STATISTICAL ANALYSIS PLAN

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

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Authors:	[redacted]

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Version Number	Date (DDMMMYYYY)	Summary of Changes, Including Rationale for Changes
Original (v1.0)	04 Aug 2016	
[Amendment 1 (v2.0)]	11 Apr 2018	The purpose of SAP amendment 1 was to provide details of the statistical analyses that have been outlined within the Protocol Amendment 7 dated 14 March 2018.
[Amendment 2 (v3.0)]	17 Jun 2019	The purpose of SAP amendment 2 is to align with the Protocol Amendment 8 dated 27 July 2018 and also to limit the scope of analysis due to early discontinuation of the study as referenced in early discontinuation memo dated 15 April 2019. The scope of the analysis is restricted to key endpoints/ parameters, for selected parts/ cohorts of the study in agreement with study team to be used for the purpose of abbreviated Clinical Study Report.

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Table of Abbreviations

Abbreviation or Term	Definition/Explanation
ADPC	Analysis Dataset for PK Concentrations
AE	Adverse Events
AUC	Area Under The Concentration-Time Curve
BMI	Body Mass Index
C_{max}	Maximum Observed Concentration
CPMS	Clinical Pharmacology Modelling And Simulation
CTCAE	Common Terminology Criteria for Adverse Events
DLRM	Dose Level Review Meeting
DLRT	Dose Level Review Team
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOI	Events of Interest
EOS	End of Study
GCP	Good Clinical Practice
GSO-DM	Global Study Operations-Data Management
H	Hour
HDL	High-Density Lipoprotein
ICH	International Conference on Harmonization
IP	Investigational Product
IPD	Important Protocol Deviation
IV	Intravenous
LD	IV Loading Dose
LDL	Low-Density Lipoprotein
MD	IV Maintenance Dose
MDAD	Multiple Daily Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PO	Oral Dose
QD	Once Daily Dosing
QTcB	Bazett-Corrected QT Interval
QTcF	Fridericia-Corrected QT Interval

Abbreviation or Term	Definition/Explanation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDAD	Single Day Ascending Dose
SE	Standard Error
TEAE	Treatment-Emergent Adverse Event
t_{max}	Time of Maximum Observed Concentration

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 Amendment **8** for Study 20150183 AMG 986 dated **27 July** 2018. The scope of this plan includes the primary analysis that is planned and will be executed by the Biostatistics department unless otherwise specified. **The scope of the analysis is restricted post the discontinuation of the study earlier than planned and includes key analyses to be performed as identified by the study team.**

2. Objectives

Primary Objective:

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

Secondary Objectives:

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

Exploratory Objectives:

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

3. Study Overview

3.1 Study Design

This study is a randomized, placebo controlled, double-blind, single day ascending dose (SDAD) study (Part A), and multiple daily ascending dose (MDAD) study (Part B), in healthy subjects and of ascending multiple doses of AMG 986 in heart failure patients (Part C). In Parts A and B of the study, subjects will receive AMG 986 by constant IV infusion or by oral administration in a fasted state. The IV infusions starting with cohort 3 will be divided into an initial loading dose (LD) for the first hour followed immediately by a maintenance dose (MD) for up to 24 hours and up to multiple days (Part B). In Part C of the study, patients with heart failure and either reduced (HFrEF) or preserved (HFpEF) ejection fraction will receive ascending doses of IP by once daily oral administration for 21 days.

Part A

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

Starting doses of 0.5 mg by IV infusion lasting 1 hour and 5 mg given by oral administration are planned. The sequence of escalation for IV dosing and PO dosing will partially overlap to achieve step-wise increases in AMG 986 exposure, as shown in the treatment schema. Dose escalations in Part A will initially be sequential, with AMG 986 dosing to begin at the starting IV dose of 0.5 mg infused over 1 hour, followed by escalation to IV Cohort 2 dosing at 3 mg infused over 1 hour. After the safety and tolerability of AMG 986 in IV Cohort 2 are demonstrated and reviewed at a DLRM, escalation to IV Cohort 3 (6 mg LD + 36 mg MD) and initiation of oral dosing at the proposed 5 mg starting dose will be permitted. Subsequent IV and oral dose cohort escalations and DLRM reviews will occur as shown in the treatment schema below. After the safety and tolerability of AMG 986 in IV Cohort 4 (20 mg LD + 120 mg MD) and PO Cohort 4 (200 mg) are demonstrated and reviewed at a DLRM, escalation to IV Cohort 5 (60 mg LD + 360 mg MD) and PO Cohort 5 (400 mg) will be permitted. Enrollment for IV Cohorts will end after IV Cohort 5.

