Statistical Analysis Plan

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

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LIST OF ABBREVIATIONS

Abbreviations pertain to the statistical analysis plan (SAP) only (not the tables, figures, and listings [TFLs])

AUC	area under the plasma concentration-time curve
AUC_{inf}	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to the last quantifiable concentration
CI	confidence interval
CL/F	apparent total plasma clearance
C_{max}	maximum plasma concentration
CK-MB	creatine kinase MB fraction
CSR	Clinical study report
CV	coefficient of variation
ΔHR	Change-from-baseline HR interval
ΔPR	Change-from-baseline PR interval
ΔQRS	Change-from-baseline QRS interval
ΔQTcF	Change-from-baseline QTcF interval
ΔΔHR	Placebo-corrected ΔHR
ΔΔPR	Placebo-corrected ΔPR
ΔΔQRS	Placebo-corrected ΔQRS
ΔΔQTcF	time-matched change from baseline in placebo-adjusted QT interval corrected for heart rate based on the Fridericia correction interval
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EOS	End of Study
ERT	eResearch Technology Inc.
FAS	full analysis set
GCP	Good Clinical Practice
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation
OM	omecamtiv mecarbil
$\%AUC_{extrap}$	percentage of area under the concentration-time curve from time 0 to infinity due to extrapolation
PI	Principal Investigator
PK	pharmacokinetic(s)
QTc	QT interval corrected for heart rate

QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RR	time interval between two successive R-waves of the QRS signal on the electrocardiogram
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time of the maximum observed plasma concentration
TQT	thorough QT
V_z/F	apparent volume of distribution

1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol for AMG 423 study 20090231 (Final Version dated 30 May 2019, Amendment 1 dated 19 July 2019, Amendment 2 dated 07 August 2019, and Amendment 3 dated 23 August 2019) and electronic case report form.

This SAP describes the planned analysis of the pharmacokinetic (PK) and safety and tolerability data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shells document. A separate SAP concerning QT/QTc and PK/QTc analysis will be provided by eResearch Technology Inc. (ERT).

In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Amgen Inc. A limited amount of information about this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are approved, they will serve as the template for this study's CSR.

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR. Any substantial deviations from this SAP will be agreed with Amgen Inc. and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline *Statistical Principles for Clinical Trials* and ICH E3 guideline *Structure and Content of Clinical Study Reports*.[1,2]

The document history is presented in Appendix 1.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of the study is:

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

2.2 Secondary Objectives

The secondary objectives of the study are:

- To assess the PK of OM after a single oral dose to healthy subjects.
- To evaluate the effect of OM on other ECG parameters (hear rate [HR], PR and QRS intervals, and treatment-emergent T-wave abnormalities and presence of U-waves).

- To evaluate the plasma concentration-effect relationship for OM on the QT/QTc interval in healthy subjects.
- To evaluate assay sensitivity by evaluation of the positive control, a single 400-mg oral dose of moxifloxacin, on the QT/QTc interval in healthy subjects.
- To evaluate the safety and tolerability of OM after a single oral dose to healthy subjects.

3. STUDY ENDPOINTS

3.1. Primary Endpoints

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

3.2. Secondary Endpoints

The secondary endpoints of the study are:

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

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

3.3. Research Hypothesis

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

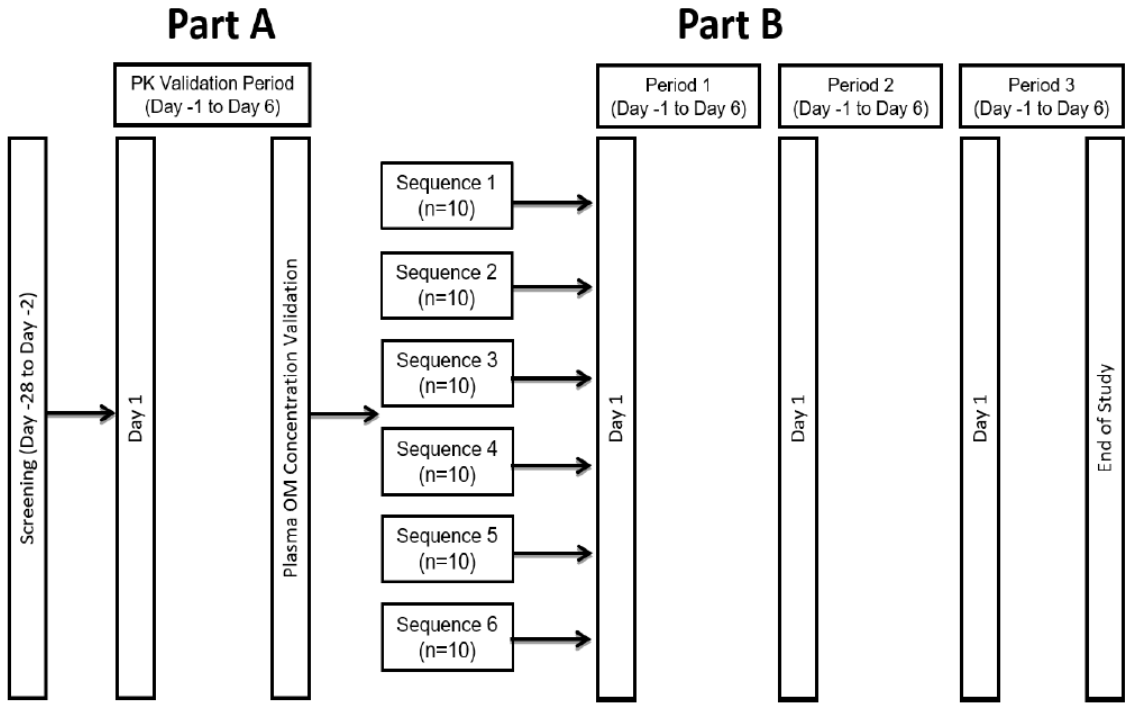
4. STUDY DESIGN

This is a single-center, single-dose (Part A; PK Evaluation Period), and randomized, 3-period, 3-treatment, crossover, single-dose (Part B) study in healthy adult subjects to determine whether OM prolongs the QTc after a single oral dose administration of 50 mg OM. The total duration of participation in the study will be approximately 55 days, including the screening period of up to 28 days.

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

A schematic of the study design is presented in Figure 1.

Figure 1: Study Design



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

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

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

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

Part A

- Treatment 1: 25-mg OM oral solution

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

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

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

Part B

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

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

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

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

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

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

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

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

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

5. SAMPLE SIZE JUSTIFICATION

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

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

Determination of sample size for assay sensitivity:

Assuming a 1-sided 5% significance level and a within-subject SD of 7 msec for ΔQTcF, a sample size of 48 evaluable subjects will provide a power of 99.9% to exclude a mean

difference of 5 msec in ΔQTcF between moxifloxacin and placebo groups from the lower bound of the 2-sided 90% CI on ΔΔQTcF at at least 1 of the 3 prespecified timepoints. With the within-subject SD of 8 msec and other similar assumptions, the power will decrease to 99%.

6. STUDY TREATMENTS

The study treatment names, abbreviations, and ordering to be used in the TFLs are presented in Table 1.

Table 1: Presentation of Study Treatment in TFLs

Study Treatment		
Part A		
Study Treatment Name	**Treatment Abbreviation**	
25-mg OM oral solution	25-mg OM	
Part B		
Study Treatment Name	**Treatment Abbreviation**	**Treatment Order in TFLs**
Treatment A: Placebo oral solution	Placebo	1
Treatment B: 50-mg OM oral solution	50-mg OM	2
Treatment C: 400-mg moxifloxacin oral tablet	Moxifloxacin	3

The study treatment sequence names, abbreviations, and ordering of Part B to be used in the TFLs are presented in Table 2.

Table 2: Presentation of Part B Study Treatment Sequences in TFLs

Study Treatment Sequence	**Abbreviation**	**Order in TFLs**
Sequence 1	Placebo/50-mg OM/Moxifloxacin	1
Sequence 2	50-mg OM/Moxifloxacin/Placebo	2
Sequence 3	Moxifloxacin/Placebo/50-mg OM	3
Sequence 4	Placebo/Moxifloxacin/50-mg OM	4
Sequence 5	Moxifloxacin/50-mg OM/Placebo	5
Sequence 6	50-mg OM/Placebo/Moxifloxacin	6

All treatments described above are the planned treatments. The TFLs will reflect the actual treatments received, and dose levels will be displayed in increasing order.

7. DEFINITIONS OF POPULATIONS

Any protocol deviations will be considered prior to database lock for their importance and taken into consideration when assigning subjects to populations.

The **full analysis set** will include all subjects who received at least 1 dose of study treatment (Omecamtiv Mecarbil, placebo or moxifloxacin).

The **completer analysis set** will include subjects in the full analysis set who completed all study treatment administrations and have non-missing values for the primary endpoint.

