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

AMG 397

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Confidentiality Notice

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Investigator's Agreement

I have read the attached protocol entitled "A Phase 1 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 397 in Subjects with Selected Relapsed or Refractory Hematological Malignancies", dated 28 March 2018, and agree to abide by all provisions set forth therein. I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 1 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 397 in Subjects With Selected Relapsed or Refractory Hematological Malignancies

Study Phase: 1

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

Primary Objectives:

- Evaluate the safety and tolerability of AMG 397
- Estimate the maximum tolerated doses (MTDs) and/or biologically active doses (eg, recommended phase 2 doses [RP2Ds]) of AMG 397

Secondary Objectives:

- Evaluate the efficacy of AMG 397
- Evaluate the pharmacokinetics (PK) of AMG 397

Exploratory Objectives:

- Explore pharmacokinetic/pharmacodynamic (PK/PD) relationships for safety and/or efficacy endpoints
- Identify metabolite(s) of AMG 397 in plasma and urine
- 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
- Evaluate patient responses according to disease-specific features in tumor cells such as chromosomal amplifications, rearrangements, gene expression profiles, protein expression as well as somatic mutations as necessary
- Evaluate changes to immune cell subsets in peripheral blood due to MCL1 inactivation
- Assess Minimal Residual Disease (MRD) status with patient response as necessary

Hypothesis:

A safe and tolerable dose of AMG 397 will have evidence of anti-tumor activity in patients with selected RR hematological malignancies as measured by Objective Response Rate (ORR).

Primary Endpoints:

- 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

Secondary Endpoints:

- Efficacy parameters:
  - ORR using response criteria per the following:
    - International Myeloma Working Group (IMWG) for MM subjects
    - Lugano Classification for NHL subjects
    - Revised International Working Group (IWG) for AML subjects
  - Duration of response
  - Progression Free Survival (PFS) and Overall Survival (OS)
- 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 ($t_{1/2}$)

Exploratory Endpoints:

- AMG 397 exposure/efficacy and exposure/safety relationships
- AMG 397 metabolites in plasma and urine
- Increased expression of BAX and Caspase 3 in monocytes or blast cells and/or decrease in circulating monocyte counts
- Patient responses according to biomarkers of tumor cells including but not limited to protein levels of pro-survival family members, FISH/cytogenetic analysis, gene expression profiling, flow cytometric phenotyping and DNA sequencing
- Immune cell subset frequencies, absolute counts and MFIs in peripheral blood
- MRD status

Study Design:

This is a first-in-human (FIH), multicenter, non-randomized, open-label, phase 1 study evaluating AMG 397 administered orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle in adult subjects with selected RR hematological malignancies.

This study will consist of dose escalation (Part 1) to evaluate safety and tolerability and estimate the MTD/RP2D of AMG 397 using a Bayesian Logistic Regression Model (BLRM) in the following groups:

- Group 1A will consist of subjects with RR MM and/or NHL
- Group 1B will consist of subjects with RR AML

This will be followed by a dose expansion (Part 2) to gain further efficacy and safety experience with AMG 397 in adult subjects with RR MM, DLBCL, and AML.

The study will be conducted at up to 20 sites globally in Australia, Europe, Japan, and the United States (US). Other countries or regions may be added.

Dose Escalation– Part 1

Dose escalation will estimate MTDs for Groups 1A and Group 1B using an adaptive, BLRM design. The Dose Level Review Team (DLRT) will review data, monitor safety, and make decisions on dose escalation/change. The table below shows the planned dose levels for dose escalation.

Planned Doses per Dose Cohort Level

Dose Cohort Levels	Dose (mg)
1	80
2	160
3	320
4	640

Dose escalation will begin with 2-4 subjects treated at the lowest planned dose level of 80 mg with enrollment from Group 1A and 1B. Dose escalation will follow the planned schedule described above with 2-4 subjects treated in each cohort.

DLRT will convene to review the safety data and determine the appropriate dose to be implemented. Dose escalation/de-escalation decisions will be guided by the BLRM model of dose toxicity. Skipping of planned dose levels is not allowed. Dose escalation decisions will not be made until all subjects in a cohort(s) are monitored through the DLT-observation period of 28 days following treatment initiation. Intermediate dose levels and alternative dosing schedule(s) may be explored based on emerging pharmacokinetic and safety data per the decision of the DLRT.

Dose escalation for both Group 1A and 1B will continue until any of the following events:

- The highest planned dose level is determined to be safe and tolerable (minimum of 6 evaluable subjects)
- MTDs are identified for each group where BLRM repeats the recommendation of a dose level (minimum of 6 evaluable subjects)
- The maximum of 30 evaluable subjects have been enrolled in each group. If fewer than 6 subjects are treated at the MTD/RP2D, additional subjects may be enrolled to confirm safety and tolerability.

There is a potential for tumor lysis syndrome (TLS) in subjects with hematologic malignancies, especially in those with bulky disease, elevated pretreatment lactate dehydrogenase (LDH) levels, elevated leukocyte count, renal dysfunction, and dehydration. To mitigate the risk of TLS:

- Tumor lysis syndrome prophylaxis must be initiated in all subjects prior to the first dose of AMG 397.
- Additionally, when an event meeting clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and Appendix L) is observed within seven days after therapy with AMG 397, lead-in dosing may be initiated to evaluate a step-wise dose escalation for all subsequent dosing. See Figure 2 for an example of lead-in dosing.
- For the management of TLS, please refer to Section 6.5.7 for more details

The DLRT will convene to review the safety data and may determine a lead-in dose, which will not exceed the dose where the TLS was observed. Once TLS criteria is resolved, this lead-in dose will be administered for the first week of dosing (cycle 1 week 1). Upon completion of the lead-in dosing period, subject(s) will receive their designated target dose level of AMG 397 per Table 3 beginning on the second week of dosing (cycle 1 week 2) and all subsequent dosing.

> **NOTE:** Once lead-in dosing is implemented, a maximum of 50% dose escalation of AMG 397 will be imposed between dose cohort levels per Table 3 for the target dose.

Decisions to modify the AMG 397 lead-in dosing period regimen, lead-in period starting dose, and dosing increments, will be made in conjunction with the investigator and Amgen medical monitor and communicated to the IRB/EC, as appropriate.

Intra-subject Dose Escalation

Subjects who complete the DLT period may proceed to a higher dose level for the following treatment cycle once the next dose cohort has been deemed safe by the DLRT and after consultation with the PI and sponsor, as long as no DLT has been reported for this subject during or after completion of the DLT period.

Dose Expansion – Part 2

Upon completing the dose escalation part of the study and depending on data obtained, dose expansion may proceed in groups with selected RR hematological malignancies below:

- Group 2A will consist of subjects with MM
- Group 2B will consist of NHL subjects with Diffuse Large B-cell Lymphoma (DLBCL)
- Group 2C will consist of subjects with AML

Dose expansion in all of these groups may take place concurrently. The maximum tolerated dose (MTD) for each indication, identified from the dose escalation phase, will inform the dose expansion phase.

Sample Size:

Up to 90 evaluable subjects will be enrolled in the study. Up to 60 evaluable subjects will be enrolled during dose escalation (up to 30 in both Groups 1A and 1B). Up to 30 evaluable subjects will be enrolled into the dose expansion part (up to 10 each for Groups 2A, 2B, and 2C).

Summary of Subject Eligibility Criteria:

Male or female subjects ≥ 18 year of age at the time of informed consent who have RR MM, NHL and AML. For a full list of eligibility criteria, refer to Section 4.1 and Section 4.2.

Investigational Product

AMG 397 is a potent and selective inhibitor of protein-protein interactions between myeloid cell leukemia sequence 1 (MCL1) and pro-apoptotic members of the lymphoma/leukemia 2 (Bcl-2) family. AMG 397 is an oral agent which will be provided as 5 mg, 20 mg, and 100 mg tablets, and will be packaged in bottles of 15 tablets.

Amgen Investigational Product Dosage and Administration:

AMG 397 is administered orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle at dose levels detailed in Table 3.

Procedures:

For all subjects, after written informed consent has been obtained, all screening tests and procedures will be performed within 21 days of administration of the first dose of AMG 397 (day 1), unless otherwise noted. Once a subject is enrolled into the study, serial clinical safety and study evaluations as per the Schedule of Assessments (Table 4 and Table 5) will be performed including physical examination, vital signs, clinical laboratory tests, ECGs, and sample collections. This treatment period will continue until the subject becomes intolerant to the investigational product, signs and symptoms of clinical progression are evident as determined by the investigator, or the subject withdraws consent. An end of treatment (EOT) visit will be conducted immediately after the decision to discontinue treatment with AMG 397.

If applicable, the subject will return 28 (+7) days after the last dose of AMG 397 for the Safety Follow-Up (SFU) visit.

In dose expansion part only, long-term follow up (LTFU) will be conducted every 3 months from the last visit for up to 1 year from the first dose of AMG 397 for all subjects who have not withdrawn consent to assess for survival and/or the commencement of subsequent cancer therapy.

For a full list of study procedures, including the timing of each procedure, please refer to the Schedule of Assessments (Table 4 and Table 5) Section 7.1.

Statistical Considerations:

The primary analysis will occur when target enrollment is complete and each subject either completes 6 months on study or withdraws from the study. During dose escalation, the DLRT will review the safety data after each cohort and make a decision on the next dose level to be explored for the estimate of RP2D/MTD based on a BLRM design. Descriptive statistics will be provided for selected demographics, safety, PK, pharmacodynamic,

efficacy and biomarker data by dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. ORR will be presented with 80% exact CI. PFS and OS will be summarized using the Kaplan-Meier method. Descriptive statistics will be provided for duration of response (DOR) and DOR summarized by the Kaplan-Meier method, as appropriate.

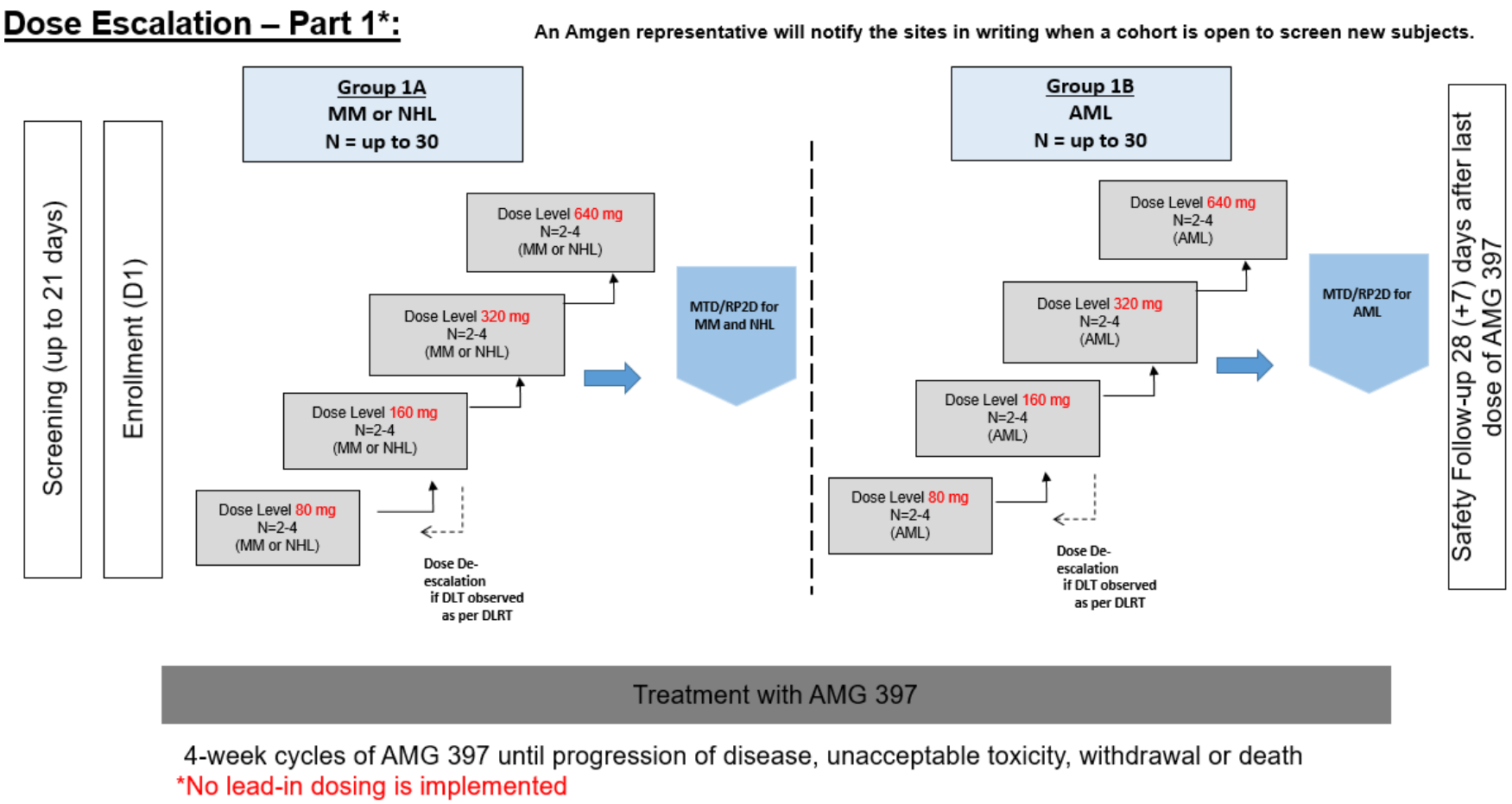
Graphical summaries of the data may also be presented.

For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: Amgen, Inc.

Study Design and Treatment Schema

Figure 1. Study Design and Treatment Schema



Dose Expansion – Part 2:

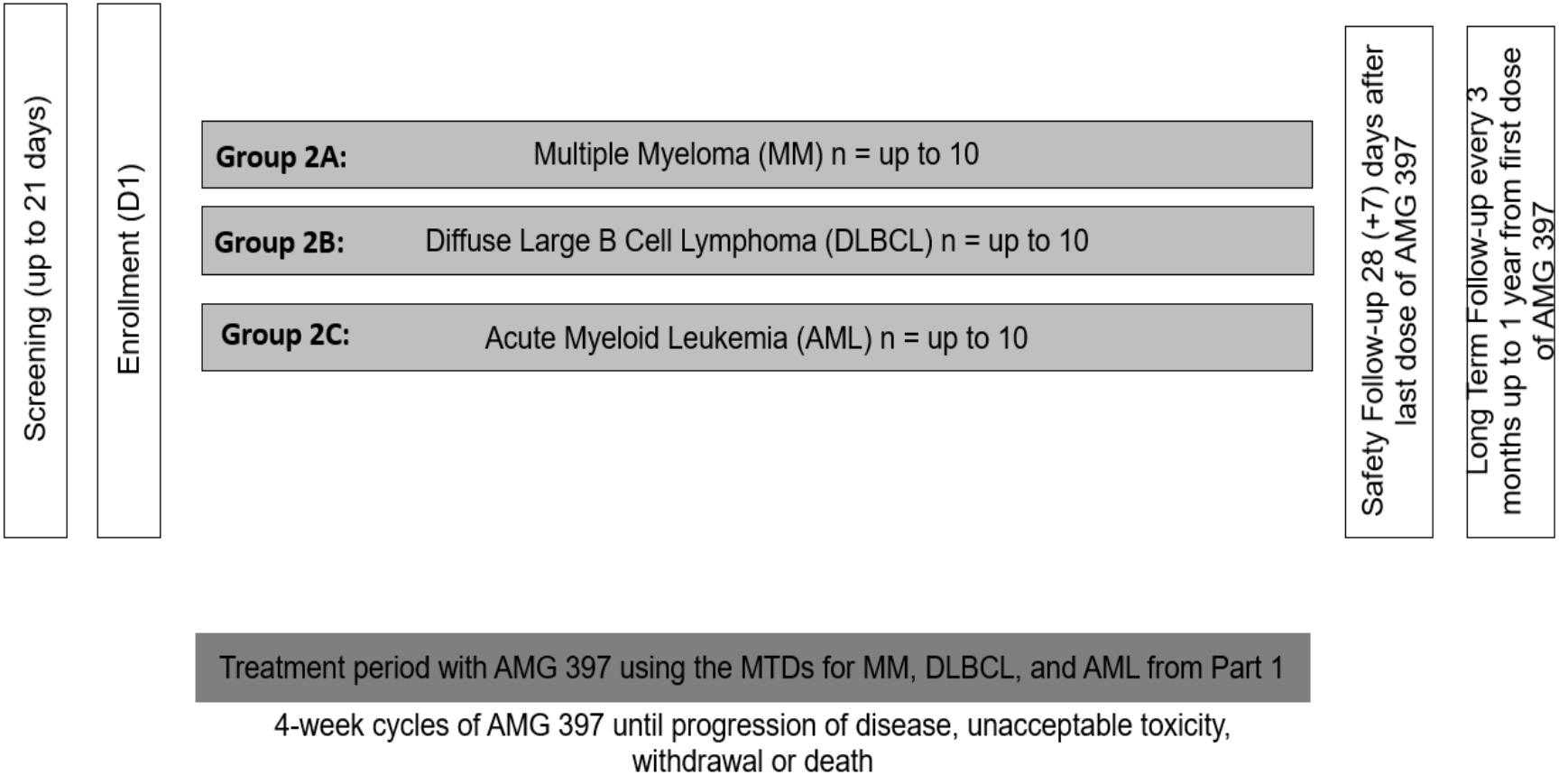
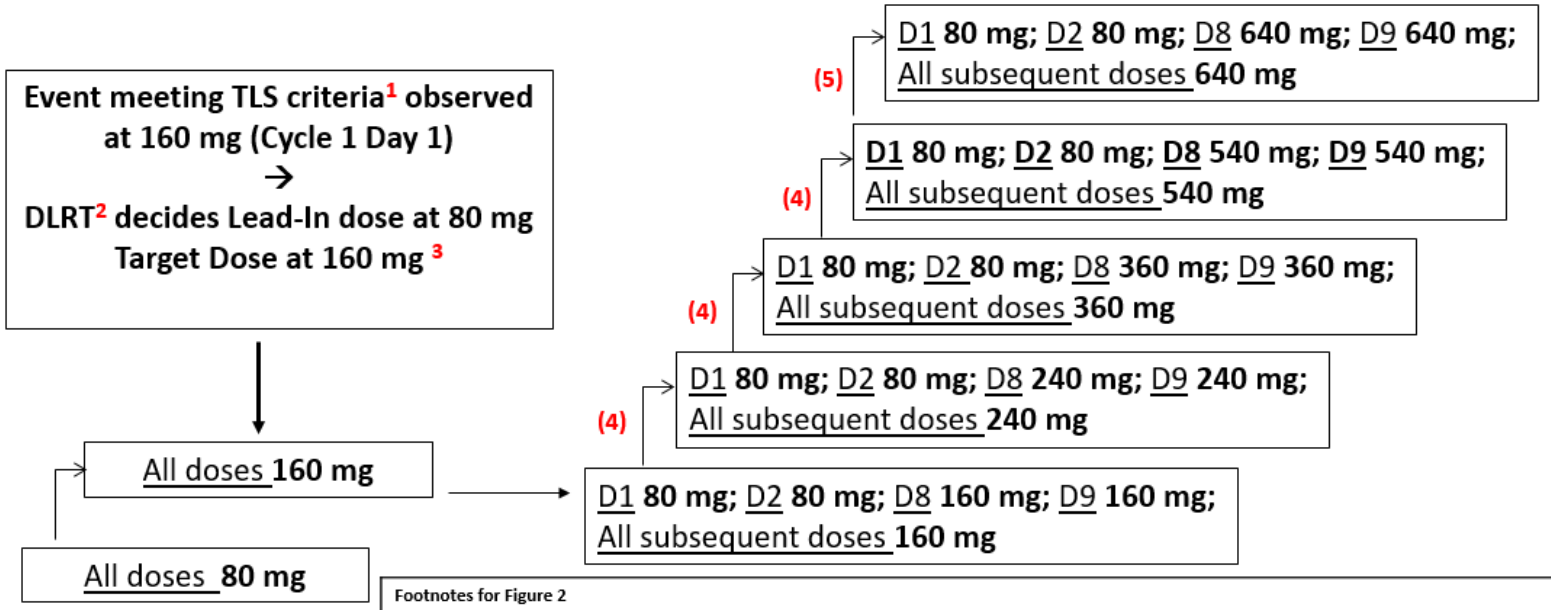


Figure 2. Example of Lead-in Dosing



Footnotes for Figure 2	
1	At 160 mg, a subject is observed to have clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and Appendix L) on Cycle 1 Day 1, lead-in dosing will be employed to evaluate a step-wise dose escalation. NOTE: Event meeting TLS criteria observed within seven days after therapy with AMG 397 will trigger evaluation for lead-in dosing
2	DLRT reviews the safety data determine a lead-in dose which will not exceed the dose where the TLS was observed (80 mg). Once TLS criteria is resolved, this lead-in dose will be administered for the first week of dosing (cycle 1 week 1
3	Upon completion of the lead-in dosing period, subject(s) will receive their designated target dose level of AMG 397 per Table 3 beginning on the second week of dosing (cycle 1 week 2) and all subsequent dosing.
4	Once lead-in dosing is implemented, a maximum of 50% dose escalation of AMG 397 will be imposed between dose cohort levels per Table 3 for the target dose.
5	Current highest dose level is 640 mg per Table 3

Study Glossary

Abbreviation or Term	Definition/Explanation
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AML	Acute myeloid leukemia
ANC	absolute neutrophil count
APML	Promyelocytic leukemia
AST	aspartate aminotransferase (SGOT)
AUC	area under the concentration-time curve
BP	blood pressure
CBC	complete blood count
CECT	Contrast-enhanced computed tomography
CI	confidence interval
CL	Clearance
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CR	complete response
Cri	Complete response/remission with incomplete recovery of peripheral blood counts
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DILI	drug-induced liver injury
DLBCL	Diffuse Large B-cell Lymphoma
DLRM	dose level review meeting
DLRT	dose level review team
DLT	dose limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELN	European Leukemia Net
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject.

Abbreviation or Term	Definition/Explanation
End of Treatment	defined as the last assessment for the protocol specified treatment phase of the study for an individual subject
End of Study (primary completion)	defined as when the last subject is assessed or receives an Intervention for the purposes of final collection of data for the primary endpoints.
End of Study	defined as when the last subject completes the safety follow-up assessments
EOI	End of infusion
eSAE	electronic serious adverse event
ESR	erythrocyte sedimentation rate
FIH	first in human
FISH	fluorescent in situ hybridization
FLC	serum light chain
FU	follow-up
GCP	Good Clinical Practice
h, hr	Hour
HBc	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
heart rate / HR	number of cardiac cycles per unit of time
HepCAb	hepatitis C antibody
HiDAC	high dose cytarabine
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMWG	International myeloma working group
IMWG-URC	International myeloma working group uniform response criteria
IND	Investigational new drug
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IV	intravenous or roman numeral 4
LAIP	Leukemia-associated immunophenotype
LTFU	Long-term follow-up
LVEF	left ventricular ejection fraction
MAD	maximum administered dose
MCL1	Myeloid Leukemia Cell 1

Abbreviation or Term	Definition/Explanation
Mg	Milligrams
MM	Multiple myeloma
MRD	minimal residual disease
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
N, n	Number
NHL	Non-Hodgkin's Lymphoma
ORR	Overall response rate
PD	phramacodynamic
PK	pharmacokinetics
PR	partial response
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
PT	prothrombin time
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
QW	Once weekly
RBC	red blood cells
RP1BD	recommended phase 1b dose
RP2D	recommended phase 2 dose
RR	Relapsed or refractory
SAE	Serious adverse event
sCR	stringent complete response
SD	standard deviation
SFLC	serum free light chain
SFU	Safety follow-up
SOA	Schedule of assessments
SPEP	serum protein electrophoresis
$T_{1/2}$	half-life
TBL	total bilirubin
TBA	Total Bile Acid
TLS	Tumor lysis syndrome

Abbreviation or Term	Definition/Explanation
t_{max}	time of maximum observed serum concentration
UA	urinalysis
ULN	upper limit of normal
UPEP	urine protein electrophoresis
WBC	White blood cell
WHO	World Health Organization

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1. OBJECTIVES

1.1 Primary

- Evaluate the safety and tolerability of AMG 397
- Estimate the maximum tolerated doses (MTDs) and/or biologically active doses (eg, recommended phase 2 doses [RP2Ds]) of AMG 397

1.2 Secondary

- Evaluate the efficacy of AMG 397
- Evaluate the pharmacokinetics (PK) of AMG 397

1.3 Exploratory

- Explore pharmacokinetic/pharmacodynamic (PK/PD) relationships for safety and/or efficacy endpoints
- Identify metabolite(s) of AMG 397 in plasma and urine
- Demonstrate AMG 397 inactivation of MCL1 by the activation of BAX and caspase 3 in circulating monocytes or blast cells, and/or the decrease of circulating monocytes
- Evaluate patient responses according to disease-specific features in tumor cells such as chromosomal amplifications, rearrangements, gene expression profiles, protein expression as well as somatic mutations as necessary
- Evaluate changes to immune cell subsets in peripheral blood due to MCL1 inactivation
- Assess Minimal Residual Disease (MRD) status with patient response as necessary

2. BACKGROUND AND RATIONALE

2.1 Disease

2.1.1 Multiple Myeloma Background

Multiple myeloma is a plasma cell neoplasia characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, production of a monoclonal protein present in the blood or urine and associated organ dysfunction (Palumbo and Anderson 2011).

Multiple myeloma is the second most common (10-15%) hematological cancer. It is responsible for 15-20% of all deaths from hematological cancer and about 2% of all cancer deaths. Recent improved understanding of the pathogenesis of myeloma has led to the development of new treatments. Survival is improving, with median overall survival in the range of 7-10 years after initial diagnosis. Nevertheless, myeloma remains an incurable cancer, and with subsequent relapses, the disease becomes refractory to current treatments. Therefore, RR multiple myeloma is still an unmet medical need (Smith and Yong 2013).

Myeloma arises from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post–germinal-center B cells. Multistep genetic and micro-environmental changes lead to the transformation of these cells into a malignant neoplasm. Myeloma is thought to evolve most commonly from a monoclonal gammopathy of undetermined clinical significance (usually known as MGUS) that progresses to smoldering myeloma and, finally, to symptomatic myeloma. Several genetic abnormalities that occur in tumor plasma cells play major roles in the pathogenesis of myeloma (Palumbo and Anderson, 2011).

The uncontrolled growth of myeloma cells has many consequences, including skeletal destruction, bone marrow failure, increased plasma volume and viscosity, suppression of normal immunoglobulin production, and renal insufficiency (Durie, 2011). Symptomatic (active) disease should be treated immediately, whereas asymptomatic (smoldering) myeloma requires clinical observation. Investigational trials are currently evaluating the ability of immunomodulatory drugs to delay the progression from asymptomatic to symptomatic myeloma. Current data would support the initiation of induction therapy with thalidomide, lenalidomide, or bortezomib plus hematopoietic stem-cell transplantation for subjects under the age of 65 years who do not have substantial heart, lung, renal, or liver dysfunction. Autologous stem-cell transplantation with a reduced-intensity conditioning regimen should be considered for older subjects or those with coexisting conditions. Less intensive approaches that limit toxic effects or prevent treatment interruption that would reduce the intended treatment effect should be considered in subjects over 75 years of age or in younger subjects with coexisting conditions. Biologic age, which may differ from chronologic age, and the presence of coexisting conditions should determine treatment choice and drug dose (Palumbo and Anderson, 2011).

Treatment of RR MM presents a special therapeutic challenge, due to the heterogeneity of disease at relapse and the absence of clear biological based recommendations regarding the choice of salvage therapies at various time points of disease progression. With increasing recognition of the inherent clonal heterogeneity and genomic instability of the plasma cells influencing both inherent and acquired therapeutic resistance, the identification of the optimal choice and sequence of therapies has become critical. Several new agents and targets are currently under development and show considerable promise. In the past 5 years, carfilzomib, pomalidomide, elotuzumab, ixazomib, daratumumab, were granted approval by US FDA for RR MM. , Despite advances in the management of multiple myeloma, however, relapse is inevitable in almost all subjects.

Recurrence of myeloma is typically more aggressive with each relapse, leading to the development of treatment-refractory disease, which is associated with a shorter survival (Dimopoulos, 2015). Thus, there remains an urgent need for treatment options for patients with RR MM.