Part B

Part B is a randomized, parallel group, double-blind, multiple day ascending dose study consisting of 6 cohorts (2 IV infusion dose cohorts and 4 oral dose cohorts). Within each cohort, a total of 8 subjects will be randomized to receive AMG 986 or placebo in a 3:1 ratio. Prior to the transition from Part A to Part B, verification of PK model assumptions is planned as AMG 986 human PK data become available from individual IV and oral single dose cohort escalations in Part A.

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

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

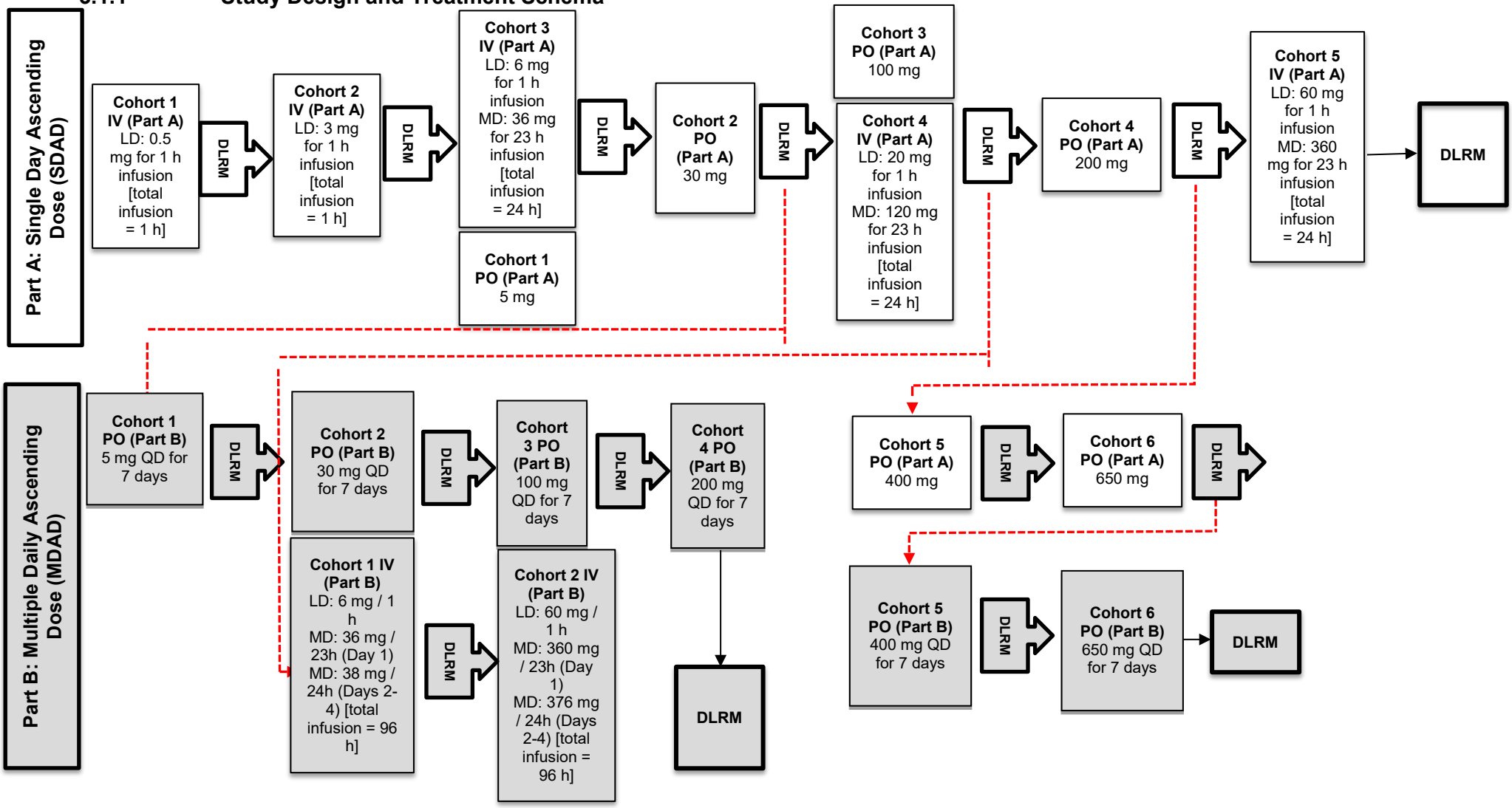
The safety and tolerability of each dose level (including the last dose cohort) in Part B will be assessed at the DLRM once safety data through at least 4 days post dose become available for all subjects in a treatment cohort. Escalation to a higher dose within a cohort, between cohorts, and enrollment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