7.1. All Subjects Population

The all subjects population will include all subjects who signed the ICF and had any study assessment recorded in the database per the protocol.

7.2. Safety Population

The safety population will include all subjects who received at least 1 dose of study treatment (Omecamtiv Mecarbil, placebo or moxifloxacin) and have at least 1 postdose safety assessment.

7.3. Pharmacokinetic Population

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

7.4. QT/QTc Analysis Set

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

7.5. PK/QTc Analysis Set

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

8. STATISTICAL METHODOLOGY

8.1. General

Listings will be provided for all data captured in the database, with the exception of medical history. Listings will include all subjects assigned to the all subjects population and include data up to the point of study completion or discontinuation. Any subject who discontinued the

study will be identified accordingly in the listings. Summaries and statistical analyses will include the subjects assigned to the relevant population based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1 and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Community Validator Version 2.2.0 will be utilized to ensure compliance with CDISC standards.

Caution should be used when interpreting results from the statistical analyses conducted in this study because the sample size is not based on power calculations.

Where reference is made to 'all calculations', this includes, but is not limited to, summary statistics, statistical analyses and any parameter derivations.

8.1.1. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.
- If number of subjects with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.
- As Early Termination data is not associated with any scheduled timepoint, it will be excluded from all calculations of summary statistics.

For categorical data the following rules will be applied:

- If the categories of a parameter are ordered (eg, adverse event severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category. If the categories are not ordered (eg, race), only those categories for which there is at least 1 subject represented will be included.
- Missing values will not be imputed, with the exception of adverse events where the 'worst-case' approach will be taken (see Section 8.6.1), or unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

8.1.2. Repeat and Unscheduled Readings

For vital signs and ECG data only, any predose value recorded in addition to the original value or a postdose value recorded within 15 minutes of the original value will be defined as a repeat value; any postdose value recorded more than 15 minutes after the original value will be defined as an unscheduled value. For all other data types (eg, laboratory parameters), any value recorded in addition to the original value will be defined as an unscheduled value.

The original value will be replaced by the last associated repeat value in all calculations.

As unscheduled values are not associated with any scheduled timepoint, they will be excluded from all calculations.

8.2. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed.

A summary table will be provided, based on the all subject population.

8.3. Screening Demographics

The screening demographics including age, sex, race, ethnicity, height, body weight, and body mass index will be listed.

A summary table will be provided, based on the safety population.

8.4. Prior and Concomitant Medication

Prior medication will be defined as medication that starts within 30 days prior to enrollment and ends prior to the first dose. Concomitant medication will be defined as medication that starts after the first dose or starts but does not end prior to the first dose.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, Format B3, Version March 2019 (or later if upversioned during the study). Prior and concomitant medications will be listed.

8.5. Pharmacokinetic Assessments

8.5.1. Pharmacokinetic Analysis

The following pharmacokinetic parameters will be determined where possible from the plasma concentrations of OM using non-compartmental methods performed using Phoenix WinNonlin (Certara USA, Inc.) version 8.1 or higher:

Parameter	Definition
AUC_{last}[a]	Area under the concentration-time curve from time 0 to the time of last quantifiable concentration (t_{last})
AUC_{inf}[a]	Area under the concentration-time curve from time 0 to infinity
C_{max}	Maximum observed concentration
t_{max}	Time to maximum observed concentration
$t_{1/2}$	Apparent terminal elimination half-life
CL/F	Apparent total plasma clearance
V_z/F	Apparent volume of distribution

[a] AUCs will be calculated using the linear trapezoidal linear interpolation rule.

The following parameters will be listed only:

Parameter	Definition
$\%AUC_{extrap}$	Percentage of AUC_{inf} that is due to extrapolation
λ_z	Apparent elimination rate constant
R^2	Correlation coefficient of terminal elimination phase
Number of points	Number of data points included in determination of λ_z
Start of exponential fit	Lower limit of the terminal phase
End of exponential fit	Upper limit of the terminal phase

Additional pharmacokinetic parameters may be determined where appropriate. Moxifloxacin plasma samples may be assayed and PK parameters (same as for OM) will be calculated only if deemed necessary.

Pharmacokinetic analysis will, where possible, be carried out using actual postdose times recorded in the raw data. If actual times are missing, nominal times may be used with sponsor approval.

Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

C_{max} and t_{max} will be obtained directly from the plasma concentration-time profiles.

For multiple peaks, the highest postdose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest t_{max} will be reported.