2.1.2 Non-hodgkin's Lymphoma Background

About 74,680 people (41,730 males and 32,950 females) will be diagnosed with Non Hodgkin's Lymphoma (NHL), and about 19,910 people will die from this malignancy. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, accounting for 30% to 40% of cases and 13% of all hematologic disorders. The incidence is approximately 8 cases per 100,000 and rises with age**;** the median age at diagnosis is 70 years (Haematological Malignancy Research Network). Morphologically similar entities have historically been treated in a similar manner as DLBCL, and thus are collectively known as aggressive B-cell lymphomas. DLBCL, as a uniform diagnostic entity, makes up approximately 85% of aggressive B-cell lymphomas (Ziepert et al, 2010). However, distinct patterns of gene expression are observed within DLBCL, with different prognostic and potentially predictive implications (Swerdlow et al, 2016). Left untreated, DLBCL is uniformly fatal. Anthracycline-based frontline chemotherapy, introduced in the 1970s, resulted in the long term cure of 30% of patients (DeVita et al, 1975). Twenty-five years later, introduction of the human-mouse chimeric monoclonal anti-CD20 immunoglobin G (IgG) rituximab increased the cure rate significantly and is now a standard agent in frontline therapy, resulting in cure for 60% of patients (Sehn and Gascoyne 2015). Patients with DLBCL who do not respond to frontline therapy, or who experience relapse after a remission, are generally considered incurable unless able to receive either high dose chemotherapy (HDT) with autologous HSCT or allogeneic HSCT (Robinson et al, 2016). HSCT is preceded by a course of salvage chemotherapy. "Chemoresponsivess", indicating a partial response (PR) or complete response (CR) to salvage chemotherapy, has been as used as 1 criterion to define HSCT eligibility, since early trials demonstrated the extremely poor outcomes of patients without an objective response to salvage chemotherapy (Philip et al, 1987). It is not known if responsiveness to newer classes of therapies, such as those that are immune-based, may also be sufficient to permit the successful use of HDT.

The most commonly used regimens in the S1 treatment of transplant-eligible patients contain rituximab and a platinum-based agent such as cisplatin (eg, R-DHAP, R-GDP, R-ESHAP) or carboplatin (eg, R-ICE) (Crump et al, 2014; Martin et al, 2008;

Witzig et al, 2008; Kewalramani et al, 2004). Patients who do not respond to S1 may be offered alternative therapies (hereafter referred to as S2) and HSCT provided that there is a response to S2 and that performance status and organ function are relatively preserved. There is no standard S2 regimen for transplant eligible patients. The ESMO and NCCN guidelines are relatively silent on appropriate S2 regimens (Zelenetz et al, 2016; Tilly et al, 2015). Results of small, single-center retrospective analyses support the conclusion that standard cytotoxic therapy is of limited value in patients not responsive to S1 chemotherapy and that novel therapies should be explored in this setting (Elstrom et al, 2010; Ardeshna et al, 2005;).

2.1.3 Acute Myeloid Leukemia Background

Acute myeloid leukemia (AML) is characterized by accumulation of abnormal blasts in the marrow. These cells disrupt normal hematopoiesis, thus contributing to the bone marrow failure that is the most common underlying cause of death. The abnormal blasts can escape into the peripheral blood, and may infiltrate organs. Diagnosis is based on demonstration that the marrow or blood has >20% blasts of myeloid origin (Estey, 2016) AML is the most common form of acute leukemia in adults in the United States (US).

In 2017, an estimated 21,380 new cases of AML are expected in the US with approximately 10,590 deaths from this disease (American Cancer Society, 2017). Outcomes for most subjects with AML remain poor (Burnett et al, 2011a). In particular, relapsed disease is associated with unsatisfactory outcomes in the majority of subjects (Ravandi, 2013). Although the majority of subjects with AML initially achieve CR, over 60% will eventually relapse after a variable period of remission. Using the traditional cytotoxic chemotherapy regimens, the likelihood of achieving a second CR is low especially if the first CR was short in duration, particularly if less than one year (Estey et al, 1996).

This is particularly true for subjects who have primary refractory disease and have never achieved a morphological response. For example, subjects with AML refractory to one course of high dose cytarabine (HiDAC) containing regimen have a median overall survival of only 3.8 months (Ravandi et al, 2010). Subjects whose initial CR duration is more than one year have been traditionally treated with HiDAC containing salvage regimens but only a minority achieve a second CR and many are not candidates for a potentially curative allogeneic hematopoietic stem cell transplant (HSCT) performed in second CR (Estey, 2000). Apart from duration of first CR, other predictors of outcome in first relapse include age, cytogenetics, and whether the patient received an allogeneic

HSCT in first CR (Breems et al, 2005). However, in the study reported by (Breems et al, 2005), only a minority of subjects with AML in first relapse had a successful long-term outcome and the long-term prognosis of the majority of subjects with relapsed or refractory AML remains dismal.

2.2 AMG 397 Product Background

AMG 397 is a potent and selective inhibitor of protein-protein interactions between MCL1 (myeloid cell leukemia sequence 1) and pro-apoptotic members of the B-cell lymphoma/leukemia 2 (Bcl-2) family. Programmed cell death or apoptosis is regulated via a complex network of protein-protein interactions between the pro-and anti-apoptotic sub-groups that make-up the Bcl-2 protein family. (Kozopas, Yang et al. 1993, Strasser, Cory et al. 2011, Czabotar, Lessene et al. 2014). MCL1 is an anti-apoptotic member of this family and promotes cell survival. In contrast, pro-apoptotic family members such as Bak, Bax, or the Bcl-2 homology 3 (BH3)-only protein family members, such as BIM and PUMA, are critical effectors for the induction of apoptosis. Upon the induction of apoptotic stimuli, pro-apoptotic BH-3 only proteins bind MCL1 and other pro-survival Bcl-2 family members, disrupting interactions between MCL1 and the pro-apoptotic effector proteins, Bak and Bax. This leads to activation and oligomerization of Bak and Bax, mitochondrial outer membrane permeabilization (MOMP), and the release of cytochrome C, caspase activation and cell death (Strasser, Cory et al. 2011) (Czabotar, Lessene et al. 2014).

Malignant transformation results in cellular stress from a variety of pro-apoptotic insults, including hypoxia and gain-of-function mutations in oncogenes**,** suggesting there is a strong selective advantage for tumors to evolve mechanisms that culminate in the evasion of apoptosis. The over-expression of anti-apoptotic Bcl-2 family members, such as MCL1 and Bcl-2, has emerged as a central mechanism by which cancers buffer pro-apoptotic stress. There is now considerable data suggesting that MCL1 is integral to the resistance of apoptosis in a substantial number of solid and hematopoietic cancers. Genetic ablation of MCL1 has been shown to protect mice from the development of acute-myeloid leukemia (AML) (Glaser, Lee et al. 2012). Additional mouse knockout studies have implicated MCL1 in the maintenance of plasma cells, an observation that suggests MCL1 may be a critical pro-survival factor in multiple myeloma (Peperzak, Vikstrom et al. 2013). MCL1 is highly expressed in a variety of human tumors, and over-expression of MCL1 has been implicated in resistance to chemotherapy and to Bcl-2/Bcl-xL inhibitors (van Delft, Wei et al. 2006,

Wertz, Kusam et al. 2011). Finally, focal amplification of the MCL1 gene has been observed in up to 10% of cancers derived from multiple tissue types, including lung and breast (Beroukhim, Mermel et al. 2010). These data suggest that the inhibition of MCL1 represents a novel and compelling therapeutic strategy for the treatment of cancer. A promising strategy for targeting MCL1 takes advantage of specific small molecules that selectively bind to MCL1 and disrupt its interactions with the BH3 domain of pro-apoptotic partner proteins such as Bak, and Bim, leading to the activation of the intrinsic apoptotic cascade and death in cells dependent on MCL1 for survival. The MCL1 inhibitor AMG 397 is a first in class therapeutic with novel MOA (disruption of protein-protein interactions) with the potential to directly induce apoptosis in cells dependent on MCL1 for survival, Furthermore, the activity of AMG 397 in pre-clinical models suggests that AMG 397 may have utility in hematological malignancies, particularly multiple myeloma, NHL and AML.

Refer to the specific section of the Investigator's Brochure for additional information related to the physical, chemical, and pharmaceutical properties and formulation(S)

2.2.1 AMG 397 Preclinical

AMG 397 neutralizes the interaction between human MCL1 and Bim in a biochemical TR-FRET based assay with an IC50 of 0.116 nM in serum free conditions. In addition, AMG 397 exhibits comparable potency against cynomolgus monkey, dog and rabbit Mcl 1, but is less potent against mouse and rat MCL1 in a serum free TR-FRET-based potency assay (IC50 values of 0.380, 0.112, and 0.144, 22.4 and 221 nM for dog, monkey, rabbit, rat and mouse MCL1, respectively) (Table 1) (Study R20150152). Examination of the AMG 397 binding pocket in human MCL1 suggests a leucine residue at amino acid position 248 contributes to the high affinity interaction between AMG 397 and human MCL1. In mouse and rat MCL1, the corresponding amino acid is a phenylalanine, which may contribute to the reduced affinity of AMG 397 for rat and mouse MCL1 (Study R20150152). AMG 397 is highly selective for MCL1 over the related Bcl-2 family members, Bcl-2 and Bcl-xL, exhibiting IC50 values of > 5000 nM in a TR-FRET BIM binding assay (Study R20150153) (Table 1).

Table 1. Binding Activity and Selectivity Profile of AMG 397 in a BIM Binding Assay

Binding Activity and Selectivity Profile in Cell-Free TR-FRET Bim Binding Assays	AMG 397
Human MCL1 IC_{50} (nM)	0.116
Dog MCL1 IC_{50} (nM)	0.380
Monkey MCL1 IC_{50} (nM)	0.112
Rabbit MCL1 IC_{50} (nM)	0.144
Mouse MCL1 IC_{50} (nM)	221
Rat MCL1 IC_{50} (nM)	22.4
Human Bcl-2 IC_{50} (nM)	> 5000
Human Bcl-xL IC_{50} (nM)	> 5000

Bcl-2 = B-cell lymphoma-2; Bcl-xL = B-cell lymphoma- extra-large; IC_{50} = half maximal inhibitory concentration; MCL1= Myeloid Cell Leukemia 1; TR-FRET = time-resolved fluorescence energy transfer
The IC_{50} values of AMG 397 were determined from duplicate measurements by fitting concentration-response data of individual replicates with a four-parameter sigmoidal model in Genedata Screener (Genedata, Basel, Switzerland).
Source: Study R20150152 and Study R20150153

AMG 397 inhibited the interaction between MCL1 and Bak in transfected HEK 293M cells with a mean IC50 of 71.1 nM in serum free growth medium (Study R20150154). Upon AMG 397 treatment for 16 hours, OPM-2 cell viability was reduced in a dose dependent manner under all conditions tested (ie, serum-free, with 10% FBS (1) and with 5% HS). The IC50 values of AMG 397 induced cell death were determined to be 0.020 ± 0.039 µM in the absence of serum, 0.0946 ± 0.025 µM in the presence of 10% FBS and 0.159 ± 0.039 µM in the presence of 5% HS (Study R20150154).

2.2.2 Pharmacology

AMG 397 interacted in vitro with several off-target receptors; however, none of these is expected to result in clinically significant effects over the proposed clinical dose range. The AMG 397 hERG 50% inhibition concentration (IC_{50}) was > 1.1 µM, the highest tested concentration that could be evaluated, thus, no clinically significant interaction with the hERG channel is expected over the proposed clinical dose range. In an isolated rabbit heart study, the no-effect concentration was 1 µM; thus, no clinically significant effects on cardiac electrical or functional activity over the proposed clinical dose range are expected. There were no AMG 397-related changes in electrocardiograms (ECGs), respiratory rate, or neurological clinical signs in the GLP 23-day dog toxicology study conducted at doses up to 15 mg/kg.

2.2.3 Pharmacokinetics

AMG 397 was characterized in vitro and in vivo preclinical studies. In animal species AMG 397 had low clearance (CL) relative to hepatic blood flow, moderate volume of distribution (Vss) and mean terminal elimination half-life ($t_{1/2z}$) ranging from 8.3 to 19 hour. The observed bioavailability was variable across species ranging from 23% in dogs and monkeys, 39% in rats and 56% in mice. In vitro, AMG 397 was highly bound to plasma proteins in all species including human (mean fraction unbound ranging from 0.0048 to 0.027), and did not partition into red blood cells. These data were used to predict the human AMG 397 PK parameters, with a CL of 0.057 L/hr/kg, Vss of 1.0 L/kg, and $t_{1/2z}$ of 12 hours. Bioavailability after oral dosing was estimated to be 31%, an average across preclinical species.

AMG 397 was an inducer of CYP2B6, CYP2C9, and CYP3A4, and reversible inhibitor of CYP2B6, CYP2C8, and CYP3A4 in vitro while it was not an inhibitor of other major drug metabolizing human CYP enzymes such as CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. AMG 397 was also a time-dependent inhibitor of CYP3A4 but not of any of the other CYPs tested. Additionally, AMG 397 was identified as an inhibitor of P-gp (IC_{50} of 8.7 µM). For BCRP, MATE1, MATE2-K, and OATP1B1, incomplete inhibition (36 - 54%) was observed at the highest test concentration (100 µM) of AMG 397, suggesting weak inhibition. Considering dose levels and frequency, based on physiologically based pharmacokinetic modelling, it was determined that AMG 397 has a potential to interact with CYP3A4 and P-gp.

2.2.4 AMG 397 Preclinical Toxicology

AMG 397 was well tolerated in a GLP 23-day rat toxicology study conducted at doses of 5, 15 and 500 mg/kg. The severely toxic dose in 10% of the animals (STD10) was ≥ 500 mg/kg. Key AMG 397-related findings in the rat included minimally to moderately increased serum transaminases and bilirubin that were associated with periportal vacuolation of hepatocytes, dilatation of lacteals and hypertrophy/hyperplasia of the mucosa in the small intestine, dilatation of the subcapsular space of the mesenteric lymph node, and atrophy of the zona glomerulosa of the adrenal gland.
AMG 397-related changes in the rat fully or partially reversed by the end of a 28-day recovery period.

In an exploratory 14-day dog toxicology study, 30 mg/kg was poorly tolerated (liquid stools, decreased food consumption, body weight loss) that resulted in early euthanasia and/or early termination of dosing of some animals. AMG 397 was generally well

tolerated in a GLP 23-day dog toxicology study at doses of 3, 7.5 and 15 mg/kg. The highest nonseverely toxic dose (HNSTD) in dogs was 15 mg/kg. Key AMG 397-related findings in the dog included soft feces, dose-dependent reductions in monocytes and other leukocyte subsets, minimally to mildly increased serum transaminase without light microscopic correlates in the liver, decreased lymphoid cellularity in lymphoid tissues, decreased bone marrow cellularity, vacuolation of the lamina propria of the small intestine, and dose-dependent decreased testes weight with the light microscopic correlate of tubular degeneration/atrophy of seminiferous tubules. Although the 23-day dog study did not include a recovery period, AMG 397-related changes are expected to be reversible based on the nature, incidence and severity of the changes.

AMG 397 was not mutagenic or clastogenic in exploratory genetic toxicology studies. AMG 397 was not phototototoxic in rats.

Overall, the results of the nonclinical safety studies support the initiation of AMG 397 clinical trials and the initial clinical plan.

Risk Assessment

AMG 397 interacted in vitro with several off-target receptors; however, none of these is expected to result in clinically significant effects over the proposed clinical dose range. The AMG 397 hERG 50% inhibition concentration (IC_{50}) was > 1.1 μM, the highest tested concentration that could be evaluated, thus, no clinically significant interaction with the hERG channel is expected over the proposed clinical dose range. In an isolated rabbit heart study, the no-effect concentration was 1 μM; thus, no clinically significant effects on cardiac electrical or functional activity over the proposed clinical dose range are expected. There were no AMG 397-related changes in electrocardiograms (ECGs), respiratory rate, or neurological clinical signs in the GLP 23-day dog toxicology study conducted at doses up to 15 mg/kg.

Potential risks are safety concerns based on mechanism of action, nonclinical data, or clinical data from AMG 397 or similar compounds that have either not yet been observed in human subjects or for which a causal association with AMG 397 has not yet been established. The potential risks and proposed clinical monitoring strategies are described below. All potential risks presented below have shown reversibility in preclinical studies:

Gastrointestinal toxicity

In the 23-day rat study, AMG 397 caused minimal to mild lacteal dilation in the small intestine. The lacteal dilation change may affect dietary lipid absorption and chylomicron synthesis (Boyle et al, 2012). In the 23-day dog study, AMG 397 caused mild vacuolation in the lamina propria of the small intestine. In an exploratory 14-day dog study, AMG 397 at a higher dose than used in the 23-day study was poorly tolerated due to GI clinical signs. There was no GI mucosal degeneration except in the pylorus where it was noted to be minimal to mild in the dog. Based on these observations, GI toxicity is a potential risk for patients.

Bone marrow toxicity

In early exploratory toxicology studies, a dose-dependent decrease in monocytes was seen in dogs. In the 23-day dog toxicology study, AMG 397-related decreased bone marrow cellularity with decreased lymphocytes, monocytes, and basophils was likely related to the primary pharmacology of AMG 397, ie, inhibition of MCL-1. White blood cell counts should therefore be monitored during clinical studies.

Reproductive toxicity (Male)

AMG 397 caused degeneration/atrophy of the seminiferous tubules with depletion of spermatogonia, spermatocytes, and spermatids of the testis along with decreased testicular weight in the dog. Patients should be advised of the potential effect on male fertility.

Drug-drug interactions

Data from in vitro nonclinical studies indicate that AMG 397 is an inhibitor of various CYP450s when tested in human liver microsomes. It is a reversible inhibitor of CYP2B6, CYP2C8, and CYP3A. AMG 397 is also a mechanism-based inhibitor of CYP3A4. Additionally, AMG 397 has the potential to be an inducer of CYP3A4, CYP2B6, and CYP2C9. It is also an inhibitor of the drug transporters, namely P-gp, MATE-1, and BCRP. AMG 397 is a substrate of P-gp and is expected to be predominantly eliminated as unchanged parent drug via biliary elimination.

Although AMG 397 inhibits multiple CYPs and transporters in vitro, based on physiologically based pharmacokinetic modeling and in considering predicted human PK and efficacious dose, AMG 397 has the potential to inhibit CYP3A and P-gp. Inhibition of other CYPs and transporters is unlikely to result in a drug-drug interaction.

Hepatobiliary toxicity

AMG 397-related elevations in total bilirubin occurred in the rat. These changes were at times accompanied by increases in urinary bilirubin and increases in AST and ALT; however, there was only minimal periportal vacuolation in the liver. Serum transaminases were also increased in the dog but without accompanying bilirubin increases or correlative light microscopic changes in the liver.

Cardiovascular toxicity

MCL1 is highly expressed in the myocardium, but its effect upon cardiac cells has not been established. In studies conducted in knockout mice with ablation of MCL-1, these animals showed reduced cardiac function. In mouse models, it has been suggested cardiac specific ablation of MCL1 resulted in fatal dilated cardiomyopathy manifested by a loss in cardiac contractility, abnormal mitochondria structure and abnormal mitochondrial respiration (Thomas et al, 2013; Wang et al, 2013). In the 23-day toxicology studies in the rat with AMG 397, reduction in cardiac weight was noted; however, there were no light microscopic correlates and no apparent clinical manifestations were noted. Additionally, no ECG, heart weight, or cardiac light microscopic changes were observed in dogs.

Tumor Lysis Syndrome

Clinical tumor lysis syndrome has been observed in a clinical trial with a drug of the same mechanism of action. Subjects with a high tumor burden or compromised renal function (eg, International Staging System [ISS] Stage II/III) may be at elevated risk for tumor lysis syndrome.

Blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) must be assessed in all subjects and any pre-existing abnormalities must be corrected prior to starting treatment with AMG 397. In addition, subjects must be appropriately hydrated prior to each dose of AMG 397. Further details regarding mandatory tumor lysis syndrome prophylaxis are provided in the study protocol in Section 6.5.7.

2.3 Rationale

MCL1 is a member of the BCL2 family of proteins integral to the control of apoptosis (programmed cell death). MCL1 is an anti-apoptotic member of the BCL2 family and promotes cell survival. In contrast, pro-apoptotic family members, such as BAK and BAX are critical effectors for the induction of apoptosis. Upon apoptotic stimuli, pro-apoptotic BH-3 only proteins (eg, Bid) bind MCL1, and disrupt the interaction between MCL1 and BAK or BAX. This leads to the oligomerization of BAK/BAX, mitochondrial outer

membrane permeabilization (MOMP), and the release of cytochrome C, caspase activation and cell death (Youle and Strasser 2008).

The acquired resistance and evasion of apoptosis, which is central to therapeutic resistance, is an established hallmark of cancer (Hanahan and Weinberg 2011). MCL1 is integral to the resistance of apoptosis in a substantial number of solid and hematopoietic cancers, as supported by a wealth of genetic and functional data. Internal efforts have demonstrated that knockdown of MCL1 expression by siRNA induces cell death in multiple cancer cell lines.

Mouse knockout studies have implicated MCL1 in the maintenance of plasma cells, an observation that suggests MCL1 may be a critical pro-survival factor in multiple myeloma (Peperzak, Vikstrom et al. 2013).

The current data package is supportive of multiple myeloma as an initial study population. MCL1 also provides a useful target for the treatment of subjects with AML as it is essential for the development and sustained growth of AML. MCL1 dependency was detected in AML mouse models (Xiang et al. 2010) and in human AML-derived cell lines. It was shown that deletion of MCL1 but not loss or pharmacological blockade of BCL-XL, BCL-2 or BCL-W induced the death of transformed AML and cured the disease in AML-afflicted mice (Glaser, et al 2012). The upregulation of MCL1 has been described at the time of AML relapse (Kaufmann et al, 1998). In FLT3-ITD AML, upregulation of MCL1 is dependent on FLT3 signaling and an essential effector of FLT3-ITD-mediated drug resistance (Bose et al 2013). Targeting MCL1 sensitizes FLT3-ITD-positive leukemia to cytotoxic therapies (Kasper et al 2012).

2.3.1 Dose Selection Rationale

2.3.1.1 Starting and Maximum Planned Doses

The proposed AMG 397 doses are 80, 160, 320, and 640 mg. During dose escalation (Part 1), AMG 397 will be given once daily for 2 consecutive days followed by 5 days break and repeated each week for 4 weeks of treatment cycle. One treatment cycle is 28 days in length and includes 8 administrations of AMG 397.

For dose expansion (Part 2), AMG 397 will be given once daily for 2 consecutive days followed by 5 days break and repeated each week for 4 weeks of treatment cycle. One treatment cycle is 28 days in length and includes 8 administrations of AMG 397. The planned dose level(s) for dose expansion (MTD/RP2D) will be determined based on data collected during dose escalation.

The proposed clinical starting dose of 80 mg is based on the highest non-severely toxic dose (HNSTD) noted in a GLP toxicology study in beagle dogs. The HNSTD dose of 15 mg/kg/day in beagle dogs corresponds, per ICH S9 Guidance, to a human daily equivalent dose of 83 mg. AMG 397 human pharmacokinetics (PK) parameters were predicted from a combination of in vitro and in vivo nonclinical data. At the starting dose of 80 mg administered orally once daily for 2 consecutive days followed by 5 days break, the predicted exposure margins of maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC) to the rat STD10 are 116-fold and 211-fold, respectively. The predicted exposure margins of Cmax and AUC to the dog HNSTD are estimated at 15-fold and 15-fold, respectively, at the starting dose administered orally once daily for 2 consecutive days followed by 5 days break.

Table 2. Predicted Human Exposures and Exposure Multiples at Steady-state After Oral Dosing of AMG 397

Clinical Dose[a]	Predicted Exposure [b]		Exposure Margins			
			AUC_{0-96} [c]		C_{max} [c]	
(mg)	AUC_{0-96} (hr·μg/mL)[c]	C_{max} (μg/mL)	Rat 4-week	Dog 4-week	Rat 4-week	Dog 4-week
80	12.2	0.35	211	15	116	15
160	24.5	0.70	105	8	58	7
320	48.9	1.39	53	4	29	4
640	97.8	2.79	26	2	15	2

AUC_{0-96} = area under the concentration time curve from 0 to 96 hr; C_{max} = maximum observed concentration; HNSTD = highest non-severely toxic dose; STD_{10} = severely toxic dose in 10% of the animals.
[a] Once daily dosing for 2 consecutive days followed by 5 days break
[b] Human PK was simulated based on human body weight of 60 kg and height of 170 cm
[c] Rat day 22 exposure at 500 mg/kg (STD_{10}): C_{max} = 40.6 μg/mL, AUC = 2580 μg/mL·hr (Study 122859). Dog (male) day 15 exposure at 15 mg/kg (HNSTD): C_{max} = 5.13 μg/mL, AUC = 186 μg/mL (Study 122859). Male value used because exposure was lower than in females.

The highest planned dose is 640 mg. Safety and tolerability data from prior dose levels will guide the dose escalations and the planned top dose for AMG 397 in the dose escalation phase. The maximum tolerated dose (MTD) identified from the dose escalation phase will inform the dose expansion phase. The planned dose level(s) for dose expansion will be determined based on data collected during dose escalation.

2.4 Clinical Hypothesis

A safe and tolerable dose of AMG 397 will have evidence of anti-tumor activity in subjects with selected RR hematological malignancies as measured by Objective Response Rate (ORR).

3. EXPERIMENTAL PLAN

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.

This study will consist of dose escalation (Part 1) to evaluate safety and tolerability and estimate the MTD/RP2D of AMG 397 using a Bayesian Logistic Regression Model (BLRM) in the following groups:

- Group 1A will consist of subjects with RR MM and/or NHL
- Group 1B will consist of subjects with RR AML

This will be followed by a dose expansion (Part 2) to gain further efficacy and safety experience with AMG 397 in adult subjects with RR MM, DLBCL, and AML.

Dose Escalation– Part 1

During dose escalation (Part 1), AMG 397 will be administered orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle.

Dose escalation will estimate MTDs for Group 1A and Group 1B using an adaptive, BLRM design. Table 3 shows the planned dose levels for dose escalation. The Dose Level Review Team (DLRT) will review data, monitor safety, and make decisions on any dose escalation/change. For more details regarding the dose escalation, please see Section 6.2.1.2

Table 3. Planned Doses per Dose Cohort Level

Dose Cohort Levels	Dose (mg) PO
1	80
2	160
3	320
4	640

Dose escalation for Group 1A and Group 1B will begin with 2-4 subjects treated at the lowest planned dose level of 80 mg. Dose escalation will follow the planned schedule described above with 2-4 subjects treated in each cohort.

DLRT will convene to review the safety data and determine the appropriate dose to be implemented. Dose escalation/de-escalation decisions will be guided by the BLRM model of dose toxicity. Skipping of planned dose levels is not allowed. Dose escalation decisions will not be made until all subjects in a cohort(s) are monitored through the DLT-observation period of 28 days following treatment initiation. Intermediate dose levels and alternative dosing schedule(s) may be explored based on emerging pharmacokinetic and safety data per the decision of the DLRT.

Dose escalation for both Group 1A and 1B respectively, will continue until any of the following events:

- The highest planned dose level for each group is determined to be safe and tolerable (minimum of 6 evaluable subjects)
- MTDs are identified for each group where BLRM repeats the recommendation of a dose level (minimum of 6 evaluable subjects)
- The maximum of 30 evaluable subjects have been enrolled in each group. If fewer than 6 subjects are treated at the MTD/RP2D, additional subjects may be enrolled to confirm safety and tolerability.

Intermediate doses and alternative dosing schedule(s) may be explored based on emerging pharmacokinetic and safety data as decided by the DLRT.

Lead-in Dosing

Due to the potential risk of TLS for subjects affected by hematologic malignancies, it is anticipated that lead-in dosing may be implemented. At any point during the study, when an event meeting clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and Appendix L) is observed within seven days after therapy with AMG 397, lead-in dosing may be initiated to evaluate a step-wise dose escalation for all subsequent dosing. See Figure 2 for an example of lead-in dosing. See Section 6.2.1.1.1 for more details

Dose Expansion – Part 2

Upon completing the dose escalation part of the study and depending on data obtained, dose expansion may proceed in groups with selected RR hematological malignancies below:

- Group 2A will consist of subjects with Multiple Myeloma (MM)
- Group 2B will consist of NHL subjects with Diffuse Large B-cell Lymphoma (DLBCL)
- Group 2C will consist of subjects with Acute Myeloid Leukemia (AML)

Dose expansion in all of these groups may take place concurrently. The maximum tolerated dose (MTD) for each indication, identified from the dose escalation phase, will inform the dose expansion phase.

Intra-subject Dose Escalation

Subjects who complete the DLT period may proceed to a higher dose level for the following treatment cycle once the next dose cohort has been deemed safe by the DLRT and after consultation with the PI and sponsor as long as no DLT has been reported for this subject during or after completion of the DLT period.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.

3.2 Number of Sites

This study will be conducted at up to 20 sites globally in Australia, Europe, Japan and the United States. Additional regions, countries, or sites may be added.

Sites that do not enroll subjects into an open cohort within 4 months of site initiation during dose escalation or expansion may be closed or replaced.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.

Up to 90 evaluable subjects will be enrolled in the study. Up to 60 evaluable subjects will be enrolled during dose escalation (up to 30 in both Groups 1A and 1B). Up to 30 evaluable subjects will be enrolled into the dose expansion part (up to 10 each for Groups 2A, 2B, and 2C). Based on emerging data, additional subjects may be enrolled.