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

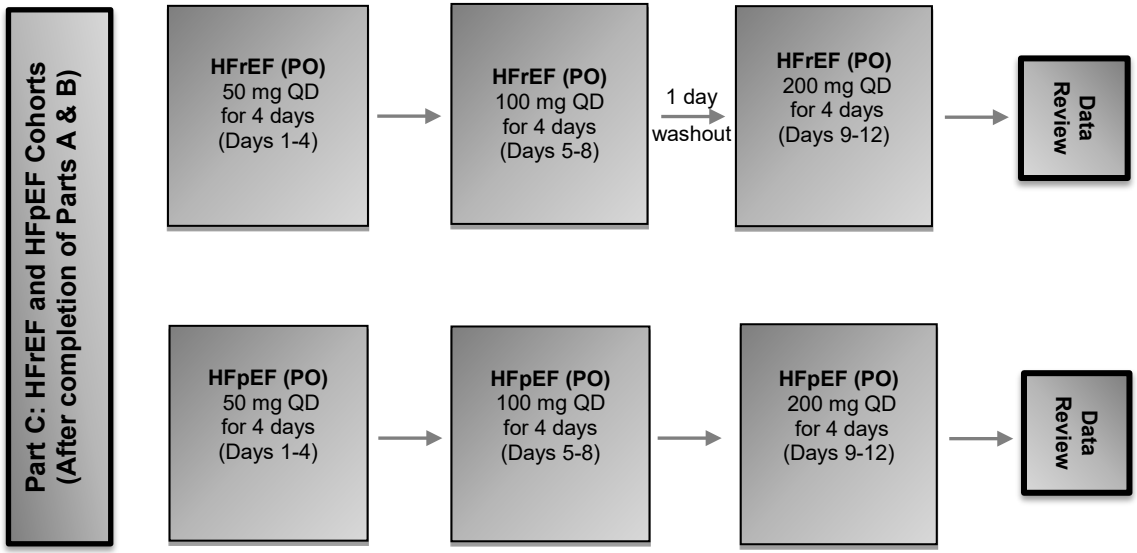
Part C

Part C is a randomized, parallel group, double-blind, multiple day ascending dose study consisting of 2 PO dose cohorts, one cohort for HFrEF patients and one cohort for HFpEF patients. Within each cohort, 20 subjects will be randomized to receive AMG 986 or placebo in a 3:1 ratio. Subjects will receive once daily oral administration of IP at 10 mg for the first 7 days, 30 mg for the next 7 days and 100 mg for the last 7 days. **As this portion of the study will enroll patients with heart failure, key eligibility criteria have been amended to reflect the severity of their underlying disease, including maximum age of enrollment (maximum age < 85 years) as specified in the study protocol.**

3.1.1 Study Design and Treatment Schema



Study Design and Treatment Schema
Part C



Abbreviations:

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

3.2 Sample Size

This is a Phase 1 study. No formal statistical hypothesis testing will be performed. The study is designed to characterize the safety, tolerability, and PK/PD following single and multiple administration of AMG 986 by descriptive summaries based on the observed data. The sample size for both Parts A and B of this study is based on practical considerations and is consistent with the number of subjects enrolled in similar studies. Approximately 152 healthy subjects (8 subjects per cohort in 11 cohorts for Part A and 8 cohorts in Part B) are expected to be enrolled. Part C will enroll an additional 40 patient subjects. For safety considerations, with up to 144 subjects receiving AMG 986 (114 healthy and 30 patients), there is a 99.94% chance of detecting an adverse event with a true incidence rate of 5% or greater and a 99.99 % chance of detecting a more common adverse event with a true incidence rate of 10%. A rare event with a true incidence rate of 1% will have a chance of 76.48% to being detected with the current total sample size receiving AMG986. For Part A, with 66 subjects receiving AMG 986, there is a 96.6% chance to detect an AE with a 5% incidence rate and for Part B, with 48 subjects receiving AMG 986, a 91.5% chance to detect and AE with the same 5% incidence. For Part C, with 30 subjects receiving AMG 986, there is a 78.5% chance of observing an AE with a 5% incidence rate and 95.7% chance of observing a more common AE with a 10% incidence rate.