8.5.1.1. Criteria for handling concentrations below the limit of quantification in Pharmacokinetic analysis

Concentration values that are below the level of quantification (BLQ) will be set to zero, with defined exceptions as follows:

- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
- If a predose concentration is missing, it will be set to 0 by default.

8.5.1.2. Criteria for the Calculation of an Apparent Terminal Elimination Rate Constant and Half-Life

8.5.1.2.1. Number of Data Points

At least three data points will be included in the regression analysis and should not include C_{max}.

8.5.1.2.2. Goodness of Fit

When assessing terminal elimination phases, the R^2 value will be used as a measure of the goodness of fit of the data points to the determined line.

Regression-based parameters (AUC_{inf}, $\%AUC_{extrap}$, $t_{1/2}$, CL/F, and V_z/F) will only be calculated if the R^2 value of the regression line is greater than or equal to 0.8.

8.5.1.2.3. Period of Estimation

The time span used for the estimation of apparent terminal elimination rate constant, where possible, will be over at least two half-lives.

Where an elimination half-life is estimated over a time span of less than two half-lives, it will be flagged in the data listings at the discretion of the Pharmacokineticist, and the robustness of the value should be discussed in the study report.

8.5.1.3. Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

- AUC_{inf} values where the percentage extrapolation is less than or equal to 20% will be reported. AUC_{inf} values where the percentage extrapolation is greater than 20% will be listed but flagged and excluded from descriptive statistics. Parameters derived using AUC_{inf} (CL/F and V_z/F) will also be flagged and excluded from descriptive statistics when the percentage extrapolation is greater than 20%.

8.5.1.4. Anomalous Values

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and study report.

Positive predose value(s) greater than 5% of C_{max} may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the Pharmacokineticist.

8.5.2. Presentation of Pharmacokinetic Data

8.5.2.1. Presentation of Pharmacokinetic Plasma Drug Concentration Data

The following rules will be applied if there are values that are BLQ or if there are missing values (e.g., no result [NR]) in a plasma concentration data series to be summarized.

- For the calculation of summary statistics, BLQ values will be set to zero.
- If an embedded BLQ value is considered anomalous within the concentration time profile, this value will be excluded from the summary statistics.
- Where there is NR, these will be set to missing.
- If there are less than three values in the data series, only the min, max and N will be presented. The other summary statistics will be denoted as not calculated (NC). BLQ is considered a value.
- If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, min and max will be presented as zero, and the geometric mean and geometric CV will be denoted as NC.
- If the value of the arithmetic mean or median is below the lower limit of quantification, these values will be presented as zero and the geometric mean and geometric CV will be denoted as NC.

8.5.2.2. Presentation of Pharmacokinetic Parameters

For the calculation of summary statistics of PK parameters, all non-reportable and NC values in a data series will be set to missing.

The AUC values will be set to NC if they were calculated using fewer than three concentrations, and/or three concentrations if the last is C_{max}.

8.5.3. Pharmacokinetic Statistical Methodology

All PK concentrations and parameters will be listed.

Summary tables, mean (+ standard deviation [SD]) figures, overlaying individual figures, and individual figures by treatment and time postdose will be provided for plasma PK concentrations. All figures will be produced on both linear and semi-logarithmic scales. The +SD bars will be only displayed on the linear scale.

Summary tables by treatment will be provided for all PK parameters, with the exception of regression-related PK parameters. Separate summary tables by treatment and time interval will be provided for excretion parameters and cumulative excretion parameters.

The analyses for this study will be performed in 2 parts.

8.5.3.1. Part A Methodology

Part A will evaluate 25-mg OM oral solution and is designed to determine the subject eligibility for Part B. Dose escalation will proceed when a safety review with an acceptable safety profile has been completed by the Safety Review Committee.

No formal statistical analysis on the safety data.

8.5.3.2. Part B Methodology

Part B of the study is designed to assess the ECG effects to determine plasma OM and moxifloxacin concentrations.

All QT/QTc-related statistical analysis will be conducted by ERT and reported in a separate SAP and TFL shells report.

Real-time safety ECG assessments will be performed by the study physician. No formal statistical analysis on the safety data.

8.6. Safety and Tolerability Assessments

8.6.1. Adverse Events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 (or higher if upversioned during the study).

A TEAE will be defined as an adverse event that starts during or after the first dose, or starts prior to the first dose and increases in severity after the first dose.

A treatment-related TEAE will be defined as a TEAE with a relationship of possibly related or related to the study treatment, as determined by the investigator.