The rationale for the number of subjects required is detailed in Section 10.3.

3.4 Replacement of Subjects

During dose escalation, subject(s) may be replaced if:

- Subject(s) is not DLT-evaluable. See Section 6.2.1.2 for definition of DLT-evaluable
- Subject(s) discontinues treatment for any reason other than a DLT during the DLT-observation period

Additional subjects may also be enrolled if Amgen’s medical monitor determines that the minimum required number(s) of evaluable subjects have not been enrolled in each cohort.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The study duration for each subject is approximately 8 months consisting of up to 21 days in the screening period, approximately 6 months of treatment period, an EOT visit, and a SFU visit approximately 28 (+ 7) days after their last dose of AMG 397.

For dose expansion part only, long-term follow up (LTFU) will be conducted every 3 months from the last visit for up to 1 year from the first dose of AMG 397, for all subjects who have not withdrawn consent to assess for survival and/or the commencement of subsequent cancer therapy.

This study duration may vary depending on the subject's disease, ability to tolerate AMG 397 and/or willingness to participate in the study.

End of study (EOS) for an individual subject: The date when the subject completes the final protocol-specified procedure or SFU/LTFU visit whichever is later. This date will be recorded on the EOS electronic CRF (eCRF)

3.5.2 End of Study

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

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

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

4. SUBJECT ELIGIBILITY

4.1 Inclusion Criteria

101. Subject has provided informed consent prior to initiation of any study-specific activities/procedures.
102. Age ≥ 18 years old

103. Pathologically-documented, definitively-diagnosed relapsed or refractory MM, NHL, or AML (Appendix G) and is intolerant to, or considered ineligible for available therapies known to provide clinical benefit.

104. MM subjects only:

- Measurable disease per the IMWG response criteria (Appendix E; assessed within 21 days prior to enrollment), as indicated by one or more of the following:
  - Serum M-protein ≥ 0.5 g/dL
  - Urine M-protein ≥ 200 mg/24 hours
  - For Subjects who do not meet 1 of the 2 prior criteria:
    - Serum Free Light Chain (sFLC) ≥ 10 mg/dL (≥ 100 mg/L) **AND** an abnormal sFLC ratio (< 0.26 or > 1.65) as per the IMWG response criteria

105. NHL subjects only:

- Radiographically measurable disease with a clearly demarcated nodal lesion at least 1.5 cm in its largest dimension or a target extranodal lesion at least 1.0 cm in its largest dimension

106. AML subjects only:

- Pathologically confirmed diagnosis of AML as defined by the WHO Classification (Appendix H)
- More than 5% blasts in bone marrow

107. MM and NHL subjects only:

- Hematological function, as follows without transfusion or growth factor support within 2 weeks prior to study day 1:
  - Absolute neutrophil count ≥ 1.0 X 10^9/L
  - Hemoglobin > 8 g/dL
  - Platelet count ≥ 75 X 10^9/L

  NOTE for MM subjects only: Platelet count ≥ 50 X 10^9/L (in subjects where < 50% of bone marrow nucleated cells were plasma cells) OR ≥ 30 X 10^9/L (in subjects where ≥50% of bone marrow nucleated cells were plasma cells) without transfusion or growth factor support are allowed into the study.

108. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 (Appendix F)

109. Life expectancy of > 3 months, based on the opinion of the investigator

110. Able to swallow and retain orally administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption

111. Hepatic function, as follows:
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 x upper limit of normal (ULN)
    - Total bilirubin (TBIL) < 1.5 X ULN (except subjects with Gilbert's syndrome)
112. Cardiac function, as follows:
    - Cardiac ejection fraction ≥ 50% and no evidence of pericardial effusion as determined by an ECHO or MUGA
    - No clinically significant ECG findings.
113. Renal function as follows:
    - Calculated or measured creatinine clearance (CrCl) of ≥ 30 mL/minute calculated using the formula of Cockcroft and Gault [(140 – Age) × Mass (kg) / (72 × serum creatinine mg/dL)]. Multiply result by 0.85 if female.

Additional criteria for Part 2 - Dose Expansion subjects

114. MM subjects only

- Pathologically documented, definitively diagnosed, relapsed or refractory disease following at least 3 lines of therapy including but not limited to a proteasome inhibitor, an immunomodulatory agent and/or CD38-targeted immunochemotherapy.

  NOTE: The investigator must be of the opinion that no other treatment option will result in a durable response.

115. NHL subjects only

- Pathologically confirmed DLBCL that has demonstrated clinical or radiographic progression on at least two prior therapies

  NOTE: For subjects with refractory disease and who have received radiotherapy, PET positivity should be demonstrated no less than 6 weeks after the last dose of radiotherapy.

116. AML subjects only

- Pathologically confirmed diagnosis of AML as defined by the WHO Classification (Appendix H) persisting or recurring following no more than 2 lines of prior therapies

4.2 Exclusion Criteria

201. Previously received an allogeneic stem cell transplant within 6 months of study day 1 OR having signs or symptoms of acute or chronic graft-versus-host disease
202. Autologous stem cell transplant < 90 days prior to study day 1
203. Candidates for stem cell transplant should have failed or are not considered eligible for either allogeneic and autologous transplant

204. History of other malignancy except:
    - Malignancy treated with curative intent and with no known active disease present for ≥ 2 years before enrollment and felt to be at low risk for recurrence by the treating physician
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately treated cervical carcinoma in situ without evidence of disease
    - Adequately treated breast ductal carcinoma in situ without evidence of disease
    - Prostatic intraepithelial neoplasia without evidence of prostate cancer
    - Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ
205. Myocardial infarction within 6 months of study day 1
206. Symptomatic congestive heart failure (New York Heart Association > Class II) (Appendix F)
207. History of arterial thrombosis (eg, stroke or transient ischemic attack) in the past 6 months prior to study day 1
208. Uncontrolled active infection requiring intravenous anti-infective treatments within 1 week of study day 1
209. Known positive results for human immunodeficiency virus (HIV)
210. Active hepatitis B and C based on the following results:
    - Positive for hepatitis B surface antigen (HBsAg) (indicative of chronic hepatitis B or recent acute hepatitis B).
    - Negative HBsAg and positive for hepatitis B core antibody: hepatitis B virus DNA by polymerase chain reaction (PCR) is necessary. Detectable hepatitis B virus DNA suggests occult hepatitis B.
    - Positive Hepatitis C virus antibody (HCVAb): hepatitis C virus RNA by PCR is necessary. Detectable hepatitis C virus RNA suggests chronic hepatitis C
211. Unresolved toxicities from prior anti-tumor therapy, defined as not having resolved to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grade 1, or to levels dictated in the eligibility criteria with the exception of grade 2 peripheral neuropathy, alopecia or toxicities from prior anti-tumor therapy that are considered irreversible (defined as having been present and stable for > 4 weeks prior to study day 1 may be allowed if they are not otherwise described in the exclusion criteria AND there is agreement to allow by both the investigator and sponsor)
212. Antitumor therapy (chemotherapy, antibody therapy, molecular-targeted therapy, retinoid therapy, or investigational agent or procedures) within 14 days of day 1.
213. Prior systemic radiation therapy must have been completed at least 28 days before study day 1. Prior focal radiotherapy completed at 14 days before study day 1.

214. Males and females of reproductive potential who are unwilling to practice an acceptable method(s) of effective birth control while on study through 3 months after receiving the last dose of study drug. Acceptable methods of effective birth control include sexual abstinence (males, females); vasectomy; bilateral tubal ligation/occlusion; or a condom with spermicide (men) in combination with barrier methods (diaphragm, cervical cap, or cervical sponge), hormonal birth control or IUD (females).

    NOTE: A woman is considered of childbearing potential (WOCBP), (ie, fertile) following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

215. Females who are lactating/breastfeeding or who plan to breastfeed while on study through 3 months after receiving the last dose of study drug.

216. Females with a positive pregnancy test or planning to become pregnant while on study through 3 months after receiving the last dose of study drug.

217. Males who are unwilling to abstain from sperm donation while on study through 3 months after receiving the last dose of study drug.

218. History or evidence of any other clinically significant disorder, condition or disease that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

219. Use of any over-the-counter or prescription medications within 14 days or 5 half-lives (whichever is longer), prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor

220. Use of herbal medicines (eg, St. John’s wort), vitamins, and supplements consumed by the subject within 14 days prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor

221. Use of any known inhibitors of P-gp within 14 days or 5 half-lives (whichever is longer) or grapefruit juice or grapefruit containing products within 7 days prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor

222. Use of known cytochrome P450 (CYP) 3A4 sensitive substrates, (**with a narrow therapeutic window**), within 14 days or 5 half-lives (whichever is longer) of the drug or its major active metabolite, whichever is longer, prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor

223. Use of known P-gp substrates (**with a narrow therapeutic window**) within 14 days or 5 half-lives (whichever is longer) prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor

224. Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, long term follow-up) to the best of the subject and investigator's knowledge

225. Known sensitivity to any of the products or component to be administered during dosing

226. MM subjects with any of the following criteria are excluded:

- Multiple myeloma with IgM subtype
- POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
- Existing plasma cell leukemia
- Waldenstrom's macroglobulinemia
- Amyloidosis

227. NHL subjects with the following criteria are excluded:

- CNS lymphoma or evidence of uncontrolled CNS disease
- Burkitt's lymphoma
- Lymphoblastic lymphoma

228. AML subjects with any of the following criteria are excluded:

- Circulating white blood cells > 25,000 /µl. Hydroxyurea to control peripheral blood leukemic cell counts, within 24 hours of study day 1 is permitted.
- Promyelocitic leukemia

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the informed consent form before commencement of study-specific activities/procedures.

A subject is considered enrolled when they have met all eligibility criteria, including completing any pre-treatment safety assessment(s) prior to initial dosing on day 1. The Investigator is to document the enrollment decision and date, in the subject's medical record and in/on the enrollment eCRF.

An Amgen representative will notify the sites in writing when a cohort is open to screen new subjects. Each subject who enters into the screening period for the study (defined as the point at which the subject signs the informed consent) receives a unique subject identification number before any study procedures are performed. The subject identification number will be assigned manually. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The unique number will consist of 11 digits: digits 1 to 3 represent the last 3 digits of the protocol (eg, 173), digits 4 to 8 the country code and site number, digits 9 to 11 the subject number at the site.

Subjects who fail to meet the eligibility criteria will be allowed to rescreen once with agreement between the Amgen Medical Monitor and PI. Re-screened subjects must perform all qualifying assessments required for eligibility, including reconsenting the subject, within 21 days of their D1 visit. The subject identification number, assigned during the original screening period must remain constant throughout the entire clinical study if a subject is rescreened.

5.1 Treatment Assignment

An Amgen representative will notify the site(s) in writing when a dose cohort/group (dose escalation part) or the dose expansion part, respectively, are open to screen and enroll new subjects. The notification will include the cohort/group and dose level in which subjects will be enrolled. The treatment assignment date is to be documented in the subject's medical record and on the enrollment eCRF.

6. TREATMENT PROCEDURES

6.1 Classification of Product

The Amgen Investigational Product used in this study is AMG 397.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 397.

6.2 Investigational Product

6.2.1 Amgen Investigational Product AMG 397

AMG 397 is an oral MCL1 inhibiting agent. AMG 397 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. AMG 397 will be provided as 5 mg, 20 mg, and 100 mg tablets, and will be packaged in bottles of 15 tablets.

AMG 397 will be dispensed and administered at the research facility by qualified staff member(s).

6.2.1.1 Dosage, Administration, and Schedule

During dose escalation (Part 1), AMG 397 will be given orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle. Table 3 shows the planned dose levels for dose escalation.

During dose expansion (Part 2) AMG 397 will be given orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle. The planned dose level(s) for dose expansion will be determined based on data collected during dose escalation.

On days of hospitalization and during clinic visits, doses will be administered at the clinic. Subjects will self-administer AMG 397 on all other designated timepoints per Table 4 and Table 5 on days without clinic visits.

AMG 397 can be taken with or without food (ie, subjects may choose to eat prior to or after taking study drug). The tablet should be swallowed whole without crushing or breaking. No tablet should be ingested if it is broken, cracked, or otherwise not intact.

Subjects will be asked to record the date, time, and number of tablets consumed in a subject drug diary that must be brought to each study visit and will be reviewed by study staff. The amount dosed, lot number of IP, and start date will be recorded on each subject's eCRF(s).

The amount dispensed, amount returned, date dispensed, date returned, and lot number of AMG 397 are to be recorded in the site's drug accountability log for each subject. Please refer to the Investigational Product Instructional Manual for more details on dosage, administration and schedule of AMG 397.

If a subject develops a reaction, subjects should acutely be treated according to best clinical practice. Medication may be administered as deemed appropriate by the investigator to control any reactions according to best clinical practice. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. All medication and symptoms should be documented in the eCRF. Amgen must be notified within 24 hours when a subject has had ≥ Grade 3 AE.

The effects of overdose of this product are not known.

6.2.1.1.1 Lead-in Dosing

There is a potential for tumor lysis syndrome (TLS) in subjects affected by hematologic malignancies especially in those with bulky disease, elevated pretreatment lactate dehydrogenase (LDH) levels, elevated leukocyte count, renal dysfunction, and dehydration. To mitigate the risk of TLS, tumor lysis syndrome prophylaxis must be initiated in all subjects prior to the first dose of AMG 397 and prior to any dose escalation (Section 6.5.7).

Additionally, when an event meeting clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and Appendix L) is observed, lead-in dosing may be initiated to evaluate a step-wise dose escalation for all subsequent dosing. See Figure 2 for an example of lead-in dosing. .

The DLRT will convene to review the safety data and may determine a lead-in dose, which will not exceed the dose where the TLS was observed. Once TLS criteria is resolved, this lead-in dose will be administered for the first week of dosing (cycle 1 week 1). Upon completion of the lead-in dosing period, subject(s) will receive their designated target dose level of AMG 397 per Table 3 beginning on the second week of dosing (cycle 1 week 2) and all subsequent dosing.

> **NOTE:** Once lead-in dosing is implemented, a maximum of 50% dose escalation of AMG 397 will be imposed between dose cohort levels per Table 3 for the target dose.

Once lead-in dosing is initiated, additional monitoring of electrolyte values is required prior to dosing at the following times (see Table 4 and Table 5):

- Prior to the Week 1, Day 1 Dose
- Prior to each dose during the Lead-in Period
- Prior to the initial dosing at the target dose level

Prior to administering AMG 397, all electrolyte values (ie, potassium, uric acid, inorganic phosphorus, calcium) must be within normal range.

> **NOTE:** Laboratory value changes must be confirmed by another laboratory test (1-2 hours later) prior to assigning a TLS grade.

Dose Adjustments for Lead-In Dosing

Evidence of TLS will be carefully monitored on study and AMG 397 will be held until resolution of TLS abnormalities. Following lead-in dosing of AMG 397, if one or more

Cairo-Bishop criteria is met (See Appendix K and Appendix L), no additional AMG 397 doses will be administered until it is resolved (eg, laboratory values are no longer within range of the values stated in Appendix K and Appendix L). Upon resolution, the subject will repeat the lead-in dosing for an additional week prior to receiving the target dose.

> **NOTE:** Lead-in dosing will be repeated if the subject is observed to meet one or more of the Cairo-Bishop criteria post-dose.

Decisions to modify the AMG 397 lead-in dosing period regimen, lead-in period starting dose, and dosing increments, will be made in conjunction with the investigator and Amgen medical monitor and communicated to the IRB/EC, as appropriate.

6.2.1.2 Dose-cohort Study Escalation and Stopping Rules

The Dose Level Review Team (DLRT) will convene before decisions to dose escalate or de-escalate is made or when cohorts are suspended per protocol. The DLRT will be composed of select Investigator(s), Amgen medical monitor, Amgen Global Safety Officer or designee, Amgen Clinical Research Study Manager (CRSM) and Biostatistics representative or designee. Additional members may be added as needed (eg, clinical pharmacologist). The DLRT voting members include the Amgen Medical Monitor and Global Safety Officer or designee, in consultation with the investigator(s) or designee. The DLRT members are responsible for dosing decisions, which may include escalation to the next nominal or intermediate dose, de-escalation to a lower nominal or intermediate dose; alternative dose frequencies, continuation, delay or termination of dosing; or repetition or expansion of a cohort; implementation of lead-in dosing, or determination of RP2D. See Section 3.1 for more details regarding the study design and the dose escalation plan for this study.

The DLT-observation period is defined as, at minimum, 28 days after the initial dose of AMG 397. Once 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.

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
- Experienced a DLT

Available study data, including data collected after the initial DLT-observation period along with demographics, IP administration, medical history, concomitant medications,

adverse events (AE), ECG, vital signs, laboratory results and PK/PD information will be reviewed. In addition to DLTs, all ≥ grade 3 toxicities not meeting DLT criteria will be reviewed and may be considered in DLRT decisions. Modeling of available potential safety risk data (eg, for thrombocytopenia) to predict safety risk for dose escalation decisions may also be considered.

Dose escalation/de-escalation decisions will be guided by the BLRM model of dose toxicity described by Appendix D. An Amgen representative will notify the sites in writing the dosing decision from the DLRM and when a cohort is open to screen new subjects.

DLTs experienced by subjects after completing the DLT period will be considered in the BLRM design to account for any late onset toxicity.

Dose escalation for each group will continue until any of the following events occur:

- The highest planned dose level is determined to be safe and tolerable (minimum of 6 evaluable subjects)
- MTDs are identified for each group where BLRM repeats the recommendation of a dose level (minimum of 6 evaluable subjects)
- The maximum of 30 evaluable subjects have been enrolled in each group. If fewer than 6 subjects are treated at the MTD/RP2D, additional subjects may be enrolled to confirm safety and tolerability.

If there are concerns about the tolerability of the current dosing schedule, alternative dosing schedules or lower dose(s) may be explored, including modification of the lead-in period dosing regimen. The alternative dose and schedule will be jointly determined by the investigators and the Amgen medical monitor, based on pharmacokinetic and safety and toxicity data.

6.2.1.3 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

NOTE: For subjects who meet clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and Appendix L) see Section 6.2.1.1.1 for dose adjustment details.

Dosage Adjustments

The subject should continue on the same dose of AMG 397 throughout the study unless the following events occur:

- For subjects experiencing an adverse event meeting the DLT definition or intolerable related adverse events BUT showing evidence of response, there will be an option to reduce the dose to the immediate next lower dose level shown to be safe and tolerable in the dose escalation part of the study.
- AMG 397 can be resumed once the adverse events recover to baseline or Grade 1 and the reintroduction of AMG 397 is deemed safe by the Investigator, Amgen's Medical Monitor, and Global Safety Officer.

NOTE: Subjects must be informed of the risk of continuing on therapy. Each subject is only allowed a single dose reduction.

Subjects should not be re-challenged with AMG 397 if the following AMG 397-related adverse events occur:

- Any life-threatening adverse events
- DILI (Drug Induced Liver Injury) meeting Hy's law
- Persistent grade 3 adverse events that do not recover to baseline or Grade 1 within 4 weeks of last dose
- Any treatment-related adverse event meeting DLT-criteria that recurs

Dosage Delays

The investigator should inform the Amgen Clinical team as soon as the unexpected dosage delay occurs. The following dosage delay rules apply:

- If the dosing delay is ≤ 3 weeks, the subject should resume the treatment as soon as possible if deemed safe by the investigator.
- If the dosing delay is more than 4 weeks (missing 1 cycle):
  - Due to treatment related AEs, the subject will be removed from the study.
  - Due to other conditions other than treatment related AEs, the case will be reviewed by Amgen medical monitor to determine whether the subject will be allowed to resume AMG 397 treatment.

Rules for Dose Withholding

AMG 397 should be withheld for any of the following:

- Suspected DLT (including AEs that meet DLT definition outside DLT-observation period)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 x ULN or total bilirubin greater than 1.5 x ULN

Rules for Restarting

AMG 397 dosing can be resumed:

- If the toxicities resolve to grade ≤ 1 or return to subjects' baseline values
- Restarting of therapy is deemed safe by the investigators and Amgen's medical monitor.

Rules for Permanent Discontinuation

Subjects will permanently discontinue from the investigational product if:

- Subjects experience adverse events meeting the DLT criteria at any time. Subjects will be followed until the DLT is resolved, returns to baseline value or is considered stable. Subjects will be withdrawn from AMG 397 treatment and will be treated as deemed appropriate by the investigator or treating physician. Except for:
  - Subjects showing evidence of response or subjects who in the opinion of the investigator may be responding to AMG 397, may have the option to continue therapy once the adverse events recover to baseline or Grade 1 and the re-introduction of AMG 397 is deemed safe by the investigator, Amgen's medical monitor, and Global Safety Officer. The subject should restart at a reduced dose.
  - Subjects who experience TLS as detail, see Section 6.2.1.1.1 for dosing details.
- Intolerability of the study treatment
- The dosing is delayed > 4 weeks due to AMG 397-related adverse events
- Disease progression according to IMWG (MM), Lugano classification (NHL), or 2017 ELN response criteria (AML) and/or per institutional guidelines as applicable
- Clinical significant deterioration of health status
- Withdrawal of informed consent
- Subject becomes pregnant or is breastfeeding
- Initiation of new systemic anti-cancer therapy not provided in this study
- Study is terminated by the sponsor.

6.2.1.4 Dose Stopping Rules

Please refer to Section 10.4 for dose stopping rules.

6.3 Other Protocol Required Therapies

6.3.1 Pre-dosing requirements for AMG 397

To mitigate risk of TLS, all subjects are to receive TLS prophylaxis prior to first dose of AMG 397 and prior to any dose escalation. Refer to Section 6.5.7 for specific requirements.

6.4 Dose Limiting Toxicities

The grading of adverse events will be based on the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (available online at http://evs.nci.nih.gov/ftp1/CTCAE/About.html). Determination of the severity of adverse events will be consistent with Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

For MM and NHL subjects only:

A DLT is defined as a treatment-related AE(s), that occur during the DLT-observation period (see Section 6.2.1.2) including any:

- ≥ Grade 3 non-hematological AE's **EXCEPT**:
  - ≥ Grade 3 fatigue if <7 days
  - Grade 3 nausea, vomiting and/or diarrhea if < 3 days and controlled with medical management
  - Laboratory parameters of grade ≥ 3 that improve with medical management to grade ≤ 2 within 3 days
- ≥ Grade 4 hematologic AE's AND:
  - ≥ Grade 3 neutropenia with fever
  - ≥ Grade 3 thrombocytopenia with Grade ≥ 2 hemorrhage
  - ≥ Grade 3 anemia with symptoms requiring intervention (eg, transfusion)

  NOTE: ≥ Grade 4 neutropenia must be lasting > 7 days
- Any grade 5 AE that is not clearly due to disease progression

For AML subjects only:

Due to the nature of AML, hematologic adverse events will not be considered DLTs. However, prolonged pancytopenia in the presence of a hypocellular bone marrow (ie, cellularity 5% or less without evidence of leukemia) that lasts longer than 42 days will be considered dose-limiting myelosuppression.

Non-hematological toxicity:

- ≥ Grade 3 nausea, vomiting or diarrhea persisting more than 3 days despite optimal medical support
- ≥ Grade 3 fatigue persisting > 7 days
- Any other ≥ Grade 3 adverse event
- Failure to recover from AMG 397 related toxicities to grade ≤ 1 or baseline severity after delaying next cycle up to 14 days

For all subjects:

- Any Clinical TLS (refer to Appendix K)

If a DLT of TLS is observed during the lead-in period, it will be attributed to the lead-in period and a modification may be made to the lead-in period regimen for subsequent cohorts. Any other DLTs observed during the lead-in and/or designated cohort dosing period may require a modification of the designated cohort dose (and/or lead-in period regimen, if appropriate) as directed per the Dose Escalation Guidelines.

Any subject meeting the criteria for Hy's Law case (ie, severe drug-induced liver injury) will be considered a DLT. A Hy's Law case is defined as: AST or ALT values of ≥ 3x ULN AND with serum total bilirubin level (TBL) of > 2x ULN without signs of cholestasis and with no other clear alternative reason to explain the observed liver-related laboratory abnormalities (see Section 6.7 for hepatotoxicity management and Appendix A for further explanation of Hy's law case and Management of Hepatic Function). Grade 3 or 4 elevation of serum lipase without clinical signs or symptoms of pancreatitis.

6.5 Potential Risk Management Guidelines for AMG 397

6.5.1 Gastrointestinal Toxicity

Evidence of gastrointestinal toxicity will be monitored in the FIH study through clinical evaluations, safety laboratory tests, stopping rules, and associated adverse events.

Management should be tailored to the appropriate treatment according to the local standard of care and institutional guidelines.

6.5.2 Bone Marrow Toxicity

Monitoring of vital signs, hematology parameters and associated adverse events will be conducted in the FIH study. Specific eligibility criteria, stopping rules and dose-hold rules, pertaining to hematology parameters, are provided in Section 6.2.1.3.

6.5.3 Reproductive Toxicity- Male

Men of reproductive potential who are unwilling to practice an acceptable method of effective birth control will be excluded from the study. See section 4.2 for list of acceptable methods of effective birth control.

6.5.4 Drug-drug interactions

A list of prohibited drugs as well as subject exclusion criteria are included in the protocol. Subjects receiving any of the drugs cited in the exclusion criteria and/or prohibited drugs as listed in the FIH protocol will be excluded from this study. Caution should be exercised when administering AMG 397 with drugs that have a narrow therapeutic window and prescribing information that includes contraindications, warnings or precautions related to their use with known inhibitors of CYP34A and P-gp.

6.5.5 Hepatobiliary Toxicity

Evidence of hepatobiliary toxicity will be monitored as outlined in the study protocol through clinical evaluations, safety laboratory tests, stopping rules, and associated adverse events.

6.5.6 Cardiovascular Toxicity

Adverse events associated with cardiac function will be monitored through blood pressure, heart rate, echocardiogram, and ECG measurements. Subsequent withholding rules, as outlined in the study protocol, will be followed.

6.5.7 Tumor Lysis Syndrome (TLS)

Prophylaxis and Management of TLS

Tumor lysis syndrome prophylaxis must be initiated in all subjects prior to the first dose of AMG 397 and prior to every dose escalation.

The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be conducted per institutional protocols (Coiffier et al, 2008; Cairo et al, 2004).

- Initiate allopurinol or equivalent to reduce uric acid level. This should be initiated at least 72 hours prior to dosing. Treatment may need to be continued for up to 5 weeks. Other agents to reduce uric acid level, such as rasburicase may be used per PI discretion. Dosing per institutional guidelines.
- All subjects will be hospitalized for intensive monitoring:
  - For the first 2 doses received, beginning 24 hours prior to first dosing day (Day -1) until 24 hours post the second dose
  - Once lead-in dosing is initiated (see Section 6.2.1.1.1):
    - For the first 2 doses received (Lead-in dosing), beginning at least 24 hours prior to first dosing day (Day -1) until 24 hours post the second dose
    - Each time an additional week of lead-in dosing is instituted (Section 6.2.1.1.1)
    - For the first 2 doses received after the dose is escalated (target dose) beginning at least 24 hours prior to dosing day (usually day 7) until 24 hours post the second dose
- During hospitalization, intensive safety laboratory monitoring per designated timepoints per Table 4 and/or Table 5 to identify and prompt management of any metabolic changes.
  - Pre-treatment serum chemistry and hematology laboratory samples must be drawn within 24 hours prior to first dose, and electrolyte values (ie, potassium, uric acid, inorganic phosphorus, calcium) must be reviewed and within normal range prior to AMG 397 dosing. The investigator's decision to proceed with AMG 397 treatment initiation may be based on these laboratory values. These labs must be reviewed in real time by the investigator.

    NOTE: If the potassium, uric acid, inorganic phosphate and/or creatinine values are higher than the normal range or the calcium is lower or higher than the normal range, dosing can be resumed following review of

laboratory values and agreement between the Amgen medical monitor and investigator.

- Prophylactic reductions of potassium, inorganic phosphorus and/or uric acid above of normal range prior to dosing are recommended per PI discretion.
- Day 2 dosing of AMG 397 should not be administered until the 24 hours post-dose laboratory values are reviewed by the investigator.
- All 24-hour laboratory assessments may be taken ± 2 hours, if necessary.

- Within the first 24 hours after either the first dose or dose escalation, if any laboratory criteria (Appendix L) are met, no additional AMG 397 doses should be administered until resolution. A rapidly rising serum potassium is a medical emergency.
- Upon admission, IV fluids (eg, D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs and as needed per Investigator discretion.
- Monitor for signs and symptoms of TLS (eg, fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour.
- Nephrology (or other acute dialysis service) consultation should be considered upon admission per institutional standards at investigators' discretion to ensure emergency dialysis is available and the appropriate staff is aware and prepared.
- Management recommendations of laboratory abnormalities as stated below:

Abnormality	Management Recommendations[1,2]
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. • At discretion of Investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the Investigator. Potassium, phosphorus, uric acid, calcium and creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology notification with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. ○ If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis.

