Statistical Analysis Plan

Protocol Title:	A Phase 1 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 397 in Subjects With Selected Relapsed or Refractory Hematological Malignancies
Short Protocol Title:	A Phase 1 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 397
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Version Number	Date	Summary of Changes, including rationale for changes
Original (v1.0)	21DEC2018	

Amendment 1 (v2.0)	10MAR2021	• Updates made as per protocol amendment 4
		  ○ Study design: Closed enrollment for Parts 1A and 1B and added Parts 2A, 2B, 2C, 3A, 3B, and 3C.
		  ○ Sample size section
		• Removed the definitions not related to analysis; updated the definitions (DOR, PFS, OS, TTR, etc.) per Data Element Standards.
		• Updated the Treatment Emergent Adverse Event definition as per the DES version 8.0 and DLT Evaluable Analysis Set definition.
		• Added the imputation rules for non-pharmacokinetic measurements above or below the upper quantification limits.
		• Added the analyses for subjects proceed to a higher dose or crossover from monotherapy to a combination therapy cohort.
		• Updated statistical methods of analysis (section 9)
		• Updated appendix A for imputation of start and stop dates
		• Updated appendix B for code fragment

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ALP	Alkaline phosphatase
AML	Acute myeloid leukemia
AST	aspartate aminotransferase (SGOT)
AUC	Area under the concentration-time curve
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed concentration
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
DLRT	Dose level review team
DLT	Dose limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
ELN	European LeukemiaNet
FIH	First in human
GSO-DM	Global study operations-data management
IMWG	International myeloma working group
IPD	Important protocol deviation
IWG	International working group
MDS	Myelodysplastic syndrome
MedDRA	Medical dictionary for regulatory activities
mg	Milligrams
MM	Multiple myeloma
MRD	Minimal residual disease
MTD	Maximum tolerated dose
NHL	Non-Hodgkin’s lymphoma
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic

Abbreviation or Term	Definition/Explanation
PFS	Progression free survival
PR	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG or partial response
PK	Pharmacokinetic
QRS	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	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	QT interval corrected for heart rate using accepted methodology
QTcF	QT interval corrected for heart rate using Fridericia's formula
RP2D	Recommended phase 2 dose
RR	Relapsed or Refractory
$t_{1/2}$	Half-life
t_{max}	Time of maximum observed serum concentration
TPI	Toxicity probability interval
TTR	Time to response
WHO	World health organization

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 4 for Study 20170173 - AMG 397 dated 09 December 2020. The scope of this plan includes the interim analysis, the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Bio-statistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

- **Indications:** Relapsed or Refractory (RR) Multiple Myeloma (MM), Non-Hodgkin's Lymphoma (NHL), Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML).

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
Part 1 QD2 Monotherapy (MM, NHL, AML) – CLOSED TO ENROLLMENT	
• Evaluate the safety and tolerability of AMG 397 QD2 monotherapy • Estimate the maximum tolerated doses (MTDs) and/or biologically active doses (eg, recommended phase 2 doses [RP2Ds]) of AMG 397	• Incidence of dose-limiting toxicities (DLTs), treatment-emergent adverse events, treatment-related adverse events and clinically-significant changes in vital signs, physical examinations, electrocardiogram (ECGs) and clinical laboratory tests
Part 2A QW Monotherapy (MDS, AML)	
• Evaluate the safety and tolerability of AMG 397 QW monotherapy in subjects with MDS or AML	• Incidence of DLTs, treatment-emergent adverse events, treatment-related adverse events and clinically-significant changes in vital signs, physical examinations, ECGs, and clinical laboratory tests
Part 2B QW Monotherapy in Japan (AML)	
• Evaluate the safety and tolerability of AMG 397 QW monotherapy in subjects in Japan with relapsed or refractory AML • Evaluate the PK of AMG 397 when administered as monotherapy (QW) in Japan	• Incidence of DLTs, treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, physical examinations, ECGs, and clinical laboratory tests • PK parameters for AMG 397 including, but not limited to C_{max}, AUC, CL, and $t_{1/2}$