All adverse events will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of the last dose for TEAEs only.

The frequency of subjects with TEAEs and the number of TEAEs will be summarized for the following categories:

- TEAEs (overall, serious, leading to discontinuation and leading to death) by treatment
- TEAEs by severity and treatment
- Treatment-related TEAEs (overall, serious, leading to discontinuation and leading to death) by treatment
- Treatment-related TEAEs by severity and treatment

The frequency of subjects will be summarized separately for TEAEs and treatment-related TEAEs by the following:

- System organ class, preferred term, and treatment
- Preferred term and treatment

For the adverse event data the following rules will apply:

- For the derivation of TEAE status: If the start date/time of an adverse event is incomplete or missing, an adverse event will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an adverse event started prior to the first dose.
- For the derivation of treatment-related TEAE status: If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to be a treatment-related TEAE.
- For the derivation of onset time: If the start date/time of an adverse event is missing, onset time will not be calculated. If the start date/time of an adverse event is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of the last dose is 01MAY2019/08:00 and recorded start date/time of an adverse event is 03MAY2019, then the minimum possible onset time will be calculated by assuming the an adverse event started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing).
- For the derivation of duration: If the end date/time of an adverse event is missing, duration will not be calculated. If the start or end date/time of an adverse event is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (eg, if the start of an adverse event date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming the adverse event ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing).
- For the calculation of summary statistics: If the severity of a TEAE is missing, a TEAE will be counted under the maximum severity possible.
- For the calculation of summary statistics: If a subject experienced multiple TEAEs with the same preferred term for the same treatment, this will be counted as 1 TEAE for that treatment under the maximum severity recorded.

8.6.2. Clinical Laboratory Parameters

All clinical laboratory parameters will be listed; any value outside the clinical reference range will be flagged. Separate listings will be provided for any parameter for which there is any individual subject value outside the respective clinical reference range.

Summary tables by timepoint will be provided for clinical chemistry and hematology parameters.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the derivation of listing flags and calculation of summary statistics, <x and ≤x values will be set to 0, whereas >x and ≥x values will be set to x.

8.6.3. Vital Signs Parameters

All vital signs parameters will be listed; any value outside the clinical reference range will be flagged.

Summary tables will be provided for all vital signs parameters.

8.6.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters will be listed; any value outside the clinical reference range will be flagged.

Summary tables by timepoint will be provided for all 12-lead ECG parameters.

8.6.5. Other Assessments

All other safety and tolerability assessments not detailed in the above sections will be listed only.

Medical history will not be listed.

8.6.6. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

9. INTERIM ANALYSES

No interim analyses are planned for this study.

10. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

There were no significant changes from the protocol-specified analyses.

11. REFERENCES

1. ICH. ICH Harmonised Tripartite Guideline: Statistical principles for clinical trials (E9). 5 February 1998.

2. ICH. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports (E3). 30 November 1995.

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

12. APPENDICES

Appendix 1: Document History

Document Version, Status, Date	Summary/Reason for Changes
Version 1, Final, 10 December 2019	Not applicable; the first version

Statistical Analysis Plan Approval Form

Sponsor Name:	Amgen Inc.
Sponsor Protocol ID:	20090231
Covance Study ID:	8405952
SAP Text Filename:	Amgen_20090231_8405952_QT_QTc_SAP_Final_10Dec2019.docx
TFL Shells Filename:	Amgen_20090231_8405952_QT_QTc_TFL_Shell_Final_10Dec2019.docx
Version:	1.0
Date:	10 December 2019

Covance Approval(s):

[redacted] Date

Signa

[redacted], Biostatistician
Printed Name/Title

[redacted] Date

Signature

[redacted], Principal Pharmacokineticist
Printed Name/Title

Sponsor Approval(s):

By signing below when the statistical analysis plan (SAP) is considered final, the signatories agree to the analyses to be performed for this study; and to the format of the associated tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based on this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

[redacted]

Signature

[redacted], Executive Director Design & Innovation, Interim GBS Non-Onc TA Head
Printed Name/Title

Please scan/email completed form(s) to the Lead Statistician listed below:

Printed Name/Title:	[redacted], Biostatistician
Email:	[redacted]

Approval Signatures

Document Name: 161-09-csr-20090231-statistical-met

Document Number: CLIN-000097281

Document Version: 1

Document Approvals	
Reason for Signing: Functional Area	Name: [redacted] Date of Signature: 10-Sep-2020 19:18:03 GMT+0000