Abnormality	Management Recommendations[1,2]
Hyperkalemia (including rapidly rising potassium) (continued)	
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq/kg IV push. ○ If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes). ○ If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	• Administer rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes). ○ When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Consult nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.

Abnormality	Management Recommendations[1,2]
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 to 2 hours STAT.

6.6 Support Care Guidelines for AMG 397

6.6.1 Management of Infections

Subjects with evidence of existing infection should be closely monitored while being treated with AMG 397. Subjects with active systemic infections requiring IV antibiotics, antivirals, or antifungals should not be dosed with AMG 397 until infection per exclusion criteria in Section 4.2. Management should be tailored to the appropriate prophylaxis and/or treatment for the underlying infection according to the local standard of care and institutional guidelines.

Subjects who may experience neutropenia are at a high risk for infectious complications. As appropriate, these subjects should be administered prophylactic antibacterial (treatment with ciprofloxacin) and antifungal (treatment with posaconazole).

These subjects should be monitored for early signs of breakthrough infections after the initiation of antibacterial therapy to prompt additional evaluation and possible therapy modification. Subjects experiencing diarrhea should be closely monitored for their electrolyte levels.

6.6.2 Management of Renal Toxicities

Renal dysfunction is one of the multiple myeloma-related organ/tissue dysfunction. Renal function must be monitored closely during treatment with AMG 397. Serum chemistry values, including BUN, serum creatinine, and urine for urinalysis and microscopic exam (microscopic exam only needed for positive dipstick), must be obtained per the schedule of assessments (see Table 4). Management should be tailored to the appropriate treatment for the underlying renal disorder according to the local standard of care and institutional guidelines.

6.7 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (eg, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBIL]) or international normalized ratio [INR]) or signs/symptoms of hepatitis may meet the criteria for withholding of investigational product. Withholding is either permanent or conditional depending upon the clinical circumstances discussed below (as specified in the FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009).

6.7.1 Criteria for Permanent Withholding of AMG 397 due to Potential Hepatotoxicity

AMG 397 should be permanently withheld and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- Increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT value	*AST or ALT elevation*
< ULN	*> 3x ULN*

AND

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

AND

- No other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or elevated TBIL values include, but are not limited to:
    - Hepatobilliary tract disease
    - Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, Cytomegalovirus, Herpes Simplex Virus, Varicella, Toxoplasmosis, and Parvovirus)
    - Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
    - Exposure to hepatotoxic agents/drugs including herbal and dietary supplements, plants, and mushrooms,
    - Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
    - Alpha-one antitrypsin deficiency
    - Alcoholic hepatitis
    - Autoimmune hepatitis
    - Wilson's disease and hemochromatosis
    - Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
    - Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

6.7.2 Criteria for Conditional Withholding of AMG 397 due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of AMG 397 outlined above and have no underlying liver disease and eligibility criteria requiring normal transaminases and TBIL at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of Amgen investigational product and other protocol-required therapies:

Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	> 8x ULN at any time
Any	> 5x ULN but < 8x ULN for ≥ 2 weeks
Any	> 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule
Any	> 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice.

- OR: TBIL > 3x ULN at any time
- OR: ALP > 8x ULN at any time

AMG 397 should be withheld pending investigation into alternative causes of DILI. If investigational product(s) is withheld, the subject should be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBIL, is discovered and the laboratory abnormalities resolve to normal or baseline.

6.7.3 Criteria for Rechallenge of AMG 397 After Potential Hepatotoxicity

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, Principal Investigator, and Amgen.

If signs or symptoms recur with rechallenge, then AMG 397 should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.2.1.3) should not be rechallenged. If signs or symptoms recur with rechallenge, then AMG 397 should be permanently discontinued.

6.8 Concomitant Therapy

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.10

Concomitant therapies are to be collected from screening start through the EOS visit. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter, herbal supplements, and IV medications, transfusions and fluids.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, G-CSF and other care as deemed appropriate, and in accordance with their institutional guidelines. For subjects with AML hydroxyurea for 7 days at a dose of 1 – 10 g/day is allowed prior to the first cycle of AMG 397 treatment for subjects with high WBC (> 25,000 cells/ul) and during the first cycle but not on dosing days at a dose of up to 5 g/day.

For all concomitant medication collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

6.9 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or

clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s), device(s), or combination product(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.10 Excluded Treatments and Procedures During Study Period

The following medications and/or therapies should not be administered during the study:

- Allogeneic stem cell transplant
- Autologous stem cell transplant
- Antitumor therapy (chemotherapy, antibody therapy, molecular-targeted therapy, retinoid therapy, or investigational agent or procedures)
- Systemic or focal radiotherapy
- Over-the-counter medication(s) that was not reviewed and approved by the principal investigator and the Amgen medical monitor
- Any known inhibitors of P-gp or grapefruit juice or grapefruit containing products that were not reviewed and approved by the principal investigator and the Amgen medical monitor
- Herbal medicines (eg, St. John's wort), vitamins, and supplements that were not reviewed and approved by the principal investigator and the Amgen medical monitor
- Any known cytochrome P450 (CYP) 3A4 sensitive substrates, with a narrow therapeutic window, that were not reviewed and approved by the principal investigator and the Amgen medical monitor

If use of any other prior or concomitant medication or procedure is in question, please refer to prescribing information and/or consult with Amgen Medical Team.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Please refer to Table 4 for Schedule of Assessments.

Once lead-in dosing is initiated follow Table 5 for Cycle 1 only. For all subsequent cycles and study periods follow Table 4.

Table 4. Schedule of Assessments

	SCREENING	TREATMENT																															EOT	SAFETY FOLLOW-UP	LTFU (26)
CYCLE(S)			1																										2			Every cycle from 3 & beyond			
WEEK(S)			1																2					3		1	2	3	1					
DAY(S)	-21 to -2	-1	1								2							3	4	8					15	22	1	8	15	1				
HOUR(S) (relative to time of dosing)			Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D2 dose	48h after D2 dose	Pre	0	2	3	5	Pre-dose unless specified									
Informed consent	X																																		
Clinical evaluation (1)	X	X	X								X								X	X	X					X	X	X	X	X	X	X	X	X	
Vital signs (T, BP, HR, RR)	X	X	X				X	X	X	X	X				X	X	X	X	X	X	X					X	X	X	X	X	X	X	X	X	
12-lead ECG (2)	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Echocardiogram or MUGA	X																																X		
Hospitalization (3)		←								→																									
TLS prophylaxis (4)		X																																	
AMG 397 Dosing (5)				X								X										X				AMG 397 is taken orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle									
Dosing diary review (5)											X							X		X					X	X	X	X	X	X	X	X		
AE Reporting					→																														
SAE Reporting	→																																		
Prior /concomitant medication(s)	→																																		

Footnotes are defined at the end of Table 5

Table 4. Schedule of Assessments

	SCREENING	TREATMENT																																					EOT	SAFETY FOLLOW-UP	LTFU (26)
CYCLE(S)			1																													2				Every cycle from 3 & beyond			
WEEK(S)			1																		2							3		1				1				EOT	SAFETY FOLLOW-UP	LTFU (26)
DAY(S)	-21 to -2	-1	1								2								3	4	8							15	22	1			8			15	1	EOT	SAFETY FOLLOW-UP	LTFU (26)
HOUR(S) (relative to time of dosing)			Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D2 dose	48h after D2 dose	Pre	0	2	3	5	Pre-dose unless specified											EOT	SAFETY FOLLOW-UP	LTFU (26)
Survival/Subsequent anti-cancer therapy (6)																																								X
LAB ASSESSMENTS																																								
AMG 397 PK (7)			X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X							X				X		
CBC with diff (8)	X	X	X								X								X	X	X					X	X	X	X	X	X				X	X	
Chemistry (9)	X	X	X				X		X	X	X				X		X	X	X	X	X					X	X	X	X	X	X				X	X	
Coagulation	X	X	X								X								X	X	X					X	X	X	X	X	X				X	X	
Pregnancy test (10)	X		X																										X			X			X	X		
Urine sample collection (11)	X		X					X			X						X				X				X				X			X						
Hepatitis serology, HIV	X																																						

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Footnotes are defined at the end of Table 5

Table 4. Schedule of Assessments

	SCREENING	TREATMENT																														EOT	SAFETY FOLLOW-UP	LTFU (26)
CYCLE(S)			1																									2			Every cycle from 3 & beyond			
WEEK(S)			1															2				3		1		2		3	1			
DAY(S)	-21 to -2	-1	1								2							3	4	8			15	22	1		8		15	1			
HOUR(S) (relative to time of dosing)			Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D2 dose	48h after D2 dose	Pre	0	2	3	5	Pre-dose unless specified								
BIOMARKER and DISEASE ASSESSMENTS																																		
Bone marrow aspirate (12)	X																																	
Whole blood Na/Hep (13)			X				X	X			X																							
Whole blood Cytochex (14)			X								X								X	X	X													
Plasma	X																																	
Serum	X																																	
Cell Pellet	X																																	
MM SUBJECTS ONLY																																		
SPEP/UPEP/ Immunofixation (15)	X																												X			X	X	
SFLC (16)	X																												X			X	X	
Beta-2 microglobulin	X																																X	
Quantitative Ig (17)	X																																X	

Footnotes are defined at the end of Table 5

Table 4. Schedule of Assessments

	SCREENING	TREATMENT																														EOT	SAFETY FOLLOW-UP	LTFU (26)
CYCLE(S)			1																									2			Every cycle from 3 & beyond			
WEEK(S)			1														2							3		1	2	3	1				
DAY(S)	-21 to -2	-1	1							2							3	4	8					15	22	1	8	15	1				
HOUR(S) (relative to time of dosing)			Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D2 dose	48h after D2 dose	Pre	0	2	3	5	Pre-dose unless specified								
Bone marrow biopsy	X																																	
Bone marrow aspirate (18)		---------- Repeat collection in case of CR ----------																																
Plasmacytoma (19)	X																																	
Skeletal survey (20)	X																																	
NHL SUBJECTS ONLY																																		
Lymph Node Biopsy	X																																	
Whole blood plasma **(Dose expansion only)** (21)	X																									X			X (21)	X			
Bone marrow biopsy (22)	X																																	
PET-CT and CECT Imaging (23)	X																									X			X (23)	X			
MRI Brain (24)	X																																	
AML SUBJECTS ONLY																																		
Bone marrow aspirate (25)																										X			X (25)	X			

Footnotes are defined at the end of Table 5

Table 5. Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)

CYCLE			**CYCLE 1 ONLY**																																					
DAY(S)	**-21 to -2**	**-1**	**1**								**2**								**3**	**4**	**7**	**8**								**9**								**10**	**11**	**15**	**22**
HOUR(S) (relative to time of dosing)			**Pre-dose**	**0**	**1**	**2**	**3**	**5**	**8**	**12**	**Pre-dose**	**0**	**1**	**2**	**3**	**5**	**8**	**12**	**24h after D2 dose**	**48h after D2 dose**		**Pre-dose**	**0**	**1**	**2**	**3**	**5**	**8**	**12**	**Pre-dose**	**0**	**1**	**2**	**3**	**5**	**8**	**12**	**24h after D9 dose**	**48h after D9 dose**		
Informed consent	X																																								
Clinical evaluation (1)	X	X	X								X								X	X	X	X								X								X	X	X	X
Vital signs (T, BP, HR, RR)	X	X	X				X	X	X	X	X				X	X	X	X	X	X	X					X	X	X	X	X				X	X	X	X	X	X	X	X
12-lead ECG (2)	X	X	X (2)		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Echocardiogram or MUGA	X																																								
Hospitalization (3)		←															→				←															→					
TLS prophylaxis (4)		X																			X																				
AMG 397 dosing (5)				X								X											X								X									X (5)	
Dosing diary review (5)											X										X																	X		X	X
AE Reporting							←																															→			
SAE Reporting			←																																			→			
Prior /concomitant medication(s)		←																																				→			

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Footnotes are defined at the end of Table 5

Table 5. Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)

CYCLE				CYCLE 1 ONLY																																					
DAY(S)	-21 to -2	-1	1								2								3	4	7	8								9								10	11	15	22
HOUR(S) (relative to time of dosing)			Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D2 dose	48h after D2 dose		Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D9 dose	48h after D9 dose		
LAB ASSESSMENTS																																									
AMG 397 PK (7)			X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		
CBC with diff (8)	X	X	X								X								X	X	X	X								X								X	X	X	X
Chemistry (9)	X	X	X				X		X	X	X				X		X	X	X	X	X	X				X		X	X	X				X		X	X	X	X	X	X
Coagulation	X	X	X								X								X	X	X	X								X								X	X	X	X
Pregnancy test (10)	X		X																																						
Urine sample collection (11)	X		X						X		X						X					X						X		X						X					
Hepatitis serology, HIV	X																																								
BIOMARKER and DISEASE ASSESSMENTS																																									
Bone marrow aspirate (12)	X																																								
Whole blood Na/Hep (13)			X				X	X			X											X				X	X			X											
Whole blood Cytochex (14)			X								X								X	X		X								X								X		X	
Plasma	X																																								
Serum	X																																								
Cell Pellet	X																																								

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Footnotes are defined at the end of Table 5

Table 5. Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)

CYCLE			CYCLE 1 ONLY																																						
DAY(S)	-21 to -2	-1	1								2								3	4	7	8								9								10	11	15	22
HOUR(S) (relative to time of dosing)			Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D2 dose	48h after D2 dose		Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D9 dose	48h after D9 dose		
BIOMARKER and DISEASE ASSESSMENTS																																									
<u>MM SUBJECTS ONLY</u>																																									
SPEP/UPEP/ Immunofixation (15)	X																																								
SFLC (16)	X																																								
Beta-2 microglobulin	X																																								
Quantitative Ig (17)	X																																								
Bone marrow biopsy	X																																								
Plasmacytoma (19)	X																																								
Skeletal survey (20)	X																																								

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Footnotes are defined at the end of Table 5

Table 5. Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)

CYCLE				CYCLE 1 ONLY																																					
DAY(S)	**-21 to -2**	**-1**	**1**								**2**								**3**	**4**	**7**	**8**								**9**								**10**	**11**	**15**	**22**
HOUR(S) (relative to time of dosing)			**Pre-dose**	**0**	**1**	**2**	**3**	**5**	**8**	**12**	**Pre-dose**	**0**	**1**	**2**	**3**	**5**	**8**	**12**	**24h after D2 dose**	**48h after D2 dose**		**Pre-dose**	**0**	**1**	**2**	**3**	**5**	**8**	**12**	**Pre-dose**	**0**	**1**	**2**	**3**	**5**	**8**	**12**	**24h after D9 dose**	**48h after D9 dose**		
<u>NHL SUBJECTS ONLY</u>																																									
Lymph Node Biopsy	X																																								
Whole blood plasma **(Dose expansion only)** (21)	X																																								
Bone marrow biopsy (22)	X																																								
PET-CT and CECT Imaging (23)	X																																								
MRI Brain (24)	X																																								

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Footnotes are defined at the end of Table 5

Footnotes for Table 4 and Table 5	
1	Clinical evaluations will be collected pre-dose on dosing days and include: physical exam, ECOG status, and weight. Medical and surgical history, and height need only be collected at the screening visit.
2	• Three baseline ECGs (pre-dose on day 1) will be collected approximately ≥ 15 minutes apart (+/- 5 minutes), with each baseline ECG in triplicate run consecutively (ie, < 30 seconds apart); Total of 9 ECGs] • Triplicate ECGs run consecutively (ie, < 30 seconds apart) , at time points designated in the schedule of assessments
3	• See Section 6.5.7 for more details regarding hospitalization for TLS prophylaxis • Hospitalization for the purpose of TLS prophylaxis will not be captured as an SAE.
4	• See Section 6.5.7 for more details regarding TLS prophylaxis.
5	• See Section 6.2.1.1 for details regarding dosage, administration, and schedule. • See Section 6.2.1.1.1 and Table 5 for details regarding dosage, administration, and schedule once lead-in dosing is implemented.
6	For Dose Expansion subjects only: o Collected during LTFU period
7	• For PK collections on Cycle 1, PK samples should be collected within +/- 15 min of the designated time points. • PK samples should be collected at the exact nominal time point as noted. If unable to collect a PK sample at the specified nominal time point collect it as close as possible and record the actual collection time in the eCRF. **Note: It is important to document the exact date and time of IP administration and PK collection.**
8	Refer to Section 7.2.15 for list CBC lab tests required. **Note: Subjects with a Grade 4 neutropenia should have their counts repeated every 24-48 hours until return to baseline and the use of G-CSF should be considered.**
9	• Refer to Section 7.2.15 for list Chemistry panel lab tests required. • See Section 6.5.7 for chemistry lab tests required for TLS prophylaxis and management
10	Serum pregnancy test performed at screening; urine or serum pregnancy test at all other timepoints for females of childbearing potential.
11	• Please collect urine for UA, which is done per local lab. • Any remaining urine will be sent to the central lab for analysis. Please refer to lab manual for preparation and transport procedures. • On cycle 1, day 1, collect urine sample at least 5 hours post-dose of AMG 397. • After cycle 1, urine sample may be collected at the following designated timepoints.
12	A bone marrow aspirate will be collected from all subjects during screening for IHC testing, to quantify percent tumor involvement, for fluorescent in situ hybridization (FISH) and other biomarker assays.
13	• Biomarker NaHep whole blood samples will be collected pre-dose on Cycle 1 day 1, 3 and 5 hours post dose on day 1, and 24 hours after day 1 during week 1 as indicated in Table 4. • Upon commencement of Lead-In dosing, additional samples will be collected indicated in Table 5 as follows: In the second week of Cycle 1, samples will be collected pre-dose on day 8, 3 and 5 hours post dose on day 8, and 24 hours after day 8.
14	• Biomarker Cytochex whole blood samples will be collected pre-dose on days 1, 2, 3, 4, and 8 as indicated in Table 4. • Upon commencement of Lead-In dosing, additional samples will be collected indicated in Table 5 as follow: pre-dose on days 9, 10, and 15.

For MM subjects only [15-20]:	
15	• Serum protein electrophoresis (SPEP) and 24-hour urine protein electrophoresis (UPEP) is required for all subjects at screening. • Thereafter, SPEP is to be done at each time point for all patients as indicated in the schedule of assessment. • UPEP with 24-hour urine collection is required at each time point only if screening UPEP shows measurable paraprotein in the urine. If screening UPEP is negative, spot urine is required at each time point. • If positive for paraprotein, a 24-hour urine collection with UPEP must be done at the next assessment and at each subsequent assessment unless the UPEP shows an absence of paraprotein. Immunofixation is required at next assessment only if SPEP or UPEP results are zero/undetectable. • See lab manual for collection and shipment details.
16	Serum free light chain (SFLC) assay and ratio will be performed at each marked time point.
17	Quantitative Immunoglobulin (Total IgG, IgA, IgM) obtained at screening and will be repeated only if clinically indicated (ie; frequent infection despite multiple myeloma disease control).
18	Additional bone marrow samples are to be collected to confirm CRs as well as for MRD biomarker analysis. Additional samples may be obtained every six months after CR and/or at time of relapse.
19	Plamacytoma survey • For subjects without a history of extramedullary disease, assessment by physical examination at screening is acceptable. • Plasmacytoma evaluation is to be repeated during treatment only to confirm a response of PR or better, to confirm PD, or if clinically indicated. If clinically indicated due to history of extramedullary disease, the same technique (may include ultrasound, x-ray, CT scan, MRI, PET, or other standard-of-care method) must be employed for each measurement.
20	Skeletal survey to be repeated Q8W if clinically indicated ie; new symptoms (bone pain) arises, consider obtaining MRI for subjects with bone pain but skeletal survey is normal.
NHL (subjects only [21-24]:	
21	**For dose expansion subjects only:** • Whole blood plasma may be obtained pre-dose on day 1 of Cycle 2, and every 8 weeks thereafter, and EOT. Samples must be collected, processed, and frozen within 4 hours of phlebotomy and per the laboratory manual. • Additional whole blood plasma samples are obtained at time of relapse.
22	Bone marrow evaluation (core biopsy with or without aspirate) may be performed if there has been previous histologic evidence of bone marrow involvement. An optional tumor biopsy may be collected at time of relapse per institutional guidelines at PI discretion.
23	PET-CT and CECT Imaging with time points at screening, Cycle 2, every 8 weeks thereafter, and EOT. If not acquired on the same day, every effort should be made to complete PET-CT and CECT within 3 days of each other.
24	For Both Part 1 (dose escalation) and Part 2 (dose expansion), all NHL subjects must have MRI/CT of the brain performed within 21 days prior to enrollment. All brain scans on protocol are required to be MRI unless MRI is contraindicated, and then CT with contrast is acceptable. Subsequently, MRI brain can be performed at any time if clinically indicated per standard of care.
25	**For AML Subjects only [25]:** • Bone marrow samples **must** be obtained at **pre-dose on day 1 of Cycle 2, every 8 weeks thereafter, and EOT**. • Additional bone marrow sampling may occur at other time points at the PI's discretion as clinically indicated throughout course of treatment
26	**For Dose Expansion subjects only:** Long-term follow up (LTFU) will be conducted every 3 months from the last visit for up to 1 year from the first dose of AMG 397 for all subjects who have not withdrawn consent by telephone or chart review to assess for survival, disease progression and/or the commencement of subsequent cancer therapy only.

7.2 Study Procedures

A signed and dated IRB-approved informed consent must be obtained before any study specific procedures are performed. All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the study.

For more information regarding subject enrollment, refer to Section 5.

7.2.1 Medical History

The Investigator or designee will collect a complete medical and surgical history that started at least 2 years prior to enrollment through the through first dose of AMG 397. Medical history will include information on the subject's concurrent medical health conditions, relevant past medical conditions, and surgical history. Record all findings on the medical history eCRF.

Relevant medical history, including antecedent hematologic or oncologic disease, other diseases/symptoms such as fatigue, bleeding and infection (resolved and ongoing) will be collected. The current toxicity grade will be collected for each condition that has not resolved.

7.2.2 Prior Therapy

The Investigator or designee will collect relevant prior therapy, which includes previous chemotherapy, radiotherapy, investigational drug, and any anticancer therapies (eg, stem cell transplant). Prior therapies that were being taken prior to enrollment through the first dose of IP should be collected.

Record all findings on the prior therapy eCRF.

7.2.3 Physical Examinations

A complete physical examination will be performed by the investigator or designee according to local practices at screening and time points specified in the Schedule of Assessments (Section 7.1).

7.2.4 Height Measurements

Height (cm) will be measured without shoes at screening.

7.2.5 Weight Measurements

Weight (kg) without shoes will be obtained at screening and time points specified in the Schedule of Assessments (see Section 7.1)

7.2.6 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure (BP), respiratory rate, heart rate and temperature. Subject must be in rested and calm state for at least 5 minutes before BP assessments are conducted. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign eCRF. Record all measurements on the vital signs eCRF.

The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs/temperature eCRF. Vital signs will be recorded by the investigator or qualified site personnel at screening and time points specified in the Schedule of Assessments (see Section 7.1).

Abnormal measurements may be repeated at the discretion of the investigator and must be reported on the corresponding eCRF page. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn.

7.2.7 Electrocardiogram Performed in Triplicate

The subject should rest for at least 5 minutes before ECG assessment is conducted. Electrocardiograms should be performed in a standardized method, in triplicate (at designated time points), and run consecutively, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

Electrocardiograms will be performed as follows:

- Three baseline ECGs (pre-dose on day 1) will be collected approximately ≥ 15 minutes apart (+/- 5 minutes), with each baseline ECG in triplicate run consecutively (ie, < 30 seconds apart); Total of 9 ECGs]
- Triplicate ECGs run consecutively (ie, < 30 seconds apart) , at time points designated in the schedule of assessments

The principal investigator or qualified site personnel will review all ECGs. Electrocardiograms will be transferred electronically to an ECG central vendor for reconciliation and storage per Amgen instructions. Once reviewed, the original ECG tracing will be retained with the subject's source documents. At the request of Amgen, a copy of the original ECG will be made available to Amgen.

Standard ECG machines should be used for all study-related ECG requirements, this will be provided to the site as ECG data will need to be transmitted to the selected vendor.

7.2.8 Echocardiogram (ECHO) / Multigated Acquisition (MUGA) Scan

ECHO or MUGA will be performed to assess cardiac ejection fraction and cardiac valve abnormalities and will be performed at time points specified in the Schedule of Assessments (see Section 7.1). Additional ECHO/MUGA, cardiac imaging and cardiac assessments are to be conducted if any clinical signs or symptoms of cardiomyopathy or other cardiac compromise are noted.

7.2.9 Dosing Diary Review

A dosing diary will be provided for subjects to record the date, time, and number of tablets consumed each dose. The dosing diary is to be brought to each study visit and reviewed by study staff (see Section 7.1).

The dates of any missed doses or instances of emesis associated with tablet administration will asked to be recorded in the subject drug diary.

7.2.10 Assessments in MM Subjects

7.2.10.1 Serum Protein Electrophoresis (SPEP) and Urine Protein Electrophoresis (UPEP)

Serum protein electrophoresis (SPEP) and 24-hour urine protein electrophoresis (UPEP) is required for all subjects at screening. Thereafter, SPEP is to be done at each time point for all subjects as indicated in the schedule of assessments.

UPEP with 24-hour urine collection is required at each time point only if screening UPEP shows measurable paraprotein in the urine and for confirmation of VGPR or CR as per IMWG-URC. If screening UPEP is negative, spot urine is required at each time point. If positive for paraprotein, a 24-hour urine collection with UPEP must be done at the next assessment and at each subsequent assessment unless the UPEP shows an absence of paraprotein. Immunofixation is required at next assessment only if SPEP or UPEP results are zero/undetectable.

7.2.10.2 Serum Free Light Chain

Serum free light chain (SFLC) assay and ratio will be performed at each time point as specified in the schedule of assessments.

7.2.10.3 Quantitative Immunoglobulin

Quantitative Immunoglobulin (Ig) will be performed at screening and at each time point as specified in the schedule of assessments. Quantitative Immunoglobulin will be repeated only if clinically indicated, ie, frequent infection despite Multiple Myeloma disease control or deemed clinically indicated by the investigator.

7.2.10.4 Beta-2 Microglobulin

Beta-2 microglobulin will be performed at baseline as part of risk stratification and at each time point as specified in the schedule of assessments.

Plasmacytoma Survey

Plasmacytoma survey will be performed at the time points as specified in the schedule of assessments (Section 7.1). For subjects without a history of extramedullary disease, assessment by physical examination at screening is acceptable.

Plasmacytoma evaluation is to be repeated during treatment only to confirm a response of PR or better, to confirm PD, or if clinically indicated. If clinically indicated due to history of extramedullary disease, the same technique (may include ultrasound, x-ray, CT scan, MRI, PET, or other standard-of-care method) must be employed for each measurement.

7.2.10.5 Skeletal Survey

Skeletal Survey (conventional radiography, whole body low-dose CT, PET-CT or MRI) will be performed at the time points as specified in the schedule of assessments (Section 7.1). It can also be done if clinically indicated, ie, new symptoms (bone pain) arise. MRI should be performed in subjects with bone pain but skeletal survey is normal.

7.2.10.6 Bone marrow

Bone marrow sample and biopsy will be collected during the screening to quantify percent myeloma involvement and for fluorescent in situ hybridization (FISH).

Additional bone marrow samples are to be collected to confirm CRs as well as for MRD biomarker analysis. Additional samples may be obtained every six months after CR and/or at time of relapse.

7.2.11 Assessments in NHL Subjects

7.2.11.1 Imaging and Disease assessments

Clinical tumor assessments will be performed as indicated in the schedule of assessments and per institutional guidelines. The Lugano Classification will be used to assess treatment response as described in Appendix I.

PET-CT and CECT scans required in this protocol will be performed according to the Imaging Manual provided by the central vendor. However, depending on scanner types and availability, as well as local regulations, institutional guidelines may be followed upon consultation with, and approval by, the central vendor. Combined PET-CT whole body scans will be acquired from base of skull to mid-thigh, with the CT portion of the

scan used only for attenuation correction. CECT anatomical coverage includes the chest, abdomen, and pelvis (and neck, if not visualized with chest), and the acquisition of separate CECT scans is strongly recommended for staging evaluation. Refer to the Imaging Manual for complete details about PET-CT and CECT scanning procedures and instructions.

PET-CT images should be converted to standardized uptake values (SUV) maps to support comparison across timepoints and to standardize viewing conditions.

If PET-CT and CECT are acquired on the same day, it is strongly recommended that PET-CT is performed prior to CECT. If acquired separately, every attempt should be made to complete PET-CT and CECT within 3 days of each other.

Refer to the Imaging Manual for additional details. Findings will be recorded per eCRF guidelines.

7.2.11.2 MRI Brain

For both Part 1 (dose escalation) and Part 2 (dose expansion), all NHL subjects must have MRI or CT of the brain performed within 21 days prior to enrollment. All brain scans on protocol are required to be MRI unless MRI is contraindicated, then CT with contrast is acceptable. Subsequently, MRI brain can be performed at any time if clinically indicated per standard of care.