In summary:

- Part A IV Dose Cohorts: 40 subjects (8 subjects per cohort)
- Part A Oral Dose Cohorts: 48 subjects (8 subjects per cohort)
- Part B IV Dose Cohorts: 16 subjects (8 subjects per cohort)
- Part B Oral Dose Cohorts: 48 subjects (8 subjects per cohort)
- Part C Oral Dose Cohorts: 40 subjects (20 subjects per cohort)

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Endpoints

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

4.1.2 Secondary Endpoints

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

4.1.3 Exploratory Endpoints

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

4.2 Planned Covariates

Baseline values may be used as a covariate in analyses as needed.

5. Hypotheses and/or Estimations

This is a Phase 1 study and no formal statistical hypothesis testing will be performed.

6. Definitions

Age at Enrollment

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

Baseline

Unless otherwise specified, baseline will be defined as the scheduled assessment closest to but before first dose administration.

Baseline and Post-Baseline Electrocardiogram (ECG) Values in Triplicate

For the three sets of triplicate pre-dose ECG, the mean of values in a triplicate should be calculated before taking the mean of the three sets of averages.

For all post-baseline ECG, the mean value for measurements taken at the same assessment will be calculated and used in the analysis.

When an ECG is missing within a triplicate, all available data will be averaged for that time point.

Bazett-corrected QT Interval (QTcB)

The Bazett correction will be calculated from the investigator reported QT (msec) and RR interval (msec): $QTcB=QT/(RR/1000)^{0.5}$

Fridericia-corrected QT Interval (QTcF)

The Fridericia correction will be calculated from the investigator reported QT (msec) and RR interval (msec): $QTcF=QT/(RR/1000)^{0.33}$

BMI

Subject's BMI will be derived in kg/m2 in the clinical database

Change From Baseline

Change from baseline is the arithmetic difference between post-baseline and baseline.

End of Investigational Product Administration Date

End of IP administration for each subject is defined as the date the decision was made to end IP as recorded on the End of IP eCRF page.

End-of-Study for Individual Subject

End of study for each subject is defined as the date the subject last completed a protocol-specified procedure. The date will be recorded on the End of Study eCRF page.

Enrollment Date

Enrollment Date is defined in the date collected on the eCRF.

Randomization Date

Randomization Date is defined as the date subject was allocated to a treatment group.

Investigational Product (IP)

The term 'investigational product' is used in reference to AMG 986 or placebo.

Last IP Dose Date

Last IP Dose Date for each subject is defined as the latest date IP is administered

Study Day

Post study day 1: study day = (date – date of Study Day 1) + 1

Pre study day 1: study day = (date – date of Study Day 1)

Study Day 1

Study day 1 is defined as the first day of administration of the investigational product after enrollment. The day prior to Study Day 1 is considered Study Day -1.

Treatment-Emergent Adverse Event (TEAE)

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.

Serious Adverse Events

Serious adverse events (SAEs) are events categorized as AEs that are 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.

7. Analysis Subsets

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

7.1 Primary Analysis Set

Since this is an Early Development Study, the Primary Set will be the same as the Safety Analysis Set.

7.2 Safety Analysis Set

The safety analysis set will consist of all study subjects who receive at least one dose of AMG 986 or placebo.

7.3 Pharmacokinetic (PK) Analysis Set

The PK analysis set will consist of all study subjects who received AMG 986 for whom at least one PK parameter or endpoint can be reliably estimated.

7.4 Pharmacodynamics (PD) Analysis Set

The PD analysis set will consist of all study subjects who received AMG 986 or placebo for whom at least one echocardiographic parameter can be reliably measured.