Part 2C QW Monotherapy (MM)	
• Evaluate the safety and tolerability of AMG 397 QW monotherapy in subjects with MM	• Incidence of DLTs, treatment-emergent adverse events, treatment-related adverse events and clinically-significant changes in vital signs, physical examinations, ECGs, and clinical laboratory tests
Part 3 QW Combination Therapy (MDS, AML, MM)	
• Evaluate the safety and tolerability of AMG 397 combination therapy – MDS/AML: AMG 397 + azacitidine – MM: AMG 397 + dexamethasone	• Incidence of DLTs, treatment-emergent adverse events, treatment-related adverse events and clinically-significant changes in vital signs, physical examinations, ECGs, and clinical laboratory tests
• Estimate the maximum tolerated or recommended combination dose (MTCD) and/or recommended phase 2 combination doses (RP2CD) of AMG 397	
Secondary	
Part 1 QD2 Monotherapy (MM, NHL, AML) – CLOSED TO ENROLLMENT	
• Evaluate the preliminary efficacy of AMG 397 monotherapy	• Overall response rate (ORR) using response criteria per the following: – International Myeloma Working Group – Uniform Response Criteria (IMWG-URC) for MM subjects – Lugano Classification for NHL subjects – Revised International Working Group (IWG) for AML subjects – Revised IWG for MDS subjects • progression-free survival (PFS) • overall survival (OS) • time to response • duration of response (DOR)

• Evaluate the pharmacokinetics (PK) of AMG 397	• AMG 397 PK parameters including, but not limited to, maximum observed concentration (C_{max}), time of maximum observed concentration (T_{max}), area under the concentration time curve (AUC), clearance (CL) and half-life ($t_{1/2}$)
Part 2A QW Monotherapy (MDS, AML), Part 2B QW Monotherapy (AML), and Part 2C QW Monotherapy (MM)	
• Evaluate the preliminary efficacy of AMG 397 monotherapy (For Part 2B: Japan subjects only)	• ORR using response criteria per the following: – Revised IWG for AML subjects – Revised IWG for MDS subjects – IMWG-URC for MM subjects • PFS • OS • time to response • DOR
• Evaluate the PK of AMG 397	• AMG 397 PK parameters including, but not limited to, C_{max}, T_{max}, AUC, CL, and $t_{1/2}$
Part 3 QW Combination Therapy (MDS, AML, MM)	
• Evaluate the preliminary efficacy of AMG 397 combination therapy	• OR based on investigator assessment per: – Revised IWG for MDS subjects – 2017 European LeukemiaNet (ELN) criteria in AML subjects – IMWG-URC for MM subjects • PFS • OS • time to response • DOR
• Evaluate the PK of AMG 397 and azacitidine (Parts 3A and 3B) or dexamethasone (Part 3C) when administered in combination	• PK parameters for the combination including, but not limited to C_{max}, AUC, CL, and $t_{1/2}$

Exploratory	
Parts 1, 2 and 3	
• Explore pharmacokinetic/ pharmacodynamic (PK/PD) relationships for safety and/or efficacy endpoints	• AMG 397 exposure/efficacy and exposure/safety relationships
• Demonstrate AMG 397 inactivation of myeloid cell leukemia sequence 1 (MCL1) by the activation of BAX and caspase 3 in circulating monocytes or blast cells, and/or the decrease of circulating monocytes or blast cells	• Expression of BAX and Caspase 3 in monocytes or blast cells, circulating monocyte counts, circulating blast counts
• Evaluate the correlation of clinical responses to disease-specific features in tumor cells	• Clinical response measures, biomarkers including but not limited to protein levels of pro-survival family members, FISH/cytogenetic analysis, gene expression profiling, flow cytometric phenotyping, and DNA sequencing
• Evaluate changes to immune cell subsets in peripheral blood due to MCL1 inactivation	• Immune cell subset frequencies, absolute counts and MFIs in peripheral blood
• Parts 3B and C only: Evaluate additional measures of efficacy via minimal residual disease negative (MRD[-]) status with patient response	• MRD[-] status at the time of complete response (CR)

2.2 Hypotheses and/or Estimations

No formal hypothesis testing will be performed. The point estimates and corresponding 2-sided 95% exact CI will be presented on ORR.

3. Study Overview

3.1 Study Design

This is a first-in-human (FIH), multicenter, non-randomized, open-label, phase 1 study evaluating AMG 397 administered orally in adult subjects with selected RR hematological malignancies.