7.2.11.3 Lymph Node and Bone Marrow Assessments

Lymph node and bone marrow biopsy are to be collected as per schedule of assessments.

Bone marrow evaluation (core biopsy with or without aspirate) should be performed if there has been previous histologic evidence of bone marrow involvement plus a negative or ambiguous PET-CT, or if bone marrow involvement is suspected with an ambiguous or negative PET-CT. An optional tumor biopsy may be collected at time of relapse per institutional guidelines at PI discretion.

Refer to the Laboratory Manual for additional information for these procedures.

7.2.11.4 Whole Blood Plasma

For dose expansion subjects (DLBCL subjects) only:

- Whole blood plasma may be obtained at pre-dose on day 1 of Cycle 2, every 8 weeks thereafter, and EOT. Samples must be collected, processed, and frozen within 4 hours of phlebotomy. See laboratory manual for more details
- Additional whole blood plasma samples are obtained at time of relapse.

7.2.12 Assessments in AML Subjects

Bone marrow aspirate will be performed for the following:

- Hematocytology and cytochemistry to establish WHO subtype of AML – local site laboratory according to local procedures using slides of bone marrow and peripheral blood
- Immunological phenotyping to verify myeloid leukemia. Additional immunological phenotyping and/or MRD will be performed/done at the investigator's discretion, for relapsed and/or for response confirmation
- Cytogenetics (gene expressions, gene mutations, cell culture and banding analysis) - a local laboratory may perform cytogenetics to determine eligibility at screening. Previous bone marrow aspirate or biopsy performed within 6 months of day 1 may be used to determine eligibility for subjects. A bone marrow biopsy or aspirate will still be required during screening for all subjects.
- Additional cytogenetics will be performed/done at the investigator's discretion, for relapsed and/or for response confirmation.
- Bone marrow biopsy for histopathology in case of dry tap

Additional bone marrow sampling may occur at other time points at the investigator's discretion as clinically indicated. Unscheduled bone marrow aspirate results will be captured in the respective eCRFs.

7.2.12.1 Disease Response in AML Subjects

Disease response assessments will be based upon review of bone marrow aspirates, and peripheral blood count. Refer to the 2017 ELN criteria in Appendix J for additional details. Complete response/complete recovery with incomplete count recovery (CRi) must be established from a bone marrow samples supplemented with neutrophil, platelet, and peripheral blast counts.

In case of transplantation, a CR or CRi must be confirmed within 4 weeks prior to transplantation.

7.2.13 Pharmacokinetic Blood Sampling

For pharmacokinetic assessment blood samples for quantitative determination of AMG 397, will be collected at time points specified in the Schedule of Assessments (Section 7.1). Sample collection, processing, storage, and shipping instructions are provided in a separate laboratory manual.

7.2.14 Blood Samples

Approximate blood volumes expected to be collected during study participation (screening, treatment period of 6 months, and EOT/SFU visits) are presented in the tables below.

Table 6. Approximate Blood Volumes Collected for MM Subjects Only

		No Lead-In Dosing		With Lead-In Dosing	
Test	Volume (mL) per Collection	Approximate Number of Collection	Approximate Total Volume (mL)	Approximate Number of Collection	Approximate Total Volume (mL)
CBC with diff	4	18	72	21	84
Chemistry • Pregnancy test (childbearing females only)	8.5	25	212.5	33	280.5
Coagulation	3	18	54	21	63
Serology (HIV, Hepatitis panel)	5	1	5	1	5
Quantitative Immunoglobulin	10	2	20	2	20
Blood samples for biomarkers	5	9	45	16	80
Blood samples for PK	5	20	100	32	160
Beta-2 microglobulin, SPEP and SFLC	10	7	70	7	70
Total approximate blood volume			**520**		**762.5**

Table 7. Approximate Blood Volumes Collected for NHL Subjects Only

		No Lead-In Dosing		With Lead-In Dosing	
Test	Volume (mL) per Collection	Approximate Number of Collection	Approximate Total Volume (mL)	Approximate Number of Collection	Approximate Total Volume (mL)
CBC with diff	4	18	72	21	84
Chemistry • Pregnancy test (childbearing females only)	8.5	25	212.5	33	280.5
Coagulation	3	18	54	21	63
Serology (HIV, Hepatitis panel)	5	1	5	1	5
Blood samples for biomarkers	5	9	45	16	80
Blood samples for PK	5	20	100	32	160
Total approximate blood volume for dose escalation			**488.5**		**672.5**
Whole blood plasma (Dose expansion subjects only)	**5**	5	25	5	25
Total approximate blood volume for dose expansion			**513.5**		**697.5**

Table 8. Approximate Blood Volumes Collected for AML Subjects Only

		No Lead-In Dosing		With Lead-In Dosing	
Test	Volume (mL) per Collection	Approximate Number of Collection	Approximate Total Volume (mL)	Approximate Number of Collection	Approximate Total Volume (mL)
CBC with diff	4	18	72	21	84
Chemistry • Pregnancy test (childbearing females only)	8.5	25	212.5	33	280.5
Coagulation	3	18	54	21	63
Serology (HIV, Hepatitis panel)	5	1	5	1	5
Blood samples for biomarkers	5	9	45	16	80
Blood samples for PK	5	20	100	32	160
Total approximate blood volume			**488.5**		**672.5**

7.2.15 Clinical Laboratory Assessments

The following laboratory analytes in Table 9 will be assessed as specified in the Schedule of Assessments (Section 7.1) collected by standard laboratory procedures.

Table 9. Clinical Laboratory Assessments

Chemistry	**Hematology**	**Urinalysis**	**Coagulation**	**For MM Subjects only:**
Albumin ALP ALT AST Bicarbonate BUN or Urea Calcium Chloride Creatinine Direct bilirubin GGT Glucose LDH Magnesium Phosphorus Potassium Sodium Total bilirubin Total protein Total bile acid Uric acid Haptoglobin	ANC Hematocrit Hemoglobin MCH MCHC MCV Platelets RBCs WBCs Differential: ▪ Neutrophils ▪ Lymphocytes ▪ Monocytes ▪ Eosinophils ▪ Basophils	Specific gravity pH Blood Protein Ketones Bilirubin Glucose Leucocytes esterase (WBC) Microscopic exam (only needed for positive dipstick and should include the following): Epithelial, Bacteria, Casts, Crystal, RBCs, WBCs	PT or INR Activated Partial Thromboplastin Time (APTT) **Other Labs** Pregnancy Hep B surface antigen Hep B antibody Hep C antibody HCV PCR (if applicable) HBV PCR (if applicable) PK (including urine for analysis) Biomarker analytes (See Section 7.3) Bone marrow aspirate as applicable Bone marrow biopsy as applicable	SPEP UPEP SFLC Quantitative Immunoglobulin Beta-2 microglobulin **For NHL subjects only:** Whole blood plasma Lymph node biopsy

7.3 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the amount of tumor growth, or predict disease progression, metastasis, and responses to AMG 397 or protocol required therapies. Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to AMG 397 to investigate and further understand the importance of the intrinsic apoptotic pathway family members in heme malignancies.

Biomarker development may be pursued by use of advanced biochemical analyses in blood, bone marrow, or tumor tissue samples, encompassing proteomic methods, genomic sequencing, or ribonucleic acid transcript profiling. Biomarkers such as pro-survival family members will be explored (eg, MCL1, BCL2, and BCL2L1 expression), as well as the larger family of apoptosis pathway proteins, chromosomal aberrations and translocations, somatic mutations, molecularly defined disease subgroups, and analysis of minimal residual disease.

Please NOTE: Sample collection, processing, storage, shipping instructions and schedules are provided in a separate laboratory manual.

7.3.1 Blood Samples

Whole blood samples are to be collected for biomarker measurement at several time points as listed in the schedule of assessments. The first set of samples will be collected for Flow cytometric analysis to measure the increase in BAX and Caspase 3 activity in circulating monocytes (MM, NHL) or peripheral blasts (AML) following treatment with AMG 397.

Initially, these blood samples will be collected on Cycle 1 pre-dose on day 1, 3 and 5 hours post-dose on day 1, as well as pre-dose on day 2 according to Table 4. If Lead-in dosing is initiated due to TLS symptoms, additional samples will be collected for remaining subjects according to Table 5 as follows: Cycle 1 pre-dose on Days 1 and 2, 3 and 5 hours post-dose on Day 1, as well as pre-dose on Days 8 and 9, 3 and 5 hours post-dose on Day 8.

In AML subjects, these whole blood samples may also be used to measure pro-survival family members (such as MCL1, BCL2, and BCL2L1 expression) in peripheral leukemic blasts.

A second set of biomarker blood collections will be used to monitor cell counts of immune cell subsets, including T cells, B cells, NK cells, monocytes, and Myeloid Derived Suppressor Cells (MDSCs) following treatment with AMG 397. Initially, these samples will be collected on Cycle 1 pre-dose on days 1, 2, 3, 4, and 8 according to Table 4 above. If Lead-in dosing is initiated due to TLS symptoms, additional samples will be collected for remaining subjects according to Table 5 as follows: Cycle 1 pre-dose on days 1, 2, 3, 4, 8, 9, 10, and 15.

For NHL subjects in Part 2 during dose expansion, additional whole blood samples may be taken to assess clinical responses through depth of minimal residual disease status as indicated in schedule of assessments.

7.3.2 Bone Marrow

During screening, bone marrow aspirates are required for all subjects. A core bone marrow biopsy is required for all multiple myeloma subjects. Samples may be analyzed for protein expression and activity using immunohistochemistry and/or flow cytometry, and RNA transcript expression using platforms including Nanostring, RNA sequencing, and/or droplet digital PCR. Analyses of tumor specific mutations or epigenetic changes may be performed using FISH, array technologies or next generation sequencing. In Part 2, minimal residual disease may be evaluated on additional bone marrow specimens as indicated in the schedule of assessments (Table 4. and/or Table 5) in MM and AML subjects.

7.3.3 Tumor Biopsy

For NHL subjects, a tumor biopsy at the primary lymph node site is required at screening. An additional tumor biopsy may be collected at time of relapse per institutional guidelines and PI discretion.

Protein expression of pro-survival family members (such as MCL1, BCL2, and BCL2L1) will be analyzed via immunohistochemical methods. Genomic and RNA transcriptional analyses may be further performed including but not limited to FISH, and determination of MRD by NGS.

7.4 General Study Procedures

Cycle 1 and 2 visits should be done on days specified as possible. All subsequent visits beginning on Cycle 3 will have a +/-1 day window unless otherwise specified.

7.4.1 Screening

The following procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Section 7.1).

- Confirmation that the Informed Consent Form has been signed
- Demographic data including sex, age, race, and ethnicity
- Clinical evaluations include physical exam, ECOG status, and weight. Medical and surgical history, and height need only be collected at the screening visit.
- Vital signs (eg, blood pressure, heart rate, respiratory rate, temperature)
- Laboratory Assessments including local and central laboratories, as applicable
- Pregnancy test as applicable
- Bone marrow aspirate or biopsy as applicable
- Biopsy Assessments, as applicable
- Imaging Assessments, as applicable
- ECG
- ECHO/MUGA
- For NHL subjects, MRI brain (See Section 7.2.11.2)
- Serious Adverse Event reporting
- Documentation of concomitant and rescue medications

Subjects may be rescreened at the discretion of the investigator after consultation with the Amgen Medical Monitor. Refer to Section 5 for instructions on rescreening and enrolling subjects.

7.4.2 Treatment

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Section 7.1). Administration of AMG 397 is to be administered as applicable during each visit that it is required.

Treatment visits to include the following:

- Hospitalization (See Section 6.5.7)
- TLS prophylaxis (See Section 6.5.7)
- Clinical evaluations will be collected pre-dose on dosing days and include: physical exam, ECOG status, and weight.
- AMG 397 dosing

- Dosing diary review
- PK (including intensive PK assessments)
- ECG
- Vital signs (eg, blood pressure, heart rate, respiratory rate, temperature)
- Laboratory assessments including local and central laboratories, as applicable
- Pregnancy tests, as applicable
- Bone marrow aspirate or biopsy as applicable
- Biopsy Assessments, as applicable
- Imaging Assessments, as applicable
- Disease assessments, as applicable
- Serious Adverse Event reporting
- Adverse Event reporting
- Documentation of concomitant medications

7.4.3 End of Treatment Visit

The end of treatment (EOT) visit will occur after the last dose of AMG 397. The end of treatment (EOT) visit will occur upon the decision to end the treatment, disease progression, intolerable adverse event, documented clinical progression or consent withdrawal.

For subjects who choose to discontinue investigational product treatment, the EOT visit should occur as soon as possible after the last dose of investigational product is administered. Serious adverse events considered related to the investigational product, by the Investigator, or Amgen will be followed until resolved or considered stable.

EOT visits to include the following:

- Clinical evaluations include: physical exam, ECOG status, and weight.
- Dosing diary review
- PK
- ECG
- Vital signs (eg, blood pressure, heart rate, respiratory rate, temperature)
- Laboratory assessments including local and central laboratories, as applicable
- Pregnancy tests, as applicable
- Bone marrow aspirate or biopsy as applicable
- Biopsy Assessments, as applicable
- Imaging Assessments, as applicable
- Disease assessments, as applicable

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

7.4.4 Safety Follow-Up (SFU) Visit

The SFU visit must be performed approximately 28 (+7) days after the last dose of AMG 397. All efforts should be made to conduct this visit. If it is not possible to conduct the SFU visit, documentation of efforts to complete the visit should be provided in the source documents and noted as not done in the eCRFs.

- Clinical Evaluation
- ECG
- Visit signs (eg, blood pressure, heart rate, respiratory rate, temperature)
- Laboratory assessments including local and central laboratories, as applicable
- Serious Adverse Event reporting
- Adverse Event reporting
- Documentation of concomitant medications

7.4.5 Long-term Follow-up (Dose expansion subjects only)

Long-term follow up (LTFU) will be conducted every 3 months from the last visit for up to 1 year from the first dose of AMG 397 for all subjects who have not withdrawn consent by telephone or chart review to assess for survival, disease progression and/or the commencement of subsequent cancer therapy only.

7.5 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be extracted and performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of MM, NHL and/or AML and to identify subjects who may have positive or negative response to AMG 397. No additional samples are collected for this part of the study.

7.6 Sample Storage and Destruction

Any blood, bone marrow or tumor sample collected according to the Schedule of Assessments (Section 7.1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the

study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the Multiple Myeloma, NHL, and AML, disease indications, the dose response and/or prediction of response to AMG 397, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the Investigator is to provide the sponsor with the required study and subject number so that any remaining blood, bone marrow, or tumor samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

Amgen is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, Amgen owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or

derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Section 7.1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and disease related events, as applicable. Subjects who have discontinued investigational product and/or protocol required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow-up that is agreed to by the subject.

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, and/or other protocol required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the

local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, pregnancy)
- death
- lost to follow-up
- decision by sponsor
- disease progression
- protocol specified criteria

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study, or involves

an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

Record a single event for each increased level of severity on the Event eCRF.

For situations when an adverse event or serious adverse event is due to Multiple Myeloma or Non-Hodgkin's Lymphoma report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, multiple myeloma).

Note: The term "disease progression" should not be used to describe the adverse event.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug induced liver injury (DILI) (see Appendix A for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the end of Safety Follow-Up(SFU)/end of study (EOS) visit are reported using the Event eCRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity [and/or toxicity per protocol],
- Assessment of relatedness to investigational product, and
- Action taken.

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to the investigational product. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product? If the severity of an adverse event changes from the date of onset to the date of resolution, record a single event for each increase in level of severity on the Adverse Event Summary eCRF.

The investigator must assess whether the adverse event is possibly related to any study mandated activity (eg, administration of investigational product, protocol-required therapies, use of medical device(s) and/or procedure (including any screening procedure(s)). This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of investigational product, protocol-required therapies, use of medical device(s)), and/or procedure"?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment

or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.1.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last day of the dosing interval of investigational product are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event eCRF.

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

The investigator must assess whether the serious adverse event is possibly related to the investigational product. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product? Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

The investigator is expected to follow reported serious adverse events until stabilization, resolution or patient death.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records.

Information provided about the serious adverse event must be consistent with that recorded on the Event eCRF.

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities.

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

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

9.2.1.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking AMG 397 report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur through 3 months after the last dose of AMG 397.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

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

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur through 3 months after the last dose of protocol-required therapies.

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

Primary Endpoints:

- 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

Secondary Endpoints:

- Efficacy parameters:
    - ORR using response criteria per the following:
        - International Myeloma Working Group (IMWG) for MM subjects
        - Lugano Classification for NHL subjects
        - Revised International Working Group (IWG) for AML subjects

- Duration of response
- Progression Free Survival (PFS) and Overall Survival (OS)
- 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 ($t^{1/2}$)

Exploratory Endpoints:

- AMG 397 exposure/efficacy and exposure/safety relationships
- AMG 397 metabolites in plasma and urine
- Increased expression of BAX and Caspase 3 in monocytes or blast cells and/or decrease in circulating monocyte counts
- Patient responses according to biomarkers of tumor cells including but not limited to protein levels of pro-survival family members, FISH/cytogenetic analysis, gene expression profiling, flow cytometric phenotyping and DNA sequencing
- Immune cell subset frequencies, absolute counts and MFIs in peripheral blood
- MRD status

10.1.1 Analysis Sets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 397. The analysis of DLT will be restricted to DLT-evaluable subjects (see Section 6.2.1.1.1). 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.

10.2 Covariates and Subgroups

The relationship between baseline covariates and safety/efficacy endpoints will be explored. Safety and efficacy endpoints will be summarized separately for each tumor type. Details regarding covariates and subgroups and respective analyses are described in the Statistical Analysis Plan.

10.3 Sample Size Considerations

Up to 90 subjects will be enrolled in the study. Up to 60 subjects will be enrolled during dose escalation (up to 30 in both Group 1A and 1B). Up to 30 subjects will be enrolled into the dose expansion part (up to 10 in each Group 2A, 2B & 2C).

The sample sizes are based on practical considerations and it is consistent with conventional oncology studies with the objective to identify the MTD. During

dose-escalation and with 3 subjects in a cohort, there is a 27 to 70% probability of observing at least one DLT if the true DLT rate is 10 to 33%. With 10 subjects respectively in in dose expansion group, there is a 40% to 65% probability of observing at least 1 adverse event if the true event rate is 5% to 10%. Exact 80% binomial CI will be provided for ORR. With the 10 subjects in each dose expansion group and a 20% ORR, the 80% CI would be 5% to 45%.

10.4 Adaptive Design

A 2-parameter Bayesian Logistic Regression Model (BLRM) is used to guide dose escalation. The MTD target Toxicity Probability Interval (TPI) for 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 d_i is assumed to follow a Bernoulli distribution with probability p_i where the logit of p_i increases linearly with the log of the standardized dose in the following 2-parameter logistic model:

$$\log [p_i / (1-p_i)] = \text{logit}(p_i) = \log[a] + \exp(\log[b]) \log (d_i / d_{ref})$$

where a and b are random variables and d_{ref} is 1 of the planned dose 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 p_i 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). Operating characteristics for this BLRM design are described in Appendix D.

During dose expansion, Amgen will conduct evaluations of the ongoing grade 4 or higher adverse event rate to assess if the threshold for early trial termination has been reached. The stopping rules use a Bayesian approach proposed by Thall, et al (1995) to terminate

the study if the posterior probability that the grade 4 or higher adverse event rate is greater than 20% is > 90%. The stopping boundaries assuming a prior distribution of Beta (0.40, 1.60) are presented in Table 10 and the operating characteristics with pre-specified batch size of 10 new subjects per batch are presented in Table 2. Subjects including in a batch may come from different tumor types. The evaluations could occur more frequently if necessary to address emerging safety concerns. The operating characteristics in Table 11 provide the probability of stopping the study early for given hypothetical true rate of grade 4 or higher adverse events, whereas the stopping criteria in Table 10 are based on situations where the empirical evidence would result in a posterior probability of ≥ 90% that the true grade 4 or higher adverse event rate is ≥ 20%.

Table 10. Stopping Boundary for Dose Expansion With Posterior Probability of 90% and Grade 4 or Higher Adverse Event Limit of 20%

Number of subjects	Stop study if observing these many grade 4 or higher adverse events
10	≥5
20	≥7
30	Study Complete

Table 11. Operating Characteristics With Batch Size of 10 Subjects

True grade 4 or higher adverse event rate	Probability of early stopping of dose expansion	Average dose expansion sample size
0.10	0.4%	29.9
0.15	2.7%	29.6
0.20	9.7%	28.7
0.25	22.9%	26.9
0.30	40.8%	24.4

10.5 Planned Analyses

10.5.1 Interim Analyses

Safety data will be reviewed on an ongoing basis. Based on accumulating toxicity information, BLRM will be used to make dosing recommendations. In dose level review team meetings (DLRMs), Amgen, in consultation with the site investigators, will review the BLRM recommended dose level and will review all available cumulative data by cohort prior to making dose escalation decisions. As a sensitivity analysis, a one-parameter Continual Reassessment Method (CRM) model may be used to estimate

the dose-toxicity relationship to help making dose escalation decisions. Adverse events and DLTs observed in all subjects will be evaluated continually and fully integrated into all DLRMs and considered in all enrollment and dosing decisions.

An interim analysis for efficacy parameters will be conducted after dose escalation is completed.

10.5.2 Dose Level Review Team (DLRT)

After reviewing all available safety data and reviewing the dose recommendation from the BLRM, the DLRT will make all dose level and dosing schedule decisions. Details regarding the DLRT and the process for making dosing decisions are described in Section 6.2.1.2.

10.5.3 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.

10.5.4 Final Analysis

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

10.6 Planned Methods of Analysis

10.6.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, pharmacodynamic and biomarker data by tumor type, dose, dose schedule, and time as appropriate. 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.

10.6.2 Primary Endpoints

Safety Endpoints:

Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the safety analysis set, which includes subjects that are enrolled and received at least 1 dose of AMG 397.

Subject incidence of DLTs will be used to fit the BLRM model to estimate the probability of having a DLT across dose levels.

Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. The number and percentage of subjects reporting

adverse events will be evaluated overall and by dose level and will also be tabulated by relationship to study drug.

Tables of adverse events, fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided.

Clinical Laboratory Tests

Clinical chemistry, hematology, and urinalysis data will be listed and reviewed for each subject. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings. Depending on the size and scope of changes in laboratory data, summaries of laboratory data over time and/or changes from baseline over time may be provided. Tables of maximum shifts from baseline for selected laboratory values may also be provided.

Vital Signs

Vital signs data will be listed and reviewed for each subject. Depending on the size and scope of changes, summaries of vital signs data over time and/or changes from baseline over time may be provided.

Electrocardiograms

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters. Subjects' maximum change from baseline in QT interval corrected by Fridericia's formula will be categorized and the number and percentage of subjects in each group will be summarized. Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects in each group will be summarized. All on-study ECG data will be listed, and select parameters of interest may be plotted.

10.6.3 Secondary Endpoints

10.6.3.1 Efficacy Endpoint Analyses

The analyses on PFS and OS will be done only using data from dose expansion subjects; other efficacy endpoints will be analyzed using data from both dose escalation and dose expansion.

The number and percentage of subjects by overall response and overall response category will be calculated and tabulated. Using the Kaplan Meier estimate, the PFS at 6 and 12 months and the OS at 6 and 12 months with corresponding 90% CI will be tabulated. Listings will be produced for all subjects indicating the OS, PFS, time to

response and duration of response. Kaplan Meier curve will be presented for OS, PFS, time to response and duration of response with estimates for rates and 80% CI at selected weeks.

10.6.3.2 Pharmacokinetics Data Analysis

For AMG 397, PK parameters including including C_{max}, T_{max}, AUC, CL and half-life will be determined from the time-concentration profile using standard non-compartmental approaches and considering the profile over the complete sampling interval. Based on the review of the data, analyses to describe the relationship between AMG 397 exposure and either pharmacodynamic effects and/or clinical outcome may also be performed.

10.6.4 Exploratory Endpoints

The following statistical analyses will be considered exploratory and will be performed only when deemed appropriate.

Summary statistics over time will be provided and graphical presentations may be used to describe the following.

- AMG 397 exposure/efficacy and exposure/safety relationships
- AMG 397 metabolites in plasma and urine
- Increased expression of BAX and Caspase 3 in monocytes or blast cells and/or decrease in circulating monocyte counts
- Patient responses according to biomarkers of tumor cells including but not limited to protein levels of pro-survival family members, FISH/cytogenetic analysis, gene expression profiling, flow cytometric phenotyping and DNA sequencing
- Immune cell subset frequencies, absolute counts and MFIs in peripheral blood
- MRD status

The relationship between AMG 397 exposure and PD effects and related biomarkers in blood, or tumor specimens and/or AMG 397 exposure and clinical outcomes (eg, tumor response) will be also explored if deemed appropriate. Based on the review of the safety and efficacy data, analyses to describe the relationship between AMG 397 exposure and safety/efficacy endpoints may also be performed.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Study Manager to the investigator.

The written informed consent form is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any investigational product(s) is/are administered.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record. The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

If a potential subject is illiterate or visually impaired, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. ***Refer to ICH GCP guideline, Section 4.8.9.***

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent

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

The investigator is responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the demographics page, in addition to the unique subject identification number, include the age at the time of enrollment.
- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in strict confidence by the investigator, except as described below.

In compliance with governmental/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named such individuals to have access to his/her study related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s), and by what mechanism, after termination of the study and before it is available commercially.

12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed eCRF, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Clinical Monitor is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study related records needed to verify the entries on the eCRFs.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic CRFs must be maintained and readily available.
- Updates to electronic CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the investigator inspected or reviewed the data on the eCRF, the data queries, and agrees with the content.

Amgen (or designee) will perform Self-Evident Corrections (SEC) to obvious data errors in the clinical trial database. SECs will be documented in the eCRF Standard Instructions and the eCRF Specific Instructions, both of these will be available through the EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit, [eg, week 4 and early termination]) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Section 7.1), the investigator can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

eCRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

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

Additional information on the current guidelines for publications can be found at the following location: http://www.icmje.org/

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The CTCAE Version 4.03 is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronicapplications/ctc.htm.

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.7 require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.1

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.7.1 and Section 6.7.2 or who experience AST or ALT elevations > 3 x ULN or 2-fold increase above baseline values for subjects with evaluated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve
- Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.
- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:
  - Complete blood count (CBC) with differential to assess for eosinophilia
  - Serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis

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

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding CRFs.

Appendix B. eSerious Event Contingency Form

AMGEN Study # 20170173 AMG 397	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

FAX # US: +888 814 8653

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

and start date: Day _____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year_____

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

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

		Prior to, or at time of Event						
		Date of Initial Dose	Date of Dose	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
IP/Amgen Device:		Day Month Year	Day Month Year					
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20170173 AMG 397	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20170173 AMG 397	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: AMG 397 20170173

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm____/ dd____/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

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

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

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

5. Pregnancy Information

Pregnant female's LMP mm____/ dd____/ yyyy____ ☐ Unknown

Estimated date of delivery mm____/ dd____/ yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm____/ dd____/ yyyy____

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

If yes, provide date of delivery: mm____/ dd____/ yyyy____

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX# US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: AMG 397 20170173

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____ / dd____/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Appendix D. Operating Characteristics for 2-Parameter BLRM Design

The operating characteristics of the two-parameter BLRM design were evaluated via simulation. The cohort size was fixed to 2 or 4 subjects. The initial multiple subject dose level is 80 mg and subsequent doses were selected based on the following rules:

After each cohort, the next dose is the one with the highest probability of the target TPI, subject to the overdose control limits.

Dose escalation was stopped given 1 or more of the following conditions:

- There have been at least 6 subjects treated at the dose recommended by the model.
- A maximum number of 30 subjects are evaluated

A total of 6 dose levels (unit: mg) were considered: 80, 160, 240, 320, 480, 640 in these simulations of the multiple subject cohorts (80, 160, 320 and 640 are planned dose levels with 240 and 480 possible intermediate dose levels).

The design was evaluated for 3 possible dose-response scenarios: "Low", "Mid", and "High" MTD. Table 1 shows the dose level and true probability of DLT for each scenario used in the simulated studies estimating the MTD. Table 2 and Table 3 report the operating characteristics from 1,000 simulated studies estimating the MTD when the target TPI is (0.20, 0.33]; Table 2 reports characteristics when the overdose control limit is 0.40 probability of an excessive or unacceptable TPI while Table 3 reports a limit of 0.25 probability of an excessive or unacceptable TPI.