7.5 Subgroup Analyses

No subgroup analyses are planned. Data from placebo-treated healthy subjects in each of Parts A and B will be pooled across the cohorts within each part for analysis. Subjects getting IV and oral dosing will be pooled separately **for summary of treatment exposure.** Data for placebo-treated subjects in Part C will not be pooled together.

The presentation of each summary is detailed out in the respective sections under section 10

8. Interim Analysis and Early Stopping Guidelines

No formal interim analysis is planned. However, dose escalation will occur after a Dose Level Review Team (DLRT) makes recommendations relating to early closure/extension or alteration of the study based on ongoing monitoring of the study data (ICH GCP 5.5.2).

All available study data including demographics, IP administration, medical history, concomitant medications, adverse events, ECG's, vital signs, plasma PK and laboratory results will be reviewed. Pharmacokinetic data for other cohorts, if available, may be reviewed at the DLRM's. The DLRM's will be conducted in an unblinded manner and all members of the DLRT will be approved to see the treatment assignments following the appropriate Amgen standard procedure. All cohorts in Part A, Part B and Part C will enroll according to the sequence shown on the Study Design and Treatment Schema above and after review of safety data at the previous dose level and modality, as indicated in the schema.

Based on these emerging safety and tolerability data and upon assessment by the Principal Investigator (PI), Medical Monitor and Global Safety Officer (DLRM members), cohorts may be removed or additional cohorts may be added. Subject numbers within each cohort may also be increased or decreased based on the decision from the DLRM.

9. Data Screening and Acceptance

9.1 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.

9.2 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.

Details of PK and external lab data transfers to the data base are provided in the corresponding study data transfer plans. See details of this section in the Data Management Plan (DMP).

An Analysis Dataset for PK Concentrations (ADPC) will be provided to the appropriate CPMS representative from Global Biostatistical Sciences.

9.2.1 Echocardiography Data

Echocardiographic data will be collected, tested for quality, and provided by ICON Imaging, Inc. to GSO-DM according to transfer protocols also described in the Data Management Plan. **Due to concerns regarding quality of echocardiographic data from Parts A and B, an additional echo core lab, Brigham and Women's Hospital Research Imaging Core (BWIC), was added to the study on 12th October 2017. While no clinically meaningful inconsistencies were noted upon review of data from both core labs, the precision of measurements from BWIC was noted to be superior and therefore, measurements from BWIC are reported for Part C in lieu of measurements from ICON Imaging while ICON Imaging measurements are reported for Part A and B.**

9.3 Handling of Missing and Incomplete Data

The following imputation for missing or incomplete data will be performed if required:

- Incomplete adverse event and concomitant medication dates missing data will be imputed as described in Appendix A. If imputed dates are used, then they will be identified as such in the final study report.

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

9.4 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 cohort. The clinical study team will identify and document the criteria for important protocol deviations.

9.5 Outliers

All confirmed outlier data will be included in the analyses presented in this statistical analysis plan unless there is sufficient scientific justification (eg, important protocol deviation leading to invalid data) to exclude them.

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 CPMS practice. All excluded observations will be detailed by CPMS along with reasons for exclusion, in accordance with standard CPMS practices.

9.6 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.

9.7 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 9.2 or later.

10. Statistical Methods of Analysis

10.1 General Principles

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

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

AMG 986 and Placebo-treated subjects in Part A and Part B will be combined to form composite **AMG 986 and** placebo groups, **respectively** for each Part, **wherever appropriate**. . Placebo-treated subjects in Part C will be separated per cohort (HFrEF versus HFpEF). Graphical summaries of the data may also be presented.

When data are summarized by time, the values recorded against the scheduled time points (refer to protocol section 7.1) listed in the protocol will be used.

Unless stated otherwise in this statistical analysis plan, the data analysis will be conducted using subjects in the safety analysis set. For statistical analyses comparing change from baseline, only subjects with both baseline and at least one post-baseline assessment will be included.

10.2 Subject Accountability

The number and percent of subjects who were enrolled, randomized, received investigational product, completed investigational product, discontinued from investigational product (including reasons for discontinuing), completed study, discontinued the study (including reasons for discontinuing) will be summarized by **pooled AMG 986 and pooled placebo** treatment groups and **all subjects** for **part A and part B of the study and by each treatment group for** each **cohort HFrEF and HFpEF and all subjects for** part **C** of the study. Key study dates for the first subject enrolled and last subject's end of study will be presented **for all subjects in part A and part B and for all subjects in each cohort HFrEF and HFpEF for part C of the study.**

A subject listing and summary table noting inclusion in each analysis subset will be provided for all subjects enrolled **by pooled AMG 986 and pooled placebo treatment groups and all subjects for part A and part B of the study and by each treatment group for each cohort HFrEF and HFpEF and all subjects for part C of the study.** A subject listing noting duration of investigational product administration, reason for discontinuation of treatment, and reason for discontinuing the study will be provided.