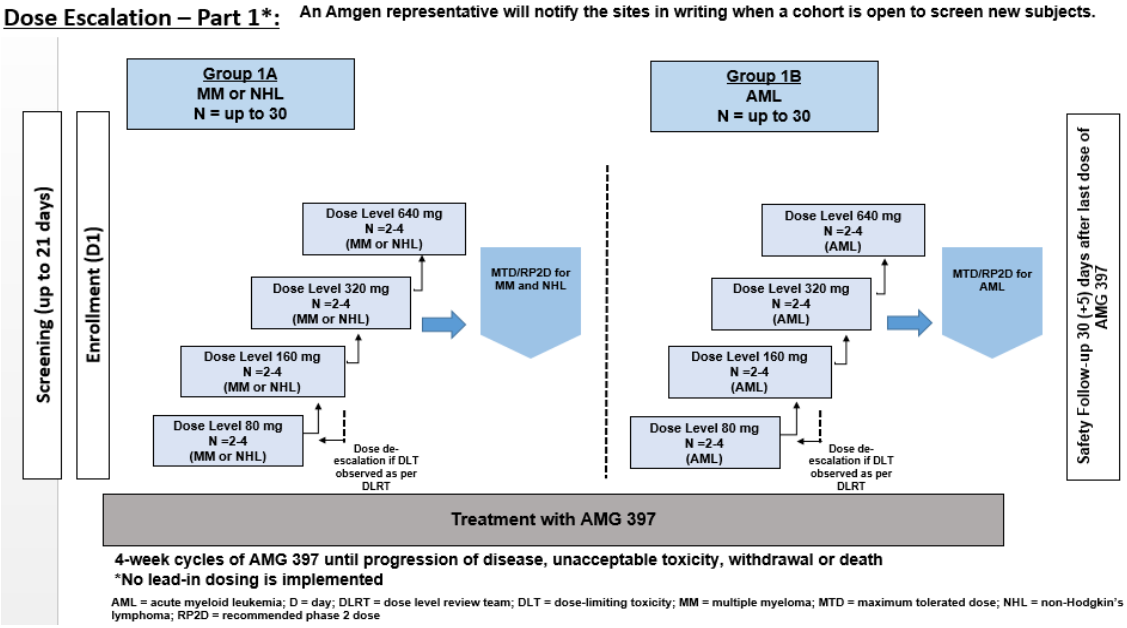
Part 1 of the study was designed to investigate AMG 397 as monotherapy on a twice weekly dosing schedule (ie, once daily for 2 consecutive days followed by 5 days break at a weekly interval [QD2]) in subjects with MM, NHL, and AML (Figure 1). In July 2019, reports of troponin elevations occurring at the highest dose level investigated of

320 mg/m^2 resulted in the clinical trial being placed on hold. In 2020, the study was redesigned to investigate low weekly doses of AMG 397 including Part 2 (Figure 2, Figure 3) and Part 3 (Figure 2) as follows:

- Parts 2A will enroll subjects with MDS or AML (monotherapy [QW]) for dose escalation and subjects with only MDS for dose expansion
- Parts 2B will enroll subjects with AML in Japan (monotherapy [QW])
- Parts 2C will enroll subjects with 1q21 amp MM (monotherapy [QW])
- Parts 3A will enroll subjects with MDS (AMG 397 + azacitidine) for dose escalation and dose expansion
- Parts 3B will enroll subjects with AML (AMG 397 + azacitidine) for dose escalation and dose expansion
- Parts 3C will enroll subjects with 1q21 amp MM (AMG 397 + dexamethasone) for dose escalation and dose expansion