Table 1. True Probability of DLT by Scenario for Simulated Studies Estimating MTD

Dose Level	80	160	240	320	480	640
MTD Scenario						
High	0.04	0.08	0.11	0.18	0.25	0.33
Mid	0.06	0.11	0.18	0.25	0.33	0.45
Low	0.09	0.18	0.25	0.33	0.45	0.55

DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

Table 2. Operating Characteristics by Scenario for Simulated Studies Estimating the MTD When the Target TPI is (0.20, 0.33) Overdose Control Limit is 0.40 Probability of an Excessive or Unacceptable TPI

MTD Scenario	High		Mid		Low	
	4 subjects per cohort	2 subjects per cohort	4 subjects per cohort	2 subjects per cohort	4 subjects per cohort	2 subjects per cohort
Number of Subjects	24	16	24	16	24	16
Median (IQR)	(20 to 28)	(12 to 18)	(20 to 28)	(14 to 18)	(20 to 28)	(14 to 18)
Number of DLTs	4	3	5	4	6	4
Median (IQR)	(3 to 5)	(2 to 4)	(4 to 6)	(3 to 5)	(4 to 7)	(3 to 6)
Proportion of DLT (%)	18	19	21	25	25	29
Median (IQR)	(13 to 21)	(14 to 25)	(19 to 25)	(19 to 29)	(21 to 30)	(25 to 33)
Percentage of studies recommending dose with DLT probability of:						
≤ 10%	2.7	3.3	4.2	4.5	9.3	12.2
> 10% and ≤ 20%	23.4	19.7	12	10.7	17.5	13.5
> 20% and ≤ 33%	73.9	77.0	72.4	66.7	57.2	50.7
> 33%	0	0	11.4	18.1	16.0	23.6
Probability of identifying MTD to have 15% to 33% DLT probability	94.8	95.0	80.3	72.6	74.7	64.2

DLT = dose-limiting toxicity; IQR = interquartile range; MTD = maximum tolerated dose; TPI = toxicity probability interval.
EAST version 6.4 software used to generate 1,000 simulated clinical trials for each scenario.

Table 3. Operating Characteristics by Scenario for Simulated Studies Estimating the MTD When the Target TPI is (0.20, 0.33) Overdose Control Limit is 0.25 Probability of an Excessive or Unacceptable TPI

MTD Scenario	High		Mid		Low	
	4 subjects per cohort	2 subjects per cohort	4 subjects per cohort	2 subjects per cohort	4 subjects per cohort	2 subjects per cohort
Number of Subjects	24	14	24	14	20	14
Median (IQR)	(20 to 28)	(12 to 16)	(20 to 28)	(12 to 18)	(16 to 24)	(10 to 18)
Number of DLTs	4	3	4	3	5	3
Median (IQR)	(3 to 5)	(2 to 3)	(3 to 6)	(2 to 4)	(4 to 6)	(2 to 5)
Proportion of DLT (%)	17	19	20	22	25	28
Median (IQR)	(13 to 21)	(14 to 25)	(17 to 25)	(18 to 29)	(20 to 29)	(22 to 36)
Percentage of studies recommending dose with DLT probability of:						
≤ 10%	4.7	10.7	5.3	15.5	16.9	28.9
> 10% and ≤ 20%	34.0	30.7	14.8	11.7	18.8	14.2
> 20% and ≤ 33%	61.3	58.6	72.2	67.7	54.5	42.7
> 33%	0	0	7.7	5.1	9.8	14.2
Probability of identifying MTD to have 15% to 33% DLT probability	93.5	87.9	79.9	72.9	73.3	56.9

DLT = dose-limiting toxicity; IQR = interquartile range; MTD = maximum tolerated dose; TPI = toxicity probability interval.
EAST version 6.4 software used to generate 1,000 simulated clinical trials for each scenario.

Appendix E. International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma (IMWG-URC)

Response Subcategory[a]	Multiple Myeloma Response Criteria
sCR[b]	• CR as defined below and • Normal SFLC ratio and • Absence of clonal cells in bone marrow[c] by immunohistochemistry or immunofluorescence[c]
CR[b]	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow[c]
VGPR[b]	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein with urine M-protein level< 100 mg/24 hours • If the serum and urine M-protein are not measurable, a decrease of ≥ 90% in the difference between the involved and uninvolved FLC levels required in place of the M-protein criteria. However, documentation of VGPR requires collection and analysis of 24 hour urine sample for UPEP and immunofixation and confirmed to be negative. • If present at Baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.
PR[b]	• ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/ 24 h • If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If serum and urine M-protein are not measureable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow cell percentage was ≥ 30% • If present at Baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
MR	• 25%–49% reduction in the level of serum M-protein and a 50%–89% reduction in 24 hour urinary M-protein, which still exceeds 200 mg per 24 hours • If the serum and urine M-protein are not measurable, a decrease of 25%-49% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If present at Baseline, a 25%–49% reduction in the size of soft tissue plasmacytomas is also required
Stable disease	• Not meeting criteria for CR, VGPR, PR, or PD

Footnotes defined on next page

Response Subcategory[a]	Multiple Myeloma Response Criteria
PD[b]	Any one or more of the following: • Increase of ≥ 25% from lowest response value in: ➢ Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL) ○ Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h) ○ Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dL ➢ Bone marrow plasma cell percentages (absolute percentage must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas[e, f, g] • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65mmol/L) that can be attributed solely to the plasma cell proliferative disorder

Page 2 of 2

Source: Durie 2006; Rajkumar 2011 (*modified for protocol purposes*).
CR = complete response; sCR = stringent complete response; FLC = serum light chain; MR = minor response; PD = progressive disease; PR = partial response; SFLC = serum free light chain; VGPR = very good partial response

Note: Patients with measurable disease in both serum (SPEP) and urine (UPEP) at study entry are required to meet response criteria in both UPEP and SPEP in order to qualify for a MR or better. Conversely, it should be noted criteria for PD only needs to be met, and confirmed, in 1 parameter. For patients without measurable protein on UPEP at Baseline, UPEP will need to be repeated to confirm a response.

[a] Patients with measurable disease in both serum (SPEP) and urine (UPEP) at study entry are required to meet response criteria in both UPEP and SPEP in order to qualify for a MR or better. Conversely, it should be noted that criteria for PD only needs to be met, and confirmed, in one parameter.

[b] **All response categories (CR, sCR, VGPR, PR) require 2 consecutive assessments** made at any time before the institution of any new therapy, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow, plasmacytoma, and skeletal survey assessments are not required to be confirmed by repeat testing. SD requires a duration of ≥ 6 weeks.

[c] Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.

[d] **Determination of PD while on study requires 2 consecutive assessments** made at any time before classification of PD and/or the institution of new therapy. Serum M-component increases of ≥ 1 g/dL from nadir are sufficient to define progression if nadir M-component is ≥ 5 g/dL.

[e] Plasmacytomas: A definite increase in the size is defined as a ≥ 50% increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion. A plasmacytoma is considered measurable if the longest diameter is at least 1 cm and the product of the cross diameters is at least 1 cm^2. Plasmacytomas of lesser size will be considered non-measurable.

[f] The requirement for bi-directional measurements applies only to plasmacytomas.

[g] The plasmacytoma specifications for PD are based on interpretation of the IMWG-URC and practical considerations for study execution.

Appendix F. ECOG Performance Status and NYHA Classification

Eastern Cooperative Oncology Group (ECOG) Performance Status

0. - Fully active, able to carry on all pre-disease performance without restriction
1. - Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2. - Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours
3. - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4. - Completely disabled. Cannot carry out any selfcare. Totally confined to bed or chair
5. – Dead

New York Heart Association Functional Classification

1. Class I No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea.
2. Class II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
3. Class III Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea.
4. Class IV Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Appendix G. Definition of Relapsed or Refractory Progressive Disease and Line of Therapies

Relapsed disease is defined as progression occurs in the absence of therapy.

Refractory disease is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy.

Progressive Disease for patients with Multiple Myeloma requires any one or more of the following:

- Increase of ≥ 25% from lowest response value in any of the following
  - Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dl)
  - Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h)
  - Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (the absolute increase must be > 10 mg/dl)
  - Bone marrow plasma cell percentage: the absolute % must be > 10%
- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder

A line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease (Rajkumar, 2011).

Progressive disease in patients with AML is defined as:

Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood:

- > 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 mo; without at least a 100% improvement in ANC to an absolute level (> 0.5 x 10^9/L [500/uL], and/or platelet count to > 50 x 10^9/L [50,000/uL] nontransfused); or
- >50% increase in peripheral blasts (WBC x % blasts) to >25 x 10^9/L (>25,000/uL) (in the absence of differentiation syndrome)†; or
- New extramedullary disease

Relapse after complete remission for patients with AML is defined as:

- Bone marrow blasts ⩾ 5%; or
- reappearance of blasts in the blood; or
- development of extramedullary disease

These response criteria were published in 2010, "Diagnosis and management of acute myeloid leukemia in adults: Recommendations from an international expert panel, on behalf of the European Leukemia Net" (Döhner et al, 2010).

The criteria for progressive disease were suggested in the 2017 ELN recommendations (Döhner et al, 2017).

Appendix H. World Health Organization Classification for Acute Myeloid Leukemia

Definition AML: ≥ 20% myeloblasts in blood or in bone marrow

Abnormal promyelocytes in acute promyelocytic leukemia, promonocytes in AML with monocytic differentiation and megakaryoblasts in acute megakaryocytic leukemia are considered blast equivalents. **Patients with APML are not eligible for this study.** First, AML should be classified as AML with recurrent cytogenetic abnormalities. If this is not applicable the leukemia is classified as AML with multilineage dysplasia or therapy related and if this subtype is also not applicable as AML not otherwise categorized. Acute Myeloid Leukemia and Related Precursor Neoplasms, and Acute Leukemias of Ambiguous Lineage (Arber et.al, 2016).

AML and related neoplasms	
AML with recurrent genetic abnormalities	AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Acute promyelocytic leukemia with *PML-RARA**
	AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*†
	AML with t(6;9)(p23;q34.1); *DEK-NUP214*
	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	AML (megakaryoblastic) with t(1;22)(p13.3;q13.3*);* *RBM15-MKL1*‡
	Provisional entity: AML with *BCR-ABL1*
	AML with mutated *NPM1*§
	AML with biallelic mutations of *CEBPA*§
	Provisional entity: AML with mutated *RUNX1*
AML with myelodysplasia-related changes‖	
Therapy-related myeloid neoplasms{	
AML, NOS	AML with minimal differentiation
	AML without maturation
	AML with maturation
	Acute myelomonocytic leukemia
	Acute monoblastic/monocytic leukemia #
	Acute megakaryoblastic leukemia
	Acute basophilic leukemia
	Acute panmyelosis with myelofibrosis

Footnotes defined on next page

Myeloid sarcoma	
Myeloid proliferations related to Down syndrome	Transient abnormal myelopoiesis Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm	
Acute leukemias of ambiguous lineage	Acute undifferentiated leukemia MPAL with t(9;22)(q34.1;q11.2); *BCR-ABL1*** MPAL with t(v;11q23.3); *KMT2A* rearranged MPAL, B/myeloid, NOS MPAL, T/myeloid, NOS

For a diagnosis of AML, a marrow blast count of ⩾20% is required, except for AML with the recurrent genetic abnormalities t(15;17), t(8;21), inv(16), or t(16;16). Adapted from Arber et al.
MPAL, mixed phenotype acute leukemia; NK, natural killer.
* Other recurring translocations involving *RARA* should be reported accordingly: for example, AML with t(11;17)(q23;q12); *ZBTB16-RARA*; AML with t(11;17)(q13;q12);*NUMA1-RARA*; AML with t(5;17)(q35;q12*); NPM1-RARA*; or AML with *STAT5B-RARA* (the latter having a normal chromosome 17 on conventional cytogenetic analysis).
† Other translocations involving *KMT2A* (MLL) should be reported accordingly: for example, AML with t(6;11)(q27;q23.3); *MLLT4-KMT2A*; AML with t(11;19)(q23.3;p13.3); *KMT2A-MLLT*1; AML with t(11;19)(q23.3;p13.1); *KMT2A-ELL*; AML with t(10;11)(p12;q23.3); *MLLT10-KMT2A*.
‡ Rare leukemia most commonly occurring in infants.
§ Diagnosis is made irrespective of the presence or absence of multilineage dysplasia.
|| At least 20% (⩾20%) blood or marrow blasts AND any of the following: previous history of MDS or MDS/MPN; myelodysplasia-related cytogenetic abnormality (see list below); multilineage dysplasia; AND absence of both prior cytotoxic therapy for unrelated disease and aforementioned recurring genetic abnormalities. Cytogenetic
abnormalities sufficient to diagnose AML with myelodysplasia-related changes are: Complex karyotype (defined as 3 or more chromosomal abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with BCRABL1); Unbalanced abnormalities: 27 or del(7q); 25 or del(5q); i(17q) or t(17p); 213 or del(13q); del(11q); del(12p) or t(12p); idic(X)(q13); Balanced abnormalities: t(11;16)(q23.3;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3;q21.2); t(2;11)(p21;q23.3); t(5;12)(q32;p13.2); t(5;7)(q32;q11.2); t(5;17)(q32;p13.2); t(5;10)(q32;q21.2); t(3;5)(q25.3;q35.1).
{ Cases should be classified with the related genetic abnormality given in the diagnosis.
The former subgroup of acute erythroid leukemia, erythroid/myeloid type (⩾50% bone marrow erythroid precursors and ⩾20% myeloblasts among nonerythroid cells) was removed; myeloblasts are now always counted as percentage of total marrow cells. The remaining subcategory AML, NOS, pure erythroid leukemia requires the presence of >80% immature erythroid precursors with ⩾30% proerythroblasts.
** *BCR-ABL1* leukemia may present as MPAL; treatment should include a tyrosine kinase inhibitor.

Appendix I. Response Assessment per the Lugano Classification for NHL

5- point scale (Deauville)

1. no uptake above background;
2. uptake ≤ mediastinum;
3. uptake > mediastinum but ≤ liver;
4. uptake moderately > liver;
5. uptake markedly higher than liver and/or new lesions;

X. new areas of uptake unlikely to be related to lymphoma.

Response	Compete Response	Partial Response	Stable Disease	Progressive Disease
PET/CT Response	Complete Metabolic Response	Partial Metabolic Response	No Metabolic Response	Progressive Metabolic Disease
Target Masses	Score 1, 2, or 3 with or without a residual mass	Score 4 or 5 reduced uptake compared with baseline residual mass(es) of any size	Score 4 or 5 no significant change in FDG uptake from baseline	Score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma
New Lesions	None	None	None	New FDG-avid foci consistent with lymphoma rather than another etiology
Bone Marrow	No FDG avid focal lesions	Residual uptake higher than uptake in normal marrow but reduced compared with baseline	No change from baseline	New or recurrent FDG-avid foci

Appendix J. European Leukemia Network (ELN) Response Criteria in AML (2017)

Category	Definition	Comment
Response		
• CR without minimal residual disease (CR_{MRD}-)	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC	Sensitivities vary by marker tested, and by method used; therefore, test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
• Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥ 1.0 x 10^9/L (1000/uL); platelet count ≥ 100 x 10^9/L (100,000/uL)	MRD^+ or unknown
• CR with incomplete hematologic recovery (CRi)	All CR criteria except for residual neutropenia (<1.0 x 10^9/L [1000/uL]) or thrombocytopenia (<100 x 10^9/L [100,000/uL])	
• Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%
• Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Especially important in the context of phase 1-2 clinical trials
Treatment failure		
• Primary refractory disease	No CR or CRi after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause	Regimens containing higher doses of cytarabine are generally considered as the best option for patients not responding to a first cycle of 7+3; the likelihood of responding to such regimens is lower after failure of a first
• Death in aplasia	Deaths occurring ≥ 7 d following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 d of death, without evidence of persistent leukemia	
• Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 d following its completion; or deaths occurring ≥ 7 d following completion of initial therapy with no blasts in the blood, but no bone marrow examination available	

Footnotes defined on next page

Category	Definition	Comment
Response criteria for clinical trials only		
• Stable disease	Absence of CR_{MRD-}, CR, CRi, PR, MLFS; and criteria for PD not met	Period of stable disease should last at least 3 mo
• Progressive disease (PD)*,†	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 mo; without at least a 100% improvement in ANC to an absolute level (> 0.5 x 10^9/L [500/uL], and/or platelet count to > 50 x 10^9/L [50,000/uL] nontransfused); or • > 50% increase in peripheral blasts (WBC x % blasts) to > 25 x 10^9/L (>25,000/uL) (in the absence of differentiation syndrome)†; or • New extramedullary disease	Category mainly applies for older patient given low intensity or single-agent "targeted therapies" in clinical trials. In general, at least 2 cycles of a novel agent should be administered. Some protocols may require blast increase in 2 consecutive marrow assessments at least 4 wk apart; the date of progression should then be defined as of the first observation date. Some protocols may allow transient addition of hydroxyurea to lower blast counts. "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms.
Relapse		
• Hematologic relapse (after CR_{MRD-}, CR, CRi)	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease	
• Molecular relapse (after CR_{MRD-})	If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by MFC	Test applied, sensitivity of the assay, and cutoff values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics)

ANC, absolute neutrophil count; IDH, isocitrate dehydrogenase; MLFS, morphologic leukemia-free state; WBC, white blood cell.

* The authors acknowledge that this new provisional category is arbitrarily defined; the category aims at harmonizing the various definitions used in different clinical trials.

† Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.

Appendix K. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

	Grade					
Complication	**0**	**1**	**2**	**3**	**4**	**5**
Creatinine*,†	≤ 1.5 × ULN	1.5 × ULN	1.5 – 3.0 × ULN	> 3.0 – 6.0 × ULN	> 6.0 × ULN	Death
Cardiac Arrhythmia*	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Seizure*	None	--	One brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death

ULN = upper limit of normal; CHF = congestive heart failure; ADL = activities of daily living

* Not directly or probably attributable to therapeutic agent.

† If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading.

Note: Laboratory tumor lysis syndrome and at least one clinical complication.

Appendix L. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Element	Value		Change from Baseline
Uric Acid	≥ 476 µmol/L (8 mg/dL)	-OR-	25% increase from baseline
Potassium	≥ 6.0 mmol/L (6 mg/L)	-OR-	25% increase from baseline
Inorganic phosphorus	≥ 1.45 mmol/L (4.5 mg/dL)	-OR-	25% increase from baseline
Calcium	≤ 1.75 mmol/L (7.0 mg/dL)	-OR-	25% decrease from baseline

Note: Two or more elements with laboratory values out of range or changes from baseline.

Amendment 1

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

AMG 397

Amgen Protocol Number AMG 397 20170173

Amendment Date: 28 March 2018

Rationale:

The following updates were made to the protocol, dated 28 March 2018:

- Addressed the following changes requested by FDA:
  - Changes to inclusion/exclusion criteria
  - Definition of DLT and criteria for DLT
  - Extended DLT window from 21 days to 28 days
  - Added safety monitoring assessments including:
    - Cardiac echocardiogram, imaging and assessments if any clinical signs or symptoms of cardiomyopathy or cardiac compromise are noted
  - Inclusion of an MRI/CT at baseline to check for CNS lymphoma or uncontrolled CNS disease
- Begin enrollment of Cohort 1B (AML) at the same time as Cohort 1A at the same doses
- Implement measures to mitigate the risk and manage tumor lysis syndrome including below:
  - Every subject will receive mandatory prophylaxis for tumor lysis syndrome (TLS) prior to the first dose of AMG 397 and prior to at all subsequent dose escalations
  - Allopurinol should be used to reduce uric acid level. This should be initiated at least 72 hours prior to dosing. Treatment may need to be continued for up to 5 weeks. Other agents to reduce uric acid level, such as rasburicase, may be used per PI discretion and the Institutional guidelines.
  - Upon admission, IV fluids (eg, D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs and as needed per Investigator discretion.

  - Monitor for signs and symptoms of TLS (eg, fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour.
  - Nephrology (or other acute dialysis service) consultation should be considered upon admission per institutional standards at investigators' discretion to ensure emergency dialysis is available and the appropriate staff is aware and prepared

- Typographical errors and inconsistencies between sections throughout the protocol were corrected.

Description of Changes:

1. **Title Page**

Removed strikethrough text, Added text in BOLD

Clinical Study Sponsor: Amgen Inc.
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Thousand Oaks, CA 91320
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Key Sponsor Contacts: [redacted] MD
Early Development Lead
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[redacted]
Clinical Research Study Manager
Phone: [redacted]
E-mail: [redacted]

Date: 30 November 2017
Amendment 1 **28 March 2018**

2. **Investigator's Agreement, page 2**

Removed strikethrough text, Added text in BOLD

Investigator's Agreement

I have read the attached protocol entitled "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", dated ~~30 November 2017~~**28 March 2018**, and agree to abide by all provisions set forth therein.

3. Protocol Synopsis; Primary Objectives, Exploratory Objectives

Added text in BOLD

Primary Objectives:

- Evaluate the safety and tolerability of AMG 397
- Estimate the maximum tolerated doses (MTDs) and/or biologically active doses (eg, recommended phase 2 doses [RP2Ds]) **of AMG 397**

Secondary Objectives:

- Evaluate the efficacy of AMG 397
- Evaluate the pharmacokinetics (PK) of AMG 397

Exploratory Objectives:

- Explore pharmacokinetic/pharmacodynamic (PK/PD) relationships for safety and/or efficacy endpoints
- Identify metabolite(s) of AMG 397 in plasma and urine
- 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
- Evaluate patient responses according to disease-specific features in tumor cells such as chromosomal amplifications, rearrangements, gene expression profiles, protein expression as well as somatic mutations as necessary
- Evaluate changes to immune cell subsets in peripheral blood due to MCL1 inactivation
- Assess Minimal Residual Disease (MRD) status with patient response as necessary

4. Protocol Synopsis; Study Design; 4th paragraph,

Removed strikethrough text, Added text in BOLD

Study Design:

This is a first-in-human (FIH), multicenter, non-randomized, open-label, phase 1 study evaluating AMG 397 administered orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle in adult subjects with selected RR hematological malignancies.

This study will consist of dose escalation (Part 1) to evaluate safety and tolerability and estimate the MTD/RP2D of AMG 397 using a Bayesian Logistic Regression Model (BLRM) in the following groups:

- Group 1A will consist of subjects with RR MM and/or NHL
- Group 1B will consist of subjects with RR AML

This will be followed by a dose expansion (Part 2) to gain further efficacy and safety experience with AMG 397 in adult subjects with RR MM, DLBCL, and AML.

The study will be conducted at up to 20 sites **globally** in Australia, ~~Canada, France~~**Europe, Japan,** and the United States (US). Other countries or regions may be added.

Dose Escalation– Part 1

Dose escalation will estimate MTDs for Groups 1A and Group 1B using an adaptive, BLRM design. The Dose Level Review Team (DLRT) will review data, monitor safety, and make decisions on dose escalation/change. The table below shows the planned dose levels for dose escalation.

Planned Doses per Dose Cohort Level

Dose Cohort Levels	Dose (mg)
1	80
2	160
3	320
4	640

Dose escalation will begin with 2-4 subjects treated at the lowest planned dose level of 80 mg with enrollment from Group 1A **and 1B**. Dose escalation will follow the planned schedule described above with 2-4 subjects treated in each cohort.

DLRT will convene to review the safety data and determine the appropriate dose to be implemented. Dose escalation/de-escalation decisions will be guided by the BLRM model of dose toxicity. Skipping of planned dose levels is not allowed. Dose escalation decisions will not be made until all subjects in a cohort(s) are monitored through the DLT-observation period of 2~~8~~**81** days following treatment initiation. Intermediate dose levels and alternative dosing schedule(s) may be explored based on emerging pharmacokinetic and safety data per the decision of the DLRT.

~~Dose escalation for Group 1B is anticipated to begin after at least one cohort from Group 1A completes the safety review for the DLT period. The starting dose level for Group 1B will be at the highest dose level from Group 1A, which the DLRT deems safe and tolerable.~~

Dose escalation for both Group 1A and 1B will continue until any of the following events:

- The highest planned dose level is determined to be safe and tolerable (minimum of 6 evaluable subjects)
- MTDs are identified for each group where BLRM repeats the recommendation of a dose level (minimum of 6 evaluable subjects)
- The maximum of 30 evaluable subjects have been enrolled in each group. If fewer than 6 subjects are treated at the MTD/RP2D, additional subjects may be enrolled to confirm safety and tolerability.

There is a potential for tumor lysis syndrome (TLS) in subjects with hematologic malignancies, especially in those with bulky disease, elevated pretreatment lactate dehydrogenase (LDH) levels, elevated leukocyte count, renal dysfunction, and dehydration. To mitigate the risk of TLS:

- **Tumor lysis syndrome prophylaxis must be initiated in all subjects prior to the first dose of AMG 397.**
- **Additionally, when an event meeting clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and Appendix L) is observed within seven days after therapy with AMG 397, lead-in dosing may be initiated to evaluate a step-wise dose escalation for all subsequent dosing. See Figure 2 for an example of lead-in dosing.**
- **For the management of TLS, please refer to Section 6.5.7 for more details**

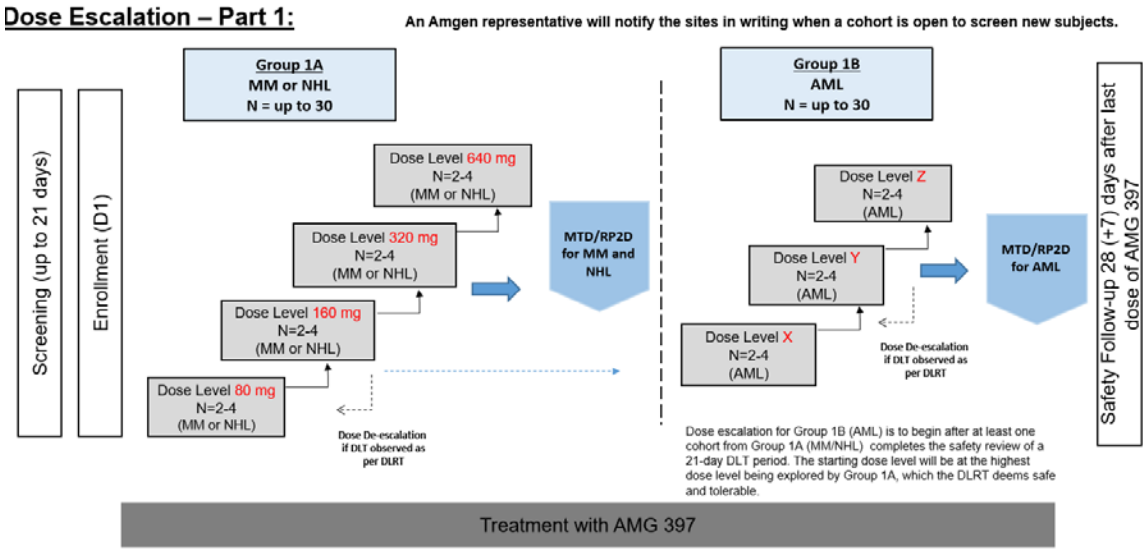
The DLRT will convene to review the safety data and may determine a lead-in dose which will not exceed the dose where the TLS was observed. Once TLS criteria is resolved, this lead-in dose will be administered for the first week of dosing (cycle 1 week 1). Upon completion of the lead-in dosing period, subject(s) will receive their designated target dose level of AMG 397 per Table 3 beginning on the second week of dosing (cycle 1 week 2) and all subsequent dosing.

NOTE: Once lead-in dosing is implemented, a maximum of 50% dose escalation of AMG 397 will be imposed between dose cohort levels per Table 3 for the target dose.

Decisions to modify the AMG 397 lead-in dosing period regimen, lead-in period starting dose, and dosing increments, will be made in conjunction with the investigator and Amgen medical monitor and communicated to the IRB/EC, as appropriate.