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol. The final IPD list is used to produce the summary of IPDs table and the List of Subjects with IPDs. **The summary of IPDs will be provided by pooled AMG 986 and pooled placebo treatment groups and all subjects for part A and part B of the study and by each treatment group for each cohort HFrEF and HFpEF and all subjects for part C of the study.** In addition, a separate listing of all inclusion and exclusion deviations may be provided.

10.4 Demographic and Baseline Characteristics

Demographic (ie, age, sex, race, ethnicity) and baseline characteristics (ie, height, weight, BMI) will be summarized using descriptive statistics **by pooled AMG 986 and pooled placebo treatment groups and all subjects for part A and part B of the study and by each treatment group for each cohort HFrEF and HFpEF and all subjects for part C of the study.** If multiple races have been reported for a subject, the subject will be categorized as multiple-race.

Demographic and baseline characteristics will be presented and reviewed for each subject. Medical and surgical history will also be presented and reviewed for each subject.

10.5 Safety Analyses (Primary Endpoints)

10.5.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 19 or later will be used to code all adverse events (AEs) to a system organ class and a preferred term. Subject incidence of all treatment-emergent AEs, serious AEs, AEs leading to withdrawal of investigational product, fatal AEs will be tabulated by system organ class and preferred term in descending order of frequency. All adverse event tables will be summarized **by pooled AMG 986 and pooled placebo treatment groups for part A and part B of the study and by each treatment group for each cohort HFrEF and HFpEF for part C of the study**.

Details of each adverse event will be presented and reviewed for each subject. Listings and/or narratives of any on-study deaths, serious and treatment-emergent adverse events, including early withdrawals due to adverse events, will also be provided should they occur.

10.5.2 Laboratory Test Results

Laboratory analytes are provided in the protocol Table 13. Summary tables of **selected** chemistry and hematology data and changes from baseline over time will be provided for each protocol scheduled visit by **pooled AMG 986 and pooled placebo treatment groups for part A and part B of the study and by each treatment group for each cohort HFrEF and HFpEF for part C of the study**..

Number and percentage of subjects of each troponin status “undetected”, “detected” and “elevated” at each scheduled assessment may be summarized **in a similar way as laboratory summaries.**. Summaries will also be presented treating troponin as a

continuous variable **in a similar way as laboratory summaries.** Troponin values below or above quantifiable limits will be treated as equal to the limits.

10.5.3 Vital Signs

Summary tables for all the vital signs parameter data **including blood pressure, heart rate, respiratory rate, and body temperature** and corresponding changes from baseline at each protocol scheduled study visit **by pooled AMG 986 and pooled placebo treatment groups for part A and part B of the study and by each treatment group for each cohort HFrEF and HFpEF for part C of the study** will be provided.

10.5.4 Physical Measurements

Subject weight, height and BMI will be presented **as part of baseline characteristics** and reviewed for all subjects.

10.5.5 Electrocardiogram (ECG)

Summaries of all ECG parameters and changes from baseline over time will be provided by **pooled AMG 986 and pooled placebo treatment groups for part A and part B of the study and by each treatment group for each cohort HFrEF and HFpEF for part C of the study**. Baseline will be defined as mentioned in section 6. The analysis of Fridericia's (QTcF) QT correction and Bazett's (QTcB) QT correction will be performed for subjects in Part A and Part B using the derived results as specified in section 6.

10.5.6 Exposure to Investigational Product

A listing of unique manufacturing lot numbers, and a subject listing of manufacturing lot number will be provided. Additionally an exposure table will be provided with the summaries of number of doses, cumulative doses and average doses for each cohort and treatment group in Part B and Part C.

10.5.7 Exposure to Concomitant Medications

Concomitant medications will not be summarized with the restricted scope of analysis post the discontinuation of the study earlier than planned.