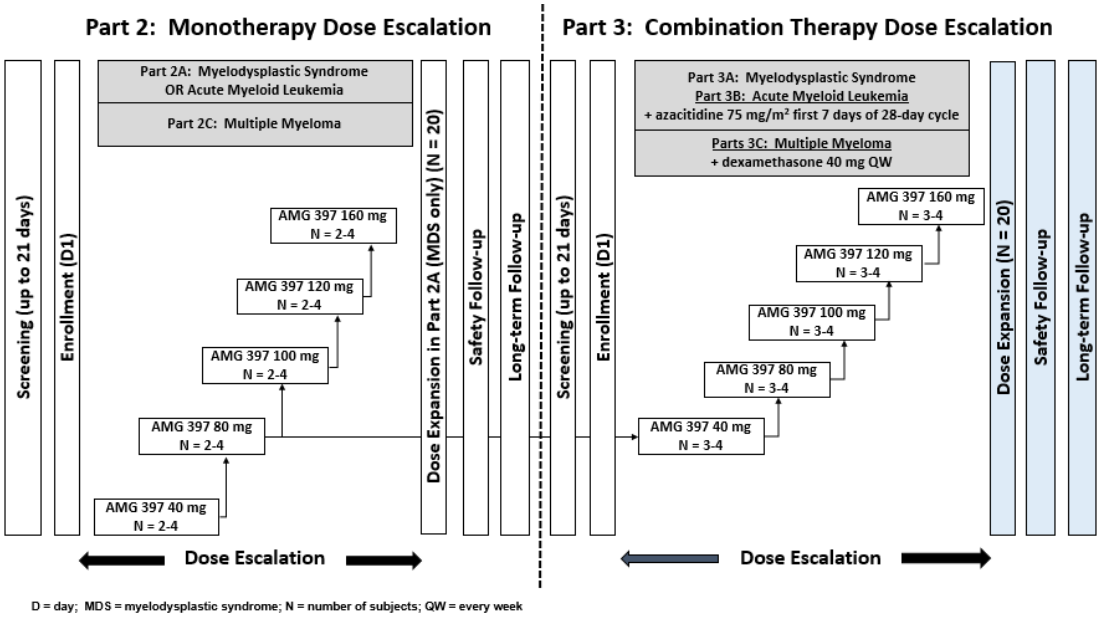
Study Design and Treatment Schema

Figure 1. Part 1 Study Design and Treatment Schema (CLOSED TO ENROLLMENT)



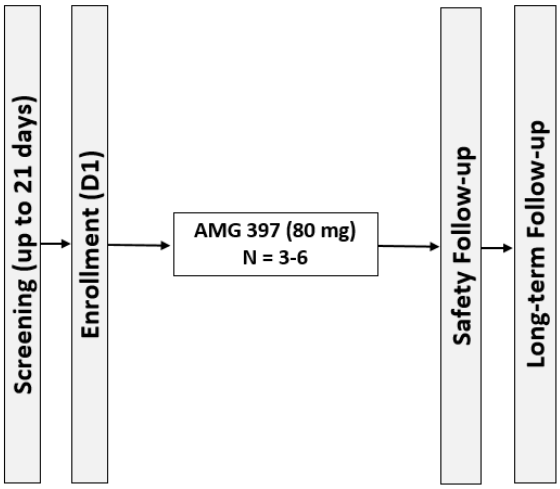
AML = acute myeloid leukemia; D = day; DLRT = dose level review team; DLT = dose-limiting toxicity; MM = multiple myeloma; MTD = maximum tolerated dose; NHL = non-Hodgkin's lymphoma; RP2D = recommended phase 2 dose

Figure 2. Parts 2A, 2C, and 3 Study Design and Treatment Schema (Dose Escalation and Dose Expansion)



D = day; MDS = myelodysplastic syndrome; N = number of subjects; QW = every week

Figure 3. Part 2B Study Design and Treatment Schema (AML Subjects in Japan)



3.2 Sample Size

Up to 240 subjects will be enrolled in the study. A total of 24 subjects were enrolled during Part 1 dose escalation (12 in both Part 1A and Part 1B). Up to 26 evaluable subjects will be enrolled into Parts 2A and 2C monotherapy dose escalation part and up to 20 evaluable subjects into Part 2A (MDS only) dose expansion. Up to 6 subjects will be enrolled into Part 2B. Up to 78 evaluable subjects will be enrolled into each of the combination therapy dose escalation parts (up to 26 each for Parts 3A, 3B, and 3C) and up to 60 evaluable subjects (up to 20 subjects each for 3A, 3B, and 3C) in dose expansion.

The sample sizes are based on practical considerations and it is consistent with conventional oncology studies with the objective to identify the MTCD. With 10 subjects, there is a 40% to 65% probability of observing at least 1 adverse event if the true event rate is 5% to 10%. Exact 95% binomial CI will be provided for ORR. With the 20 subjects in each dose expansion group and a 20% ORR, the 2-sided 95% exact CI would be 6% to 44%.

3.3 Adaptive Design

Part 1

A two-parameter Bayesian Logistic Regression Model (BLRM) is used to guide dose escalation. The maximum tolerated dose (MTD) target Toxicity Probability Interval (TPI) for dose-limiting toxicity (DLT) is (0.20, 0.33] and TPIs of (0.33, 0.60] and (0.60, 1.00] are defined as excessive and unacceptable, respectively. The design seeks to identify a dose most likely to have a DLT rate in the target TPI, but with overdose control that limits

the possibility the dose has an excessive or unacceptable DLT rate (Babb et al, 1998). The overdose control limit is defined as less than a 0.40 probability of an excessive or unacceptable TPI. Based on accumulating safety data, the DLRT may implement an overdose control limit of less than a 0.25 probability of an excessive or unacceptable TPI. The probability of a DLT at dose level di is assumed to follow a Bernoulli distribution with probability pi where the logit of pi increases linearly with the log of the standardized dose in the following 2-parameter logistic model:

log [pi / (1-pi)] = logit(pi) = log[a] + exp(log[b]) log (di / dref)

Where a and b are random variables and dref is one of the planned doses selected as the reference dose.