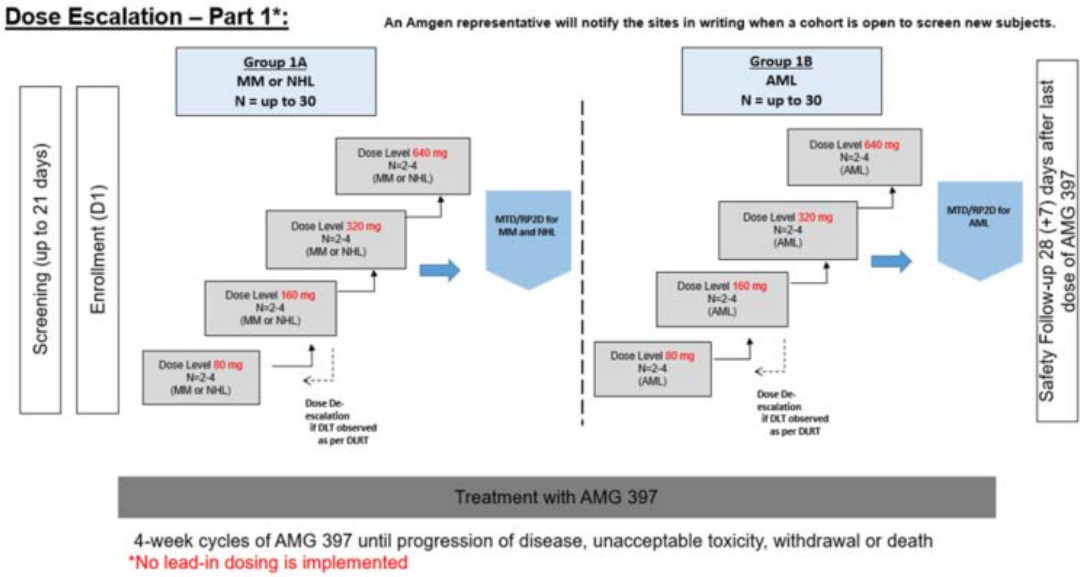
5. Protocol Synopsis; Study Design and Treatment Schema

Removed old figure:



Replaced Figure with Below:

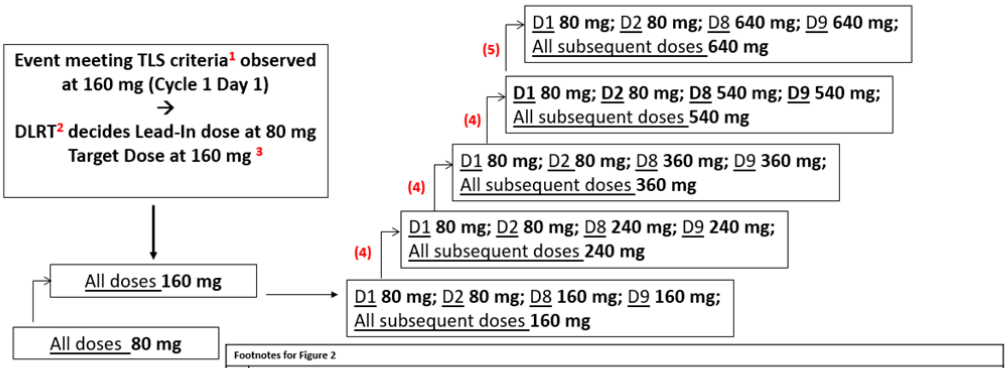
Study Design and Treatment Schema



6. Protocol Synopsis; Study Design and Treatment Schema

Added Figure 2:

Figure 2. Example of Lead-In Dosing



Footnotes for Figure 2	
1	At 160 mg, a subject is observed to have clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and Appendix L) on Cycle 1 Day 1, lead-in dosing will be employed to evaluate a step-wise dose escalation. NOTE: Event meeting TLS criteria observed within seven days after therapy with AMG 397 will trigger evaluation for lead-in dosing
2	DLRT reviews the safety data determine a lead-in dose which will not exceed the dose where the TLS was observed (80 mg). Once TLS criteria is resolved, this lead-in dose will be administered for the first week of dosing (cycle 1 week 1
3	Upon completion of the lead-in dosing period, subject(s) will receive their designated target dose level of AMG 397 per Table 3 beginning on the second week of dosing (cycle 1 week 2) and all subsequent dosing.
4	Once lead-in dosing is implemented, a maximum of 50% dose escalation of AMG 397 will be imposed between dose cohort levels per Table 3 for the target dose.
5	Current highest dose level is 640 mg per Table 3

7. Section 2.1.1 Multiple Myeloma Background, full Section

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Multiple myeloma is a plasma cell neoplasia characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, production of a monoclonal protein present in the blood or urine and associated organ dysfunction (Palumbo and Anderson 2011).

Multiple myeloma is the second most common (10-15%) ~~of all~~ hematological cancer. It is responsible for 15-20% of **all** deaths from hematological cancer and about 2% **of all** cancer deaths. Recent improved understanding of the pathogenesis of myeloma has led to the development of new treatments. Survival is improving, with median overall survival in the range of 7-10 years after initial diagnosis. Nevertheless, myeloma remains an incurable cancer, and with subsequent relapses, the disease becomes refractory to current treatments. Therefore, RR multiple myeloma is still an unmet medical need (Smith and Yong 2013).

Myeloma arises from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post–germinal-center B cells. Multistep genetic and micro-environmental changes lead to the transformation of these cells into a malignant neoplasm. Myeloma is thought to evolve most commonly from a monoclonal gammopathy of undetermined clinical significance (usually known as MGUS) that progresses to smoldering myeloma and, finally, to symptomatic myeloma. Several genetic abnormalities that occur in tumor plasma cells play major roles in the pathogenesis of myeloma (Palumbo and Anderson, 2011).

The uncontrolled growth of myeloma cells has many consequences, including skeletal destruction, bone marrow failure, increased plasma volume and viscosity, suppression of normal immunoglobulin production, and renal insufficiency (Durie, 2011). Symptomatic (active) disease should be treated immediately, whereas asymptomatic (smoldering) myeloma requires ~~only~~ clinical observation~~, since early treatment with conventional chemotherapy has shown no benefi~~t. Investigational trials are currently evaluating the ability of immunomodulatory drugs to delay the progression from asymptomatic to symptomatic myeloma. ~~The treatment strategy is mainly related to age.~~ Current data would support the initiation of induction therapy with thalidomide, lenalidomide, or bortezomib plus hematopoietic stem-cell transplantation for subjects under the age of 65 years who do not have substantial heart, lung, renal, or liver dysfunction. Autologous stem-cell transplantation with a reduced-intensity conditioning regimen should be considered for older subjects or those with coexisting conditions. ~~Conventional therapy combined with thalidomide, lenalidomide, or bortezomib should be administered in subjects older than 65 years of age.~~ Less intensive approaches that limit toxic effects or prevent treatment interruption that would reduce the intended treatment effect should be considered in subjects over 75 years of age or in younger subjects with coexisting conditions. Biologic age, which may differ from chronologic age, and the presence of coexisting conditions should determine treatment choice and drug dose (Palumbo and Anderson, 2011).

Treatment of RR MM presents a special therapeutic challenge, due to the heterogeneity of disease at relapse and the absence of clear biological based recommendations regarding the choice of salvage therapies at various time points of disease progression. With increasing recognition of the inherent clonal heterogeneity and genomic instability of the plasma cells influencing both inherent and acquired therapeutic resistance, the identification of the optimal choice and sequence of therapies has become critical.

Several new agents and targets are currently under development and show considerable promise. ~~Besides~~ **In the past 5 years,** carfilzomib, ~~and~~ **pP**omalidomide**, elotuzumab, ixazomib, daratumumab,** ~~that~~ were granted approval by US FDA ~~in 2012 and 2013 respectively~~ for RR MM. , ~~the next generation proteasome inhibitors (PIs) (ixazomib, marizomib and oprozomib), other molecularly targeted therapies directed at specific cell signaling pathways (including histone deacetylase inhibitors, PI3K/AKT/mTOR inhibitors, Hsp90 inhibitors, cell cycle inhibitors, kinesin spindle protein inhibitors) are currently in development. Even newer approaches such as monoclonal antibodies targeting SLAMF7, CD38, CD138, and others have also demonstrated promising anti-myeloma activity (Nooka, 2014).~~ Despite advances in the management of multiple myeloma**, however,** ~~as described,~~ relapse is inevitable in almost all subjects. Recurrence of myeloma is typically more aggressive with each relapse, leading to the development of treatment-refractory disease, which is associated with a shorter survival (Dimopoulos, 2015). **Thus, there remains an urgent need for treatment options for patients with RR MM.** ~~More treatment options are still warranted.~~

8. **Section 2.1.2 Non-Hodgkin's Lymphoma Background, first paragraph**

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About 74,680 people (41,730 males and 32,950 females) will be diagnosed with Non Hodgkin's Lymphoma (NHL), and about 19,910 people will die from this malignancy. ~~The annual incidence of Non-Hodgkin's Lymphoma (NHL) in Europe and the United States is estimated to be 15 to 20 cases/100,000 (Fisher and Fisher, 2004).~~ Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, accounting for 30% to 40% of cases and 13% of all hematologic disorders. The incidence is approximately 8 cases per 100,000 and rises with age; the median age at diagnosis is 70 years (Haematological Malignancy Research Network). Morphologically similar entities have historically been treated in a similar manner as DLBCL, and thus are collectively known as aggressive B-cell lymphomas. DLBCL as a uniform diagnostic entity, makes up approximately 85% of aggressive B-cell lymphomas (Ziepert et al, 2010). However, distinct patterns of gene expression are observed within DLBCL, with different prognostic and potentially predictive implications (Swerdlow et al, 2016). Left untreated, DLBCL is uniformly fatal. Anthracycline-based frontline chemotherapy, introduced in the 1970s, resulted in the long term cure of 30% of patients (DeVita et al, 1975). Twenty-five years later, introduction of the human-mouse chimeric monoclonal anti-CD20 immunoglobin G (IgG) rituximab increased the cure rate significantly and is now a standard agent in frontline therapy, resulting in cure for 60% of patients (Sehn and Gascoyne 2015). Patients with DLBCL who do not respond to

9. Section 2.2.3 Pharmacokinetics, second paragraph

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AMG 397 was an inducer of CYP2B6, CYP2C9, and CYP3A4, and reversible inhibitor of CYP2B6, CYP2C8, and CYP3A4 in vitro while it was not an inhibitor of other major drug metabolizing human CYP enzymes such as CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. AMG 397 was also a time-dependent inhibitor of CYP3A4 but not of any of the other CYPs tested. Additionally, AMG 397 was identified as an inhibitor of P-gp (IC_{50} of 8.7 µM). **For BCRP, MATE1, MATE2-K, and OATP1B1, incomplete inhibition (36 – 54%) was observed at the highest test concentration (100 µM) of AMG 397, suggesting weak inhibition.** ~~At the highest test concentration (100 µM) of AMG 397, incomplete inhibition was observed for additional transporters; BCRP (51%), MATE1 (54%), MATE2-K (48%), and OATP1B1 (36%). AMG 397 was not an inhibitor of OATP1B3, OAT1, OAT3, OCT1, or OCT2~~. Considering dose **levels** and ~~dosing~~ frequency~~, and~~ based on physiologically based pharmacokinetic modelling, it was determined that AMG 397 has a potential to interact with CYP3A4 and P-gp.

10. Section 2.2.4 AMG 397 Preclinical Toxicology, last paragraph

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Tumor Lysis Syndrome

Tumor lysis syndrome has been observed in a clinical trial with a drug of the same mechanism of action (AMG 176). Administration of AMG 176 has been associated with tumor lysis syndrome with fatal outcome. Subjects with a high tumor burden or compromised renal function (eg, International Staging System [ISS] Stage II/III) may be at elevated risk for tumor lysis syndrome.

Blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) must be assessed in all subjects and any pre-existing abnormalities must be corrected prior to starting treatment with AMG 397. In addition, subjects must be appropriately hydrated prior to each dose of AMG 397. Further details regarding mandatory tumor lysis syndrome prophylaxis are provided in the study protocol in Section 6.5.7.

11. Section 3.1 Study Design; Dose Escalation – Part 1

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Dose Escalation– Part 1

During dose escalation (Part 1) AMG 397 will be administered orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle.

Dose escalation will estimate MTDs for Group 1A and Group 1B using an adaptive, BLRM design. Table 3 shows the planned dose levels for dose escalation. The Dose Level Review Team (DLRT) will review data, monitor safety, and make decisions on any dose escalation/change. For more details regarding the dose escalation, please see Section 6.2.1.2.

Table 3. Planned Doses per Dose Cohort Level

Dose Cohort Levels	Dose (mg) PO
1	80
2	160
3	320
4	640

Dose escalation for Group ~~1a~~**1A and Group 1B** will begin with 2-4 subjects treated at the lowest planned dose level of 80 mg. Dose escalation will follow the planned schedule described above with 2-4 subjects treated in each cohort.

DLRT will convene to review the safety data and determine the appropriate dose to be implemented. Dose escalation/de-escalation decisions will be guided by the BLRM model of dose toxicity. Skipping of planned dose levels is not allowed. Dose escalation decisions will not be made until all subjects in a cohort(s) are monitored through the DLT-observation period of ~~21~~ **28** days following treatment initiation. Intermediate dose levels and alternative dosing schedule(s) may be explored based on emerging pharmacokinetic and safety data per the decision of the DLRT.

~~Dose escalation for Group 1B is anticipated to begin after at least one cohort from Group 1A completes the safety review for the DLT period. The starting dose level for Group 1B will be at the highest dose level from Group 1A, which the DLRT deems safe and tolerable.~~

Dose escalation for both Group 1A and 1B **respectively,** will continue until any of the following events:

- The highest planned dose level **for each group** is determined to be safe and tolerable (minimum of 6 evaluable subjects)
- MTDs are identified for each group where BLRM repeats the recommendation of a dose level (minimum of 6 evaluable subjects)
- The maximum of 30 evaluable subjects have been enrolled in each group. If fewer than 6 subjects are treated at the MTD/RP2D, additional subjects may be enrolled to confirm safety and tolerability.

Intermediate doses and alternative dosing schedule(s) may be explored based on emerging pharmacokinetic and safety data as decided by the DLRT.

Lead-in Dosing
Due to the potential risk of TLS for subjects affected by hematologic malignancies, it is anticipated that lead-in dosing may be implemented. At any point during the study, when an event meeting clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and Appendix L) is observed within seven days after therapy with AMG 397, lead-in dosing may be initiated to evaluate a step-wise dose escalation for all subsequent dosing. See Figure 2 for an example of lead-in dosing. See Section 6.2.1.1.1 for more details

12. Section 3.2; Number of Sites

This study will be conducted at up to 20 sites **globally** in Australia, ~~Canada,~~ ~~France~~**Europe, Japan** and ~~the United States~~**the United States**. Additional regions, countries, or sites may be added.

Sites that do not enroll subjects into an open cohort within 4 months of site initiation during dose escalation or expansion may be closed or replaced.

13. Section 3.4; Replacement of Subjects

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During dose escalation, subject**(**s**)** ~~that are not DLT-evaluable~~ may be replaced **if:**

- ~~. A subject is n~~**Subject(s) is not**~~ot~~ DLT-evaluable. **See Section 6.2.1.2 for definition of DLT-evaluable**
- ~~if the s~~**S**ubject**(s)** discontinues treatment for any reason other than a DLT **during the DLT-observation period** ~~prior to completing the first 21 days of AMG 397 treatment.~~

Additional subjects may **also** be enrolled if Amgen's medical monitor determines that the minimum required number(s) of evaluable subjects have not been enrolled in each cohort.

14. Section 4.1; Inclusion Criteria

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4. SUBJECT ELIGIBILITY

4.1 Inclusion Criteria

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

102. Age ≥ 18 years old

103. Pathologically-documented, definitively-diagnosed relapsed or refractory MM, NHL, or AML (**Appendix G**~~Appendix G~~) ~~for~~ **and is intolerant to, or considered ineligible for available therapies known to provide clinical benefit.**

~~103. which no standard therapy is available or the subject refuses standard therapy~~

104. MM subjects only:

- Measurable disease per the IMWG response criteria (**Appendix E**~~Appendix E~~; assessed within 21 days prior to enrollment), as indicated by one or more of the following**:**
  - Serum M-protein ≥ 0.5 g/dL
  - Urine M-protein ≥ 200 mg/24 hours
  - For Subjects who do not meet 1 of the 2 prior criteria:
    - Serum Free Light Chain (sFLC) ≥ 10 mg/dL (≥ 100 mg/L) ~~and~~**AND** an abnormal sFLC ratio (< 0.26 or > 1.65) as per the IMWG response criteria

105. NHL subjects only:

- Radiographically measurable disease with a clearly demarcated nodal lesion at least 1.5 cm in its largest dimension or a target extranodal lesion at least 1.0 cm in its largest dimension

106. AML subjects only:

- Pathologically confirmed diagnosis of AML as defined by the WHO Classification (**Appendix H**~~Appendix H~~)
- More than 5% blasts in bone marrow

15. Section 4.1 Inclusion Criteria; Additional criteria for Part 2 – Dose Expansion Subjects

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Additional criteria for Part 2 - Dose Expansion subjects

114. MM subjects only

- Pathologically documented, definitively diagnosed, relapsed or refractory disease following at least **3**~~2~~ lines of therapy including **but not limited to** a proteasome inhibitor, an immunomodulatory agent and/or CD38-targeted immunochemotherapy.

  NOTE: The investigator must be of the opinion that no other treatment option will result in a durable response.

115. NHL subjects only

- Pathologically confirmed ~~de novo DLBCL, or~~ DLBCL **who have failed at least two prior therapies** ~~transformed from previously diagnosed indolent lymphoma following front line treatment of standard multiagent chemotherapy containing an anthracycline AND an approved anti-CD20 agent. Examples of appropriate therapy include but are not limited to R-CHOP (14 or 21), R-CHOEP, and DA-R-EOCH.~~

  NOTE: For subjects with refractory disease and who have received radiotherapy, PET positivity should be demonstrated no less than 6 weeks after the last dose of radiotherapy.

116. AML subjects only

- Pathologically confirmed diagnosis of AML as defined by the WHO Classification (**Appendix H**~~Appendix H~~) persisting or recurring following no more than 2 lines of prior therapies

16. Section 4.2 Exclusion Criteria

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4.2 Exclusion Criteria

201. Previously received an allogeneic stem cell transplant within 6 months of study day 1 OR having signs or symptoms of acute or chronic graft-versus-host disease

202. Autologous stem cell transplant < 90 days prior to study day 1

~~202.~~**203.** **Candidates for stem cell transplant should have failed or are not considered eligible for either allogeneic and autologous transplant**

~~203.~~**204.** History of other malignancy except:

- Malignancy treated with curative intent and with no known active disease present for ≥ 2 years before enrollment and felt to be at low risk for recurrence by the treating physician
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated cervical carcinoma in situ without evidence of disease
- Adequately treated breast ductal carcinoma in situ without evidence of disease
- Prostatic intraepithelial neoplasia without evidence of prostate cancer
- Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ

205. Myocardial infarction within 6 months of study day 1

~~204.~~**206.** Symptomatic congestive heart failure (New York Heart Association > Class II) (**Appendix F**~~Appendix F~~)

~~205.~~**207.** History of arterial thrombosis (eg, stroke or transient ischemic attack) in the past 6 months prior to study day 1

~~206.~~**208.** **Uncontrolled active** ~~i~~infection requiring intravenous anti-infective treatments within 1 week of study day 1

~~207.~~**209.** Known positive results for human immunodeficiency virus (HIV)

17. Section 4.2 Exclusion Criteria; pages 45-47

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214. Males and females of reproductive potential who are unwilling to practice an acceptable method(s) of effective birth control while on study through 3 months after receiving the last dose of study drug. Acceptable methods of effective birth control include sexual abstinence (males, females); vasectomy; bilateral tubal ligation/occlusion; or a condom with spermicide (men) in combination with barrier methods (diaphragm, cervical cap, or cervical sponge), hormonal birth control or IUD (females).

NOTE: A woman is considered of childbearing potential (WOCBP), (i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

- **A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.**

~~213.~~**215.** Females who are lactating/breastfeeding or who plan to breastfeed while on study through 3 months after receiving the last dose of study drug.

~~218.~~**220.** Use of herbal medicines (eg, St. John's wort), vitamins, and supplements consumed by the subject within ~~the 30 days~~**14 days** prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor

227. NHL subjects with the following criteria are excluded:

- **CNS lymphoma or evidence of uncontrolled CNS disease**
- **Burkitt's lymphoma**
- **Lymphoblastic lymphoma**

~~225.~~**228.** **AML subjects with any of the following criteria are excluded:**

- Circulating white blood cells > 25,000 /µl. Hydroxyurea to control peripheral blood leukemic cell counts, within 24 hours of study day 1 is permitted.
- Promyelocitic leukemia

18. Section 6.2.1.1 Dosage, Administration and Schedule

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During dose escalation (Part 1), ~~and dose expansion (Part 2)~~ AMG 397 will be given orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle. **Table 3 shows the planned dose levels for dose escalation.**

~~2. On days especially when PK samples will be taken, doses will be administered in clinic. Subjects will self-administer AMG 397 on all other days.~~

~~The planned dose levels for escalation are 80, 160, 320, and 640 mg.~~ **During dose expansion (Part 2) AMG 397 will be given orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle.** The planned dose level(s) for dose expansion will be determined based on data collected during dose escalation.

On days of hospitalization and during clinic visits, doses will be administered at the clinic. Subjects will self-administer AMG 397 on all other designated timepoints per Table 4 and 5 on days without clinic visits.

AMG 397 can be taken with or without food (i.e., subjects may choose to eat prior to or after taking study drug). ~~A missed dose will not be made up.~~ The tablet should be swallowed whole without crushing or breaking. No tablet should be ingested if it is broken, cracked, or otherwise not intact.

Subjects will be asked to record the date, time, and number of tablets consumed in a subject drug diary that must be brought to each study visit and will be reviewed by study staff. **The amount dosed, lot number of IP, and start date will be recorded on each subject's eCRF(s).**

The amount dispensed, amount returned, date dispensed, date returned, **and** lot number of AMG 397 are to be recorded in the site's drug accountability log for each subject. ~~The amount dosed, lot number of IP, and start date will be recorded on each subject's eCRF(s).~~ **Please refer to the Investigational Product Instructional Manual for more details on dosage, administration and schedule of AMG 397.**

~~Pre-dosing considerations for AMG 397~~

~~No routine pre-medication should be administered prior to the first dose of AMG 397.~~ If a subject develops a reaction, subjects should acutely be treated according to best clinical practice. Medication may be administered as deemed appropriate by the investigator to control any reactions according to best clinical practice. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. All medication and symptoms should be documented in the eCRF. Amgen must be notified within 24 hours when a subject has had ≥ Grade 3 AE.

The effects of overdose of this product are not known.

19. Section 6.2.1.1.1 Lead-in Dosing

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There is a potential for tumor lysis syndrome (TLS) in subjects affected by hematologic malignancies especially in those with bulky disease, elevated pretreatment lactate dehydrogenase (LDH) levels, elevated leukocyte count, renal dysfunction, and dehydration. To mitigate the risk of TLS, tumor lysis syndrome prophylaxis must be initiated in all subjects prior to the first dose of AMG 397 and prior to any dose escalation (Section 6.5.7).

Additionally, when an event meeting clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and Appendix L) is observed, lead-in dosing may be initiated to evaluate a step-wise dose escalation for all subsequent dosing. See Figure 2 for an example of lead-in dosing. .

The DLRT will convene to review the safety data and may determine a lead-in dose which will not exceed the dose where the TLS was observed. Once TLS criteria is resolved, this lead-in dose will be administered for the first week of dosing (cycle 1 week 1). Upon completion of the lead-in dosing period, subject(s) will receive their designated target dose level of AMG 397 per Table 3 beginning on the second week of dosing (cycle 1 week 2) and all subsequent dosing.

> NOTE: Once lead-in dosing is implemented, a maximum of 50% dose escalation of AMG 397 will be imposed between dose cohort levels per Table 3 for the target dose.

Once lead-in dosing is initiated, additional monitoring of electrolyte values is required prior to dosing at the following times (see Table 4 and Table 5):

- Prior to the Week 1, Day 1 Dose
- Prior to each dose during the Lead-in Period
- Prior to the initial dosing at the target dose level

Prior to administering AMG 397, all electrolyte values (ie, potassium, uric acid, inorganic phosphorus, calcium) must be within normal range.

> NOTE: Laboratory value changes must be confirmed by another laboratory test (1-2 hours later) prior to assigning a TLS grade.

Dose Adjustments for Lead-In Dosing
Evidence of TLS will be carefully monitored on study and AMG 397 will be held until resolution of TLS abnormalities. Following lead-in dosing of AMG 397, if one

or more Cairo-Bishop criteria is met (See Appendix K and Appendix L), no additional AMG 397 doses will be administered until it is resolved (eg, laboratory values are no longer within range of the values stated in Appendix K and Appendix L). Upon resolution, the subject will repeat the lead-in dosing for an additional week prior to receiving the target dose.

NOTE: Lead-in dosing will be repeated if the subject is observed to meet one or more of the Cairo-Bishop criteria post-dose.

Decisions to modify the AMG 397 lead-in dosing period regimen, lead-in period starting dose, and dosing increments, will be made in conjunction with the investigator and Amgen medical monitor and communicated to the IRB/EC, as appropriate.

20. Section 6.2.1.2 Dose-cohort Study Escalation and Stopping Rules

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6.2.1.2 Dose-cohort Study Escalation and Stopping Rules

The Dose Level Review Team (DLRT) will convene before decisions to dose escalate or de-escalate is made or when cohorts are suspended per protocol. The DLRT will be composed of select Investigator(s), Amgen medical monitor, Amgen Global Safety Officer or designee, Amgen Clinical Research Study Manager (CRSM) and Biostatistics representative or designee. Additional members may be added as needed (eg, clinical pharmacologist). The DLRT voting members include the Amgen Medical Monitor and Global Safety Officer or designee, in consultation with the investigator(s) or designee. The DLRT members are responsible for dosing decisions, which may include escalation to the next nominal or intermediate dose, de-escalation to a lower nominal or intermediate dose; alternative dose frequencies, continuation, delay or termination of dosing; or repetition or expansion of a cohort; or determination of RP2D.

See Section 3.1 for more details regarding the study design and the dose escalation plan for this study.

The DLT-observation period is defined as, at minimum, 28 days after the initial dose of AMG 397. Once 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.

A subject is deemed ~~A subject is classified as~~ DLT-evaluable **if during the DLT-observation period, the subject:** ~~if~~

- ~~he/she experiences a DLT (and follow up is sufficient to determine the incidence of DLT), or if he/she otherwise R~~**R**eceive~~s~~**d** at least **7**~~8~~5% of the planned dose of AMG 397 ~~in the DLT window.~~
- ~~The DLT window is defined as 21 days after the initial dose of AMG 397.~~**Experienced a DLT**

Available study data, including data collected after the initial ~~DLT window~~**DLT-observation period** along with demographics, IP administration, medical history, concomitant medications, adverse events (AE), ECG, vital signs, laboratory results and PK/PD information will be reviewed. In addition to DLTs, all ≥ grade 3 toxicities not meeting DLT criteria will be reviewed and may be considered in DLRT decisions. Modeling of available potential safety risk data (eg, for thrombocytopenia) to predict safety risk for dose escalation decisions may also be considered.

Dose escalation/de-escalation decisions will be guided by the BLRM model of dose toxicity described by **Appendix D**~~Appendix D~~. An Amgen representative will notify the sites in writing the dosing decision from the DLRM and when a cohort is open to screen new subjects.

DLTs experienced by subjects after completing the DLT period will be considered in the BLRM design to account for any late onset toxicity.

Dose escalation for each group will continue until any of the following events occur:

- The highest planned dose level is determined to be safe and tolerable (minimum of 6 evaluable subjects)
- MTDs are identified for each group where BLRM repeats the recommendation of a dose level (minimum of 6 evaluable subjects)
- The maximum of 30 evaluable subjects have been enrolled in each group. If fewer than 6 subjects are treated at the MTD/RP2D, additional subjects may be enrolled to confirm safety and tolerability.

If there are concerns about the tolerability of the current ~~continuous~~ dosing schedule, alternative dosing schedules or lower dose(s) may be explored, including modification of the lead-in period dosing regimen. The alternative dose and schedule will be jointly determined by the investigators and the Amgen medical monitor, based on pharmacokinetic and safety and toxicity data.

21. Section 6.2.1.3, Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

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NOTE: For subjects who meet clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and L) see Section 6.2.1.1.1 for dose adjustment details.

Dosage Adjustments

The subject should continue on the same dose of AMG 397 throughout the study unless the following events occur:

- For subjects experiencing an adverse event meeting the DLT definition or intolerable related adverse events BUT showing evidence of response, there will be an option to reduce the dose to the immediate next lower dose level shown to be safe and tolerable in the dose escalation part of the study.
- AMG 397 can be resumed once the adverse events recover to baseline or Grade 1 and the reintroduction of AMG 397 is deemed safe by the Investigator, Amgen's Medical Monitor, and Global Safety Officer.

  NOTE: Subjects must be informed of the risk of continuing on therapy. Each subject is only allowed a single dose reduction.

Subjects should not be re-challenged with AMG 397 if the following AMG 397-related adverse events occur:

- Any life-threatening adverse events
- DILI (Drug Induced Liver Injury) meeting Hy's law
- Persistent grade 3 adverse events that do not recover to baseline or Grade 1 within 4 weeks of last dose
- Any treatment-related adverse event meeting DLT-criteria that recurs

Dosage Delays

The investigator should inform the Amgen Clinical team as soon as the unexpected dosage delay occurs. The following dosage delay rules apply:

~~During the DLT window, if the dosing is delayed for more than 48 hours the subject will be removed from the study and will be replaced.~~

~~After DLT window:~~

- If the dosing delay is ≤ 3 weeks, the subject should resume the treatment as soon as possible if deemed safe by the investigator.
- If the dosing delay is more than 4 weeks (missing 1 cycle):
  - Due to treatment related AEs, the subject will be removed from the study.
  - Due to other conditions other than treatment related AEs, the case will be reviewed by Amgen medical monitor to determine whether the subject will be allowed to resume AMG 397 treatment.

