not Covered by This Plan

None.

14. Appendices

Appendix A. Imputation Rules for Partial or Missing Stop Dates

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. If the stop date is entirely missing, assume the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or conmed stopped and the stop date will be imputed, if partial.

Imputation Rules for Partial or Missing Start Dates.

	Stop Date							
		Complete: yyyymmdd		**Partial: yyyymm**		**Partial: yyyy**		
Start Date		**< 1st Dose**	**≥ 1st Dose**	**< 1st Dose yyyymm**	**≥ 1st Dose yyyymm**	**< 1st Dose yyyy**	**≥ 1st Dose yyyy**	**Missing**
Partial: yyyymm	**= 1st Dose yyyymm**	2	1	2	1	N/A	1	1
	≠ 1st Dose yyyymm		2		2	2	2	2
Partial: yyyy	**= 1st Dose yyyy**	3	1	3	1	N/A	1	1
	≠ 1st Dose yyyy		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose
2 = Impute the first of the month
3 = Impute January 1 of the year
4 = Impute January 1 of the stop year

Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month.

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.