A bi-variate normal prior distribution (Neuenschwander et al, 2008) is used for

theta = (log a, log b) where the probability that the true DLT rate is ≤ 0.40 at the lowest planned dose of 80 mg is 0.90 and the probability the true DLT rate is ≤ 0.05 at the reference dose of 640 mg is 0.05. These values are selected such that pi is 0.05 for the starting dose and 0.25 for the reference dose. Model sensitivity to the prior will also be investigated and in particular the BLRM will be examined using a prior having a lower reference dose (eg, 320 mg).

Part 2 and Part 3

Each dose cohort will initially enroll 2-4 subjects in Parts 2A and 2C and 3-4 subjects in Part 3; and up to 10 subjects at the highest dose level or MTD/MTCD may be enrolled. After reviewing all available safety and tolerability data, dose level decisions will be made by the DLRT using a mTPI model based on all evaluable subjects that have been enrolled at current dose. Dose escalation is considered to be complete if one of the following rules is met:

- **The highest planned dose level is evaluated, MTCD has not been defined and no DLTs occur at any dose level.**
- **An MTD or MTCD is identified.**

At least 6 evaluable subjects need to be treated at the dose level of MTCD.

Guidelines for dose level decisions can be found in Table 1. Please note one exception to the guidelines provided in Table 1, a single grade 3 treatment related troponin elevation will result in dose de-escalation regardless of number of subjects treated at current dose.

Table 1. Guidelines for Dose Level Decisions for Parts 2A and 2C and Part 3

	Number of DLTs		
No. of DLT-evaluable[a] subjects treated at current dose	**Escalate**	**Stay at current dose**	**De-escalate[b]**
1	0	-	1
2	0	-	≥ 1
3	0	1	≥ 2
4	0	1	≥ 2
5	0	1	≥ 2
6	0-1	-	≥ 2
7	0-1	2	≥ 3
8	0-1	2	≥ 3
9	0-1	2	≥ 3
10[c]	0-1	2-3	≥ 4

DLT = dose-limiting toxicity.
[a] See Section 6 for definition of DLT evaluable.
[b] De-escalate guideline applies only when current dose level and enrollment is allowed to a lower dose level.
[c] The maximum number of evaluable subjects at one dose level is 10.

The MTCD is defined as the highest dose with a probability of DLT lower than or close to a targeted toxicity probability of 0.2.

4. Covariates and Subgroups

There are no planned covariates in this study.

If appropriate the following baseline variables may be used to evaluate efficacy endpoints in subgroup analysis: Age at baseline (< 65, ≥ 65), sex, race, prior lines of anti-cancer therapy (1, 2, >2).

5. Definitions

Age at Enrollment

Subject age at enrollment will be determined using the age in years reported in the clinical database.

Baseline

Unless otherwise specified, baseline will be defined as the last assessment before the first dose of investigational product (AMG 397).

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

For the three baseline triplicate ECG, the mean of values in a triplicate should be calculated before taking the mean of the three baseline 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 within that assessment visit 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): $QTcB=QT/(RR/1000)^{1/2}$

Best Overall Response (BOR)

Best overall response for a subject is the best observed post-baseline disease response based on investigator assessment. Response criteria are as follows:

- **IMWG-URC for MM**
- **2017 ELN criteria for AML**
- **Revised IWG for MDS**
- **Lugano Classification for NHL**

Dose Limiting Toxicity (DLT)

Unless otherwise specified, investigators determine whether an adverse event qualifies as a DLT per the definition described in the protocol.

DLT Observation Period

The DLT observation period is defined as, at minimum, 28 days after the initial dose of AMG 397. If lead-in dosing period is initiated, the DLT-observation period is defined as the amount of time for subject(s) for each dose cohort to receive at least 1 week of lead-in dose and 3 weeks of target dose.

Duration of Response (DOR)

Duration of response is calculated for subjects who have achieved response (PR or better). It is defined as time from the first observation indicating a response to the subsequent date of disease progression or death, whichever is earlier.