Rules for Dose Withholding

AMG 397 should be withheld for any of the following:

- Suspected DLT (including AE**s** that meet DLT definition outside ~~DLT window~~**DLT-observation period**)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 x ULN or total bilirubin greater than 1.5 x ULN

Rules for Restarting

AMG 397 dosing can be resumed:

- If the toxicities resolve to grade ≤ 1 or return to subjects' baseline values
- Restarting of therapy is deemed safe by the investigators and Amgen's medical monitor.

Rules for Permanent Discontinuation

Subjects will permanently discontinue from the investigational product if:

- Subjects experience adverse events meeting the DLT criteria at any time. Subjects will be followed until the DLT is resolved, returns to baseline value or is considered stable. Subjects will be withdrawn from AMG 397 treatment and will be treated as deemed appropriate by the investigator or treating physician. Except for:
  - Subjects showing evidence of response or subjects who in the opinion of the investigator may be responding to AMG 397, may have the option to continue therapy once the adverse events recover to baseline or Grade 1 and the re-introduction of AMG 397 is deemed safe by the investigator, Amgen's medical monitor, and Global Safety Officer. The subject should restart at a reduced dose.
  - **Subjects who experience TLS as detail, see Section 6.2.1.1.1 for dosing details.**
- Intolerability of the study treatment
- The dosing is delayed > 4 weeks due to AMG 397-related adverse events
- Disease progression according to IMWG (MM), Lugano classification (NHL), or 2017 ELN response criteria (AML) and/or per institutional guidelines as applicable
- Clinical significant deterioration of health status
- Withdrawal of informed consent
- Subject becomes pregnant or is breastfeeding
- Initiation of new systemic anti-cancer therapy not provided in this study
- Study is terminated by the sponsor.

22. Section 6.3.1; Pre-dosing requirements for AMG 397

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6.3 Other Protocol Required Therapies

6.3.1 Pre-dosing requirements for AMG 397

To mitigate risk of TLS, all subjects are to receive TLS prophylaxis prior to first dose of AMG 397 and prior to any dose escalation. Refer to Section 6.5.7 for specific requirements.

23. Section 6.4; Dose Limiting Toxicities

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~~6.36.4~~ **Dose Limiting Toxicities**

The grading of adverse events will be based on the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (available online at http://evs.nci.nih.gov/ftp1/CTCAE/About.html). Determination of the severity of adverse events will be consistent with Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. ~~The relationship of an adverse event to investigational product will be determined by the Investigator. An event should be considered related to treatment if, in the Investigator's medical judgment, there is a reasonable possibility that the event may have been caused by AMG 397.~~

For MM and NHL subjects only:

A DLT is defined as a ~~clinically significant,~~ treatment-related AE(s), ~~with certain exceptions, below~~ that occur during the ~~DLT window~~**DLT-observation period** (~~day 1 through day 21 after the administration of the first dose of AMG 397~~**see Section 6.2.1.2**) **including any** ~~that is~~:

- **≥ Grade 3 non-hematological AE's EXCEPT:**
  - **≥ Grade 3 fatigue if <7 days**
  - **Grade 3 nausea, vomiting and/or diarrhea if < 3 days and controlled with medical management**
  - **Laboratory parameters of grade ≥ 3 that improve with medical management to grade ≤ 2 within 3 days**
- **≥ Grade 4 hematologic AE's AND:**
  - ≥ Grade 3 neutropenia with fever
  - ≥ Grade 3 thrombocytopenia with Grade ≥ 2 hemorrhage
  - ≥ Grade 3 anemia with symptoms requiring intervention (eg, transfusion)

  NOTE: ≥ Grade 4 neutropenia must be lasting > 7 days
- **Any grade 5 AE that is not clearly due to disease progression**

~~≥ Grade 3 non-hematological AE~~

~~≥ Grade 4 or higher hematologic AE~~

~~DLT toxicities do not include fatigue, nausea, diarrhea, vomiting, acute kidney injury, neutropenia, anemia, thrombocytopenia, and lymphopenia unless the following criteria are met:~~

~~Hematological toxicity:~~

~~≥ Grade 4 neutropenia lasting > 7 days~~

~~≥ Grade 3 neutropenia with fever > 38.5°C~~

~~≥ Grade 3 thrombocytopenia with ≥ Grade 2 hemorrhage~~

~~≥ Grade 4 thrombocytopenia lasting > 7 days~~

~~≥ Grade 3 anemia with symptoms or required intervention (eg, transfusion)~~

~~≥ Grade 4 anemia~~

~~Non-hematological toxicity:~~

~~≥ Grade 3 nausea, vomiting or diarrhea persisting more than 3 days despite optimal medical support~~

~~≥ Grade 3 fatigue persisting > 7 days~~

~~≥ Grade 3 acute kidney injury (creatinine >3 X baseline or > 4.03 mg/dL) lasting > 3 days~~

For AML subjects only:

Due to the nature of AML, hematologic adverse events will not be considered DLTs. However, prolonged pancytopenia in the presence of a hypocellular bone marrow (ie, cellularity 5% or less without evidence of leukemia) that lasts longer than 42 days will be considered dose-limiting myelosuppression.

Non-hematological toxicity:

- ≥ Grade 3 nausea, vomiting or diarrhea persisting more than 3 days despite optimal medical support
- ≥ Grade 3 fatigue persisting > 7 days
- Any other ≥ Grade 3 adverse event
- Failure to recover from AMG 397 related toxicities to grade ≤ 1 or baseline severity after delaying next cycle up to 14 days

For all subjects: ~~Tumor Lysis Syndrome:~~

- **Any Clinical TLS ~~(~~refer to Appendix K~~J~~)**

If a DLT of TLS is observed during the lead-in period, it will be attributed to the lead-in

period and a modification may be made to the lead-in period regimen for subsequent

cohorts. Any other DLTs observed during the lead-in and/or designated cohort dosing
period may require a modification of the designated cohort dose (and/or lead-in period
regimen, if appropriate) as directed per the Dose Escalation Guidelines.

Any subject meeting the criteria for Hy's Law case (ie, severe drug-induced liver injury) will be considered a DLT. A Hy's Law case is defined as: AST or ALT values of ≥ 3x ULN AND with serum total bilirubin level (TBL) of > 2x ULN without signs of cholestasis and with no other clear alternative reason to explain the observed liver-related laboratory abnormalities (see Section ~~6.6~~**6.7** for hepatotoxicity management and **Appendix A**~~Appendix A~~ for further explanation of Hy's law case and Management of Hepatic Function). Grade 3 or 4 elevation of serum lipase without clinical signs or symptoms of pancreatitis.

24. Section 6.5.7; Tumor Lysis Syndrome (TLS)

Added below text

Prophylaxis and Management of TLS

Tumor lysis syndrome prophylaxis must be initiated in all subjects prior to the first dose of AMG 397 and prior to every dose escalation.

The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be conducted per institutional protocols (Coiffier et al, 2008; Cairo et al, 2004).

- Initiate allopurinol or equivalent to reduce uric acid level. This should be initiated at least 72 hours prior to dosing. Treatment may need to be continued for up to 5 weeks. Other agents to reduce uric acid level, such as rasburicase may be used per PI discretion. Dosing per institutional guidelines.
- All subjects will be hospitalized for intensive monitoring:
    - For the first 2 doses received, beginning 24 hours prior to first dosing day (Day -1) until 24 hours post the second dose
    - Once lead-in dosing is initiated (see Section 6.2.1.1.1):
        - For the first 2 doses received (Lead-in dosing), beginning at least 24 hours prior to first dosing day (Day -1) until 24 hours post the second dose
        - Each time an additional week of lead-in dosing is instituted (Section 6.2.1.1.1)
        - For the first 2 doses received after the dose is escalated (target dose) beginning at least 24 hours prior to dosing day (usually day 7) until 24 hours post the second dose
- During hospitalization, intensive safety laboratory monitoring per designated timepoints per Table 4 and/or 5 to identify and prompt management of any metabolic changes.
    - Pre-treatment serum chemistry and hematology laboratory samples must be drawn within 24 hours prior to first dose, and electrolyte values (ie, potassium, uric acid, inorganic phosphorus, calcium) must be reviewed and within normal range prior to AMG 397 dosing. The investigator's decision to proceed with AMG 397 treatment initiation may be based on these laboratory values. These labs must be reviewed in real time by the investigator.

      NOTE: If the potassium, uric acid, inorganic phosphate and/or creatinine values are higher than the normal range or the calcium is lower or higher than the normal range, dosing can be resumed following review of laboratory values and agreement between the Amgen medical monitor and investigator.

  - Prophylactic reductions of potassium, inorganic phosphorus and/or uric acid above of normal range prior to dosing are recommended per PI discretion.
  - Day 2 dosing of AMG 397 should not be administered until the 24 hours post-dose laboratory values are reviewed by the investigator.
  - All 24 hour laboratory assessments may be taken ± 2 hours, if necessary.
- Within the first 24 hours after either the first dose or dose escalation, if any laboratory criteria (Appendix L) are met, no additional AMG 397 doses should be administered until resolution. A rapidly rising serum potassium is a medical emergency.
- Upon admission, IV fluids (eg, D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs and as needed per Investigator discretion.
- Monitor for signs and symptoms of TLS (eg, fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour.
- Nephrology (or other acute dialysis service) consultation should be considered upon admission per institutional standards at investigators' discretion to ensure emergency dialysis is available and the appropriate staff is aware and prepared.
- Management recommendations of laboratory abnormalities as stated below:

Abnormality	Management Recommendations[1,2]
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. • At discretion of Investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the Investigator. Potassium, phosphorus, uric acid, calcium and creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology notification with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. ○ If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis.

Abnormality	Management Recommendations[1,2]
Hyperkalemia (including rapidly rising potassium) (continued)	
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq/kg IV push. ○ If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes). ○ If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	• Administer rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes). ○ When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Consult nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.

Abnormality	Management Recommendations[1,2]
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 to 2 hours STAT.

References:

1. Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26(16):2767-78.

2. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004;127(1):3-11.

25. Section 6.8; Concomitant Therapy

Added text in BOLD:

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, G-CSF and other care as deemed appropriate, and in accordance with their institutional guidelines. For subjects with AML hydroxyurea for 7 days at a dose of 1 – 10 g/day is allowed prior to the first cycle of AMG 397 treatment for subjects with high WBC (> 25,000 cells/ul) and during the first cycle but not on dosing days at a dose of up to 5 g/day.

26. Section 6.10; Excluded Treatments and Procedures During Study Period

Removed strikethrough text, Added text in BOLD

~~6.96.10~~ **Excluded Treatments and Procedures During Study Period**

The following medications and/or therapies should not be administered ~~within the timeframes specified prior to enrollment or~~ during the study ~~(unless otherwise specified)~~:

- Allogeneic stem cell transplant ~~within 6 months of study day 1~~
- Autologous stem cell transplant ~~< 90 days prior to study day 1~~
- Antitumor therapy (chemotherapy, antibody therapy, molecular-targeted therapy, retinoid therapy, or investigational agent or procedures)
  - ~~within 14 days of study day 1.~~
  - ~~Prior s~~**S**ystemic ~~radiation therapy must have been completed at least 28 days before study day 1. Prior~~ **or** focal radiotherapy ~~completed at 14 days before study day 1.~~
  - Over-the-counter ~~or prescription~~ medication**(**s**)** ~~within 14 days or 5 half lives (whichever is longer), prior to study day 1~~ that was not reviewed and approved by the principal investigator and the Amgen medical monitor
  - ~~Use of a~~**A**ny known inhibitors of P-gp ~~within 14 days or 5 half lives (whichever is longer)~~ or grapefruit juice or grapefruit containing products ~~within 7 days prior to study day 1~~ that w**ere**~~as~~ not reviewed and approved by the principal investigator and the Amgen medical monitor
- ~~Use of h~~**H**erbal medicines (eg, St. John's wort), vitamins, and supplements ~~consumed by the subject within the 30 days prior to study day 1~~ that w**ere**~~as~~ not reviewed and approved by the principal investigator and the Amgen medical monitor
- ~~Use of~~**Any** known cytochrome P450 (CYP) 3A4 sensitive substrates, with a narrow therapeutic window, ~~within 14 days or 5 half lives (whichever is longer) of the drug or its major active metabolite prior to study day 1~~ that wa**were**~~s~~ not reviewed and approved by the principal investigator and the Amgen medical monitor

If use of any **other** prior or concomitant medication or procedure is in question, please refer to prescribing information and/or consult with Amgen Medical Team.

27. Section 7.1, Schedule of Assessments

Removed strikethrough text, Added text in BOLD

7.1 Schedule of Assessments

Please refer to Table 4 for Schedule of Assessments.

Once lead-in dosing is initiated follow Table 5 for Cycle 1 only. For all subsequent cycles and study periods follow Table 4.

Table 4. Schedule of Assessments

	SCREENING	TREATMENT																																EOT	SAFETY FOLLOW-UP	LTFU (24~~6~~)
CYCLE(S)			1																											2				Every cycle from 3 & beyond			
WEEK(S)			1																		2							3		1	2	3	1			
DAY(S)	-21 to -2	-1	1								2								3	4	8							15	22	1	8	15	1 ~~45~~			
HOUR(S) (relative to time of dosing)			Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D2 dose	48h after D2 dose	Pre	0	2	3	5	Pre-dose unless specified										
Informed consent	X																																	X		
Clinical evaluation (1)	X	X	X																X	X	X					X	X	X	X	X	X			X	X	
Vital signs (T, BP, HR, RR)	X	X	X				X	X	X	X	X				X	X	X	X	X	X	X					X	X	X	X	X	X			X	X	
12-lead ECG (2)	X	X	X ~~(2)~~		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X			X	X	
Echocardiogram or MUGA	X																																	X		
Hospitalization (3)			←															→																		
TLS prophylaxis (4)		X																																		
AMG 397 Dosing (5)				X								X										X				AMG 397 is taken orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle										
Dosing diary review (~~52~~1)											X								X		X					X	X	X	X	X	X			X		
AE Reporting					←																													→		
SAE Reporting	←																																	→		
Prior /concomitant medication(s)	←																																	→		
Survival/Subsequent anti-cancer therapy (~~62~~1)																																				X

	SCREENING	TREATMENT																																EOT	SAFETY FOLLOW-UP	LTFU (246)
CYCLE(S)			1																										2			Every cycle from 3 & beyond			
WEEK(S)			1																			2							3			1	2	3	1			
DAY(S)	-21 to -2	-1	1									2									3	4	8						15	22	1	8	15	1 46			
HOUR(S) (relative to time of dosing)			Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D2 dose	48h after D2 dose	Pre	0	2	3	5	Pre-dose unless specified										
LAB ASSESSMENTS																																				
AMG 397 PK (73)			X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X								X			
CBC with diff (48)	X	X	X				X	X	X	X	X				X	X	X	X	X	X	X					X	X	X	X	X	X	X	X	X	X	
Chemistry (94)	X	X	X				X		X	X	X				X	X	X	X	X	X	X					X	X	X	X	X	X	X	X	X	X	
Coagulation (4)	X	X	X								X								X	X	X					X	X	X	X	X	X	X	X	X	X	
Pregnancy test (510)	X		X																											X			X	X		
Urine sample collection (11)	X		X						X		X					X					X				X				X			X				
Hepatitis serology, HIV	X																																			
BIOMARKER and DISEASE ASSESSMENTS																																				
Bone marrow aspirate (127)	X																																			
Whole blood Na/Hep (413)			X				X	X			X					X			X	X																
Whole blood Cytochex (Dose escalation only) (914)			X								X								X	X	X					X										
Plasma	X																																			
Serum	X																																			

	SCREENING	TREATMENT																																EOT	SAFETY FOLLOW-UP	LTFU (246)
CYCLE(S)			1																										2			Every cycle from 3 & beyond			
WEEK(S)			1																			2							3			1	2	3	1			
DAY(S)	-21 to -2	-1	1									2									3	4	8						15	22	1	8	15	1 46			
HOUR(S) (relative to time of dosing)			Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D2 dose	48h after D2 dose	Pre	0	2	3	5	Pre-dose unless specified										
Cell Pellet	X																																			
MM SUBJECTS ONLY																																				
SPEP/UPEP/ Immunofixation (1015)	X																													X			X	X		
SFLC (116)	X																													X			X	X		
Beta-2 microglobulin	X																																	X		
Quantitative Ig (127)	X																																	X		
Bone marrow biopsy	X																																			
Bone marrow aspirate (18)		Repeat collection in case of CR																																		
Plasmacytoma (149)	X																																			
Skeletal survey (2015)	X																																			
NHL SUBJECTS ONLY																																				
Lymph Node Biopsy	X																																			
Whole blood plasma (Dose expansion only) (2116)	X																													X			X (1621)	X		
Bone marrow biopsy (2217)	X																																			

28. Section 7.1, Schedule of Assessments

Added Table 5

Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)

CYCLE			CYCLE 1 ONLY																																						
DAY(S)	-21 to -2	-1	1								2								3	4	7	8								9								10	11	15	22
HOUR(S) (relative to time of dosing)			Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D2 dose	48h after D2 dose		Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D9 dose	48h after D9 dose		
Informed consent	X																																								
Clinical evaluation (1)	X	X	X								X								X	X	X	X								X								X	X	X	X
Vital signs (T, BP, HR, RR)	X	X	X				X	X	X	X	X				X	X	X	X	X	X	X					X	X	X	X	X				X	X	X	X	X	X	X	X
12-lead ECG (2)	X	X	X (2)		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Echocardiogram or MUGA	X																																								
Hospitalization (3)		←———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———→				←———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———→				
TLS prophylaxis (4)		X																			X																				
AMG 397 dosing (5)				X								X											X								X									X (5)	
Dosing diary review (5)											X										X																	X		X	X
AE Reporting						←———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———→			
SAE Reporting			←———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———→			
Prior /concomitant medication(s)		←———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———→			

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Footnotes are defined on page 64

Table 5. Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)

CYCLE				CYCLE 1 ONLY																																					
DAY(S)	-21 to -2	-1	1								2								3	4	7	8								9								10	11	15	22
HOUR(S) (relative to time of dosing)			Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D2 dose	48h after D2 dose		Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D9 dose	48h after D9 dose		
LAB ASSESSMENTS																																									
AMG 397 PK (7)			X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		
CBC with diff (8)	X	X	X								X								X	X	X	X								X								X	X	X	X
Chemistry (9)	X	X	X				X		X	X	X				X		X	X	X	X	X	X				X		X	X	X				X		X	X	X	X	X	X
Coagulation	X	X	X								X								X	X	X	X								X								X	X	X	X
Pregnancy test (10)	X		X																																						
Urine sample collection (11)	X		X						X		X						X					X						X		X						X					
Hepatitis serology, HIV	X																																								
BIOMARKER and DISEASE ASSESSMENTS																																									
Bone marrow aspirate (12)	X																																								
Whole blood Na/Hep (13)			X				X	X			X											X				X	X			X											
Whole blood Cytochex (14)			X								X								X	X		X								X								X		X	
Plasma	X																																								
Serum	X																																								
Cell Pellet	X																																								

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Footnotes are defined on page 64

Table 5. Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)

CYCLE			CYCLE 1 ONLY																																						
DAY(S)	-21 to -2	-1	1								2								3	4	7	8								9								10	11	15	22
HOUR(S) (relative to time of dosing)			Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D2 dose	48h after D2 dose		Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D9 dose	48h after D9 dose		
BIOMARKER and DISEASE ASSESSMENTS																																									
MM SUBJECTS ONLY																																									
SPEP/UPEP/ Immunofixation (15)	X																																								
SFLC (16)	X																																								
Beta-2 microglobulin	X																																								
Quantitative Ig (17)	X																																								
Bone marrow biopsy	X																																								
Plasmacytoma (19)	X																																								
Skeletal survey (20)	X																																								

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Footnotes are defined on page 64

Table 5. Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)

CYCLE				CYCLE 1 ONLY																																					
DAY(S)	-21 to -2	-1	1								2								3	4	7	8								9								10	11	15	22
HOUR(S) (relative to time of dosing)			Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D2 dose	48h after D2 dose		Pre-dose	0	1	2	3	5	8	12	Pre-dose	0	1	2	3	5	8	12	24h after D9 dose	48h after D9 dose		
NHL SUBJECTS ONLY																																									
Lymph Node Biopsy	X																																								
Whole blood plasma **(Dose expansion only)** (21)	X																																								
Bone marrow biopsy (22)	X																																								
PET-CT and CECT Imaging (23)	X																																								
MRI Brain (24)	X																																								

Page 4 of 4

Footnotes are defined on page 64

29. Section 7.1, Footnotes for Table 4 and Table 5

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Footnotes for Table 4 and Table 5~~Table 4~~	
1	Clinical evaluations will be collected pre-dose on dosing days and include: physical exam, ECOG status, and weight. Medical and surgical history, and height need only be collected at the screening visit.
2	• Three baseline ECGs (pre-dose on day 1) will be collected approximately ≥ 15 minutes apart (+/- 5 minutes), with each baseline ECG in triplicate run consecutively (ie, <30 seconds apart); Total of 9 ECGs] • Triplicate ECGs run consecutively (ie, <30 seconds apart) , at time points designated in the schedule of assessments
3	• **See Section 6.5.7 for more details regarding hospitalization for TLS prophylaxis** • **Hospitalization for the purpose of TLS prophylaxis will not be captured as an SAE.**
4	• **See Section 6.5.7 for more details regarding TLS prophylaxis.**
5	• **See Section 6.2.1.1 for details regarding dosage, administration, and schedule.** • **See Section 6.2.1.1.1 and Table 5 for details regarding dosage, administration, and schedule once lead-in dosing is implemented.**
6	**For Dose Expansion subjects only:** o **Collected during LTFU period**
~~7~~3	• For PK collections on Cycle 1, PK samples should be collected within +/- 15 min of the designated time points. • PK samples should be collected at the exact nominal time point as noted. If unable to collect a PK sample at the specified nominal time point collect it as close as possible and record the actual collection time in the eCRF. **Note: It is important to document the exact date and time of IP administration and PK collection.**
~~8~~4	Refer to Section 7.2.15 ~~7.2.15~~ for list ~~of Safety~~CBC lab tests required. **Note: Subjects with a Grade 4 neutropenia should have their counts repeated every 24-48 hours until return to baseline and the use of G-CSF should be considered.**
9	• **Refer to Section 7.2.15 for list Chemistry panel lab tests required.** • **See Section 6.5.7 for chemistry lab tests required for TLS prophylaxis and management**
~~10~~5	Serum pregnancy test performed at screening; urine or serum pregnancy test at all other timepoints for females of childbearing potential.
~~11~~6	• **Please collect urine for UA which is done per local lab.** • **Any remaining urine will be sent to the central lab for analysis. Please refer to lab manual for preparation and transport procedures.** • On cycle 1, day 1, collect urine sample at least 5 hours post-dose of AMG 397. • After cycle 1, urine sample may be collected at the following designated timepoints.
~~12~~7	A bone marrow aspirate will be collected from all subjects during screening for IHC testing, to quantify percent tumor involvement, for fluorescent in situ hybridization (FISH) and other biomarker assays.
8	~~• Biomarker NaHep whole blood samples will be collected pre-dose on Cycle 1 day 1, 3 and 5 hours post dose on days 1 and 2, and 24 hours after day 2 1 during week 1. In th second week of Cycle 1, samples will be collected pre dose on day 8, 3 and 5 hours post dose on day 8, and 24 hours after day 8.~~ ~~A CBC with differential will be tested locally with each whole blood biomarker during cycle 1. (See Footnote 4)~~
13	• **Biomarker NaHep whole blood samples will be collected pre-dose on Cycle 1 day 1, 3 and 5 hours post dose on day 1, and 24 hours after day 1 during week 1 as indicated in Table 4.** • **Upon commencement of Lead-In dosing, additional samples will be collected indicated in Table 5 as follows: In th second week of Cycle 1,**

Footnotes for Table 4 and Table 5~~Table 4~~	
149	• ~~For Dose escalation subjects only: Biomarker Cytochex whole blood samples will be collected pre-dose on days 1, pre-dose day 2, 3, 4, 8, 9, 10, and 15~~24 hours after day 2, and pre-dose day 8, in the first treatment cycle.Biomarker Cytochex whole blood samples will be collected pre-dose on days 1, 2, 3, 4, and 8 as indicated in Table 4. • Upon commencement of Lead-In dosing, additional samples will be collected indicated in Table 5 as follow: pre-dose on days 9, 10, and 15.
For MM subjects only [~~10~~ 15 ~~20~~]:	
150	• Serum protein electrophoresis (SPEP) and 24-hour urine protein electrophoresis (UPEP) is required for all subjects at screening. • Thereafter, SPEP is to be done at each time point for all patients as indicated in the schedule of assessment. • UPEP with 24-hour urine collection is required at each time point only if screening UPEP shows measurable paraprotein in the urine. If screening UPEP is negative, spot urine is required at each time point. • If positive for paraprotein, a 24-hour urine collection with UPEP must be done at the next assessment and at each subsequent assessment unless the UPEP shows an absence of paraprotein. Immunofixation is required at next assessment only if SPEP or UPEP results are zero/undetectable. • See lab manual for collection and shipment details.
161	Serum free light chain (SFLC) assay and ratio will be performed at each marked time point.
172	Quantitative Immunoglobulin (Total IgG, IgA, IgM) obtained at screening and will be repeated only if clinically indicated (ie; frequent infection despite multiple myeloma disease control).

Footnotes for Table 4 and Table 5	
183	Additional bone marrow samples are to be collected to confirm CRs as well as for MRD biomarker analysis. Additional samples may be obtained every six months after CR and/or at time of relapse.
194	Plamacytoma survey • For subjects without a history of extramedullary disease, assessment by physical examination at screening is acceptable. • Plasmacytoma evaluation is to be repeated during treatment only to confirm a response of PR or better, to confirm PD, or if clinically indicated. If clinically indicated due to history of extramedullary disease, the same technique (may include ultrasound, x-ray, CT scan, MRI, PET, or other standard-of-care method) must be employed for each measurement.
2015	Skeletal survey to be repeated Q8W if clinically indicated ie; new symptoms (bone pain) arises, consider obtaining MRI for subjects with bone pain but skeletal survey is normal.
NHL (~~DLBCL for dose expansion~~) subjects only [~~2116~~2418]:	
2116	**For dose expansion subjects only:** • Whole blood plasma may be obtained pre-dose on day 1 of Cycle 2, and every 8 weeks thereafter, and EOT. Samples must be collected, processed, and frozen within 4 hours of phlebotomy and per the laboratory manual. • Additional whole blood plasma samples are obtained at time of relapse.
2217	Bone marrow evaluation (core biopsy with or without aspirate) may be performed if there has been previous histologic evidence of bone marrow involvement. An optional tumor biopsy may be collected at time of relapse per institutional guidelines at PI discretion.
2318	PET~~/~~-CT **and CECT** Imaging with time points at screening, Cycle 2, every 8 weeks thereafter, and EOT. **If not acquired on the same day, every effort should be made to complete PET-CT and CECT within 3 days of each other.**
24	**For Both Part 1 (dose escalation) and Part 2 (dose expansion), all NHL subjects must have MRI/CT of the brain performed within 21 days prior to enrollment. All brain scans on protocol are required to be MRI unless MRI is contraindicated, then CT with contrast is acceptable. Subsequently, MRI brain can be performed at any time if clinically indicated per standard of care.**
2519	**For AML Subjects only [~~2518~~]:** • Bone marrow samples **must** be obtained at **pre-dose on day 1 of Cycle 2, every 8 weeks thereafter, and** EOT. • Additional bone marrow sampling may occur at other time points at the PI's discretion as clinically indicated throughout course of treatment
260	**For Dose Expansion subjects only:** Long-term follow up (LTFU) will be conducted every 3 months from the last visit for up to 1 year from the first dose of AMG 397 for all subjects who have not withdrawn consent by telephone or chart review to assess for survival, disease progression and/or the commencement of subsequent cancer therapy only.

30. Section 7.2.8, Echocardiogram (ECHO) / Multigated Acquisition (MUGA) Scan

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~~7.1.87.2.8~~ **Echocardiogram (ECHO) / Multigated Acquisition (MUGA) Scan**

ECHO or MUGA will be performed to assess cardiac ejection fraction and cardiac valve abnormalities and will be performed at time points specified in the Schedule of Assessments (see Section 7.1). Additional ECHO/MUGAA, **cardiac** ~~assessments~~ **imaging and cardiac assessments are to be conducted if any clinical signs or symptoms of cardiomyopathy or other cardiac compromise are noted.**

31. Section 7.2.9 Dosing Diary Review

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7.2.9 Dosing Diary Review

A dosing diary will be provided for subjects to record the date, time, and number of tablets consumed each dose. The dosing diary is to be brought to each study visit and reviewed by study staff (see Section 7.1).

The dates of any missed doses or instances of emesis associated with tablet administration will asked to be recorded in the subject drug diary.

32. Section 7.2.11.1 Imaging and Disease assessments, 2nd paragraph

Added text in BOLD

PET-CT and CECT scans required in this protocol will be performed according to the Imaging Manual provided by the central vendor. However, depending on