10.6 Pharmacokinetic/Pharmacodynamic Analyses

10.6.1 PK Parameters for AMG 986

The pharmacokinetic **endpoints calculation and** analyses will **not** be performed by the CPMS group **with the restricted scope of analysis post the discontinuation of the study earlier than planned.**

Plasma samples will be analyzed for AMG 986 concentrations using a validated assay **and a listing for** individual concentration-time **data will be provided by the CPMS**

group. Additionally, CPMS group will also provide plots to present exposure-response relationship for echocardiographic **measures of stroke volume and ejection fraction.**

10.6.2 Echocardiographic Measures

Echocardiographic parameters of left ventricular systolic function including left ventricular ejection fraction, stroke volume by **volumetric (MoD) and Doppler assessment (LVOT) will be summarized along with changes from baseline and relative (percent)** changes from baseline for these parameters by treatment group **for HFrEF cohort of Part C. Figures will be** produced to plot mean and SE of **left ventricular ejection fraction and to plot mean relative (percent) change from baseline in left ventricular ejection fraction and stroke volume by volumetric (MoD) and Doppler assessment (LVOT) by treatment group. The summary will be based on PD analysis set.**

For the purpose of study data tabulation model (SDTM), echocardiographic data collected from both vendors ICON and BWIC will be utilized for all parts of the study. For analysis data model (ADaM), ICON vendor data will be used for Part A and Part B of the study and BWIC vendor data will **be used for Part C of the study.**

10.7 Exploratory Endpoints Analyses

Exploratory endpoints will not be analyzed with the restricted scope of analysis post the discontinuation of the study earlier than planned**. However, bio-marker group will provide the mean plots by treatment group and a listing for NT-pro BNP data for HFrEF cohort for Part C of the study.**

11. Changes From Protocol-specified Analyses

We have redefined some of the analyses to be by “treatment group” instead of by “cohort” to emphasize the role of the placebos. As **decided by the study team post discontinuation of the study, most of the summaries (except exposure to investigational product) are not presented by cohort levels for each treatment group and are provided by pooled AMG 986 and pooled placebo groups.** In other places we use the wording “study cohort” to emphasize the different dose levels.

To restrict the scope of analysis post the discontinuation of the study earlier than planned, following changes were made in the reporting of results from protocol-specified analysis:

- Subject-level data listings will not be presented and reviewed for vital signs (protocol section 10.5.2.1.2) and ECG (protocol section 10.5.2.1.3),
- Summary of maximum change from baseline in QTcF and QTcB and maximum post-baseline values in QTcF and QTcB as stated in protocol section 10.2.5.2.1.3 will not be provided.
- Analysis of pharmacokinetic endpoints as stated in protocol section 10.5.3.1 will not be performed by the CPMS group.
- Analysis of echocardiographic measures as stated in protocol section 10.5.3.2 will not be performed. The analysis is restricted to HFrEF cohort for Part C of the study for selected parameters of left ventricular systolic function including left ventricular ejection fraction, stroke volume by volumetric (MoD) and Doppler assessment (LVOT). The summary will be based on PD analysis set.

Analysis of exploratory endpoints as stated in protocol section 10.5.4 will not be performed

12. Data Not Covered by This Plan

All data are covered by this plan and this section is no longer applicable post the discontinuation of the study earlier than planned.

13. Literature Citations / References

Nelson, CH, Wang L, Fang L, Weng W, Cheng F, Hepner, M, Lin J, Garnett C, and Ramanathan, S (2015) “A Quantitative Framework to Evaluate Proarrhythmic Risk in a First-in-Human Study to Support Waiver of a Thorough QT Study” Clinical Pharmacology and Therapeutics v. 98 (6) December, 2015.

Murphy PJ, Yasuda S, Nakai K, Yoshinaga T, Hall N, Zhou M, Aluri J, Rege B, Moline M, Ferry J, Darpo B, “Concentration response modeling of ECG data from early phase clinical studies as an alternative clinical and regulatory approach to assessing QT risk - experience from the development program of lemborexant” J. Clinical Pharmacology *ePub* ahead of print, 24-Jun-2016.

ICH E14 Questions & Answers (R3) December 10, 2015 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Q_As_R3__Step4.pdf.

14. Appendices

Appendix A. Handling of Missing or Incomplete Dates for Adverse Events and Concomitant Medications

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.