DOR time in months: (date of disease progression or death - date of the first observation of response +1)/30.4

Subjects without disease progression or death until the analysis data cut-off date will be censored at the last adequate disease assessment date.

Fridericia-corrected QT Interval (QTcF)

The Fridericia correction will be calculated from the investigator reported QT (msec) and RR interval (msec): $QTcF=QT/(RR/1000)^{1/3}$

Investigational Product (IP)

IP is used in reference to AMG 397.

Overall Response Rate (ORR)

ORR is the incidence of either PR or better based on investigator assessment. All subjects that do not meet the criteria for response (PR or better) by the analysis cutoff date will be considered as non-responders.

Progression-free survival (PFS)

PFS time is calculated as time from first dose of IP date to disease progression date or death due to any cause, whichever is earlier.

PFS time in months: (date of disease progression or death - first dose of IP date +1)/30.4

Subjects without disease progression or death until the analysis data cut-off date will be censored at the last adequate disease assessment date. If no post-baseline disease assessment, censoring is at the first dose of IP date.

Overall survival (OS)

OS is defined as the time from first dose of IP date until death due to any cause.

OS time in months: (date of death - first dose of IP date +1)/30.4

Patients without event will be censored at their last date known to be alive.

Study Day

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

Pre study day 1: study day = (date –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 Day -1.

Treatment-Emergent Adverse Event (TEAE)

A treatment-emergent adverse event is any adverse event starting on or after the first dose of investigational product, as determined by "Did event start before first dose of investigational product" equal to "No" or missing on the Events eCRF, and up to and including 30 days after the last dose of investigational product excluding events reported after end of study date.

Time to Response (TTR)

Time to response is defined as the time from the first dose of IP until the first documentation of objective response. Only subjects who have achieved objective response will be evaluated for TTR.

TTR time in months: (date of the first observation of response - first dose of IP date +1)/30.4

6. Analysis Sets

6.1 Full Analysis Set

Full Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 397. The analysis of all endpoints, unless noted otherwise, will be conducted on the Full Analysis Set.

6.2 DLT Evaluable Analysis Set

A subject is deemed DLT evaluable if during the DLT-observation period the subject met at least one of the following criteria:

- **received at least 75% of the planned dose of AMG 397**
  - **in Parts 3A/3B: and received at least 85% of the planned dose of azacitidine**
  - **in Part 3C: and received at least 75% of the planned dose of dexamethasone**
- experienced a DLT

6.3 Pharmacokinetic Analysis Set

The PK Analysis Set will contain all subjects who have received at least 1 dose of AMG 397 and have at least 1 PK sample collected. These subjects will be evaluated for PK analysis unless the number of data points required for analysis is not enough, or

significant protocol deviations have affected the data, or if key dosing or sampling information is missing.

7. Planned Analyses

The planned analyses are described in following sections.

7.1 Interim Analysis and Early Stopping Guidelines

No formal interim efficacy analysis is planned. Safety data will be reviewed on an ongoing basis. Interim safety analyses will be performed for each dose level of each cohort to support the evaluation of safety by the DLRT. After reviewing all available safety data and reviewing the dose recommendation from mTPI, the DLRT will make all dose level and dosing schedule decisions.

Upon the completion of each cohort or each part, interim analyses can be performed to evaluate safety and efficacy data.

7.2 Primary Analysis

The primary analysis will occur when target enrollment is complete and each subject either completes 6 months on study or withdraws from the study.

7.3 Final Analysis

The final analysis will occur after all subjects have ended the study.

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.

8.3 Handling of Missing and Incomplete Data

The following imputation of missing values will be done:

Incomplete adverse event, concomitant medication dates and dates used for the derivation of time to efficacy endpoints will be imputed as per Appendix A.

Non-pharmacokinetic measurements that are above or below the quantification limits will be considered equal to the upper or lower limit of quantification for all analyses unless explicitly noted otherwise.

8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by listing important protocol violations by cohort and site.

8.5 Outliers

Outlier data will not be excluded unless scientifically justified.

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 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

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.

For each indication, efficacy and safety data will be summarized by dose level.

For the subjects who complete the DLT period and proceed to a higher dose level or crossover to a combinational therapy cohort for the following treatment cycle,

efficacy and safety data will be summarized per their initial assigned dose level.

9.2 Subject Accountability

The number and percent of subjects who are enrolled (including the dates for the first subject enrolled and last subject completed study), receive investigational product, complete investigational product, discontinue from investigational product (including reasons for discontinuing), complete study, discontinue the study (including reasons for discontinuing) will be summarized by cohort.

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. **IPDs and eligibility deviation will be summarized.**

9.4 Demographic and Baseline Characteristics

The following descriptive summaries of the demographic and baseline characteristics will be produced: Demographic (ie, age, age groups **[18 < 65, 65 to < 75, 75 to < 85, >= 85 years**], sex, race, and ethnicity) and baseline characteristics (**height, weight, disease type/sub-type, prior lines of therapy, and Eastern Cooperative Oncology Group [ECOG] Performance Status)** will be summarized using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple.

9.5 Efficacy Analyses

Table 2. Efficacy Endpoints

Endpoint	Statistical Analysis Methods
Overall response rate	**The proportion of subjects with response to treatment with corresponding 2-sided exact 95% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) for the Full Analysis Set. Refer Appendix B for code fragment.**
DOR, PFS, and OS	**Kaplan-Meier estimates and Kaplan-Meier curve will be provided for the Full Analysis Set.**
TTR	**Descriptive statistics will be provided for subjects with response.**
MRD[-] status at CR (Parts 3B and 3C only)	**Proportion of MRD[-] at CR will be provided for subjects with CR.**

For time to event endpoints (including DOR, TTR, OS, and PFS), summary table or figure may not be generated if the number of events is less than 10. The individual subject-level data will be provided.

9.6 Safety Analyses

9.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version **23.1** or later will be used to code all events categorized as adverse events to a system organ class and a preferred term. The severity of each adverse event will be graded using (CTCAE) version 4.03 (Appendix C).

Subject incidence of all treatment-emergent adverse events, serious adverse events, grade 3 or higher, treatment-related, serious treatment-related, adverse events leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term by dose level.

Subject incidence of DLTs will be summarized by dose level and preferred term using the DLT Evaluable Analysis Set.

9.6.2 Laboratory Test Results

The analyses of safety laboratory data will include summary statistics at the scheduled time points by dose cohort. Shifts in CTCAE grades of safety laboratory parameters between baseline and the worst post-baseline value for select blood chemistry analytes (creatinine, total bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase [ALP]) and hematology analytes (hemoglobin, platelet count, total neutrophils) will be tabulated by dose cohort.

A summary of potential hepatoxicity by Hy's Law will be tabulated. The criteria are defined as AST or ALT > 3 times upper limit of normal (ULN), total bilirubin ≥ 2 times ULN, and ALP < 2 times ULN for baseline and on study assessed within 7 days.

Subject incidence of troponin elevation will be summarized.

9.6.3 Vital Signs

Vital signs (systolic / diastolic blood pressure, heart rate) over time and change from baseline will be summarized.

9.6.4 Physical Measurements

The physical measurement to each scheduled assessment time point will be provided.

9.6.5 Electrocardiogram

All on-study ECG data including PR, QRS, QT, RR, QTcB, and QTcF interval will be summarized.

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters.

Subjects will be categorized into the following groups per their maximum change from baseline in QTcB and QTcF. Unscheduled assessments will be included in the determination of the maximum change.

- <=30 msec
- >30 – 60 msec
- >60 msec

The number and percentage of subjects in each group will be summarized.

Subjects will also be categorized into the following groups per their maximum post baseline QTcF. Unscheduled assessments will be included in the determination of the maximum post baseline value.

- <=450 msec
- >450 – 480 msec
- >480 – 500 msec
- >500 msec

The number of subjects in each group will be summarized for each dosing group.

In addition, the relationship between PK concentration of AMG 397 and change from baseline in QTcF may be explored graphically.

Analysis of the relationship between AMG 397 serum concentrations and change from baseline in QTcF will be conducted and plots of the relationship between AMG 397 serum concentrations and change from baseline in QTcF will be provided.

9.6.6 Antibody Formation

The incidence of subjects who develop anti-AMG 397 antibodies at any time will be tabulated.

9.6.7 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to AMG 397 by dosing schedule. Number of cycles initiated, number of doses, duration of treatment, average dose delivered per day, average dose delivered per treated week and cumulative dose will be summarized. Subject incidence of dose modification along with the reason for dose modification will be summarized.

A listing of the unique manufacturing lot numbers, and a listing of the subjects administered each manufacturing lot number will be provided.

9.6.8 Exposure to Other Protocol-required Therapy

Descriptive statistics will be provided to describe the exposure to azacytidine and dexamethasone. The number of cycles initiated, completed, discontinued, the duration of therapy and total dose will be summarized. Subject-level data may be provided instead of the summary if the subject incidence is low or single dose is given.

9.6.9 Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medications will be summarized by preferred term as coded by the World Health Organization Drug (WHO DRUG) dictionary.

9.7 Analyses of Exploratory Endpoints

Analyses of exploratory endpoints may include, but not limited to, biomarkers, pharmacodynamics biomarker measurements, and genomic aberrations. Identification of metabolite(s) of AMG 397 in plasma and the relationships between PK/PD for safety and efficacy may also be explored.

Details of the exploratory analysis will be provided in a supplemental analysis plan.

9.8 Other Analyses

9.8.1 Analyses of Pharmacokinetic Endpoints

PK parameters will include, but are not limited to, C_{max}, T_{max}, AUC, CL and $t_{1/2}$. These parameters will be estimated using standard non-compartmental PK methods and summarized by dose groups using n, means, standard deviations, medians, coefficients of variation, geometric mean, minimums and maximums.

PK analyses will be provided by the Department of Clinical Pharmacology, Modeling & Simulation (CPMS). Details regarding the analyses will be provided in a separate analysis plan by CPMS.

9.8.2 Analyses of Biomarker Endpoints

The analysis of biomarker will be described and performed by Clinical Biomarker Group.

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometricka. 1934;26:404-413.

12. Prioritization of Analyses

There is no prioritization of analyses.

13. Data Not Covered by This Plan

The analyses of PK and biomarkers are not covered by this plan.

14. Appendices

Appendix A. Imputation Rules

Imputation Rules for Partial or Missing Dates for Adverse Events and Concomitant Medications

Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date						
		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		
		< 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: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Imputation rules for partial or missing stop dates:

- Initial imputation
  a. For partial stop date mmyyyy, impute the last of the month.
  b. For partial stop date yyyy, impute December 31 of the year.
  c. For completely missing stop date, do not impute.
- If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.
- If the stop date imputation leads to a stop date that is before the start date, then set the stop date as missing.

Imputation rules for partial or missing death dates:

- **If death year and month are available but day is missing:**
  a. If YYYYMM for the date last known to be alive equals YYYYMM for death date, set death date to the day after the date last known to be alive.

b. If YYYYMM for the date last known to be alive is less than the YYYYMM for death date, set death date to the first day of the death month.

c. If YYYYMM for the date last known to be alive is greater than YYYYMM for death date, data error, do not impute and censor subject survival time.

- **If month and day are missing and year of death is known:**
  - **a. If YYYY for the date last known to be alive equals the YYYY for death date, set death date to the day after last known to be alive date.**
  - **b. If YYYY for the date last known to be alive is less than the YYYY for death date, set death date to the first day of the death year.**
  - **c. If YYYY for the date last known to be alive is greater than YYYY for death date, data error, do not impute and censor the subject survival time.**
- **If a death date is totally missing, do not impute and censor the subject survival time.**

General Imputation rules for time to event efficacy endpoints

Unless otherwise specified, the partial/missing event dates will be imputed as follows:

- **If event year and month are available but the day is missing:**
  - **a. If mmyyyy for the date last known to be event-free equals mmyyyy for event date, set event date to the day after the date last known to be event-free.**
  - **b. If mmyyyy for the date last known to be event-free is less than the mmyyyy for event date, set event date to the first day of the event month.**
  - **c. If mmyyyy for the date last known to be event-free is greater than mmyyyy for event date, data error and do not impute.**
- **If month and day are missing and year of event is known:**
  - **a. If yyyy for the date last known to be event-free equals the yyyy for event date, set event censor date to the date last known to be event-free.**
  - **b. If yyyy for the date last known to be event-free is less than the yyyy for event date, set OS censor date to last day of the prior year.**
  - **c. If yyyy for the date last known to be event-free is greater than yyyy for event date, data error and do not impute.**
- **If an event date is totally missing, do not impute.**

Appendix B. Code Fragments

The ORR and its 95% CI can be calculated in SAS using PROC FREQ. The sample code is provided below, where RESP is the status of response (eg., 1=responder, 2=non-responder). The CI using the exact method can be found in the OUT data labeled as 'Exact Conf Limits'.

```
proc freq data=TEST;
  tables RESP / binomial alpha=0.05;
  ods output Binomial=OUT;
run;
```

Appendix C. Reference Values/Toxicity Grades

Adverse Event Grading Scale
The CTCAE is available at the following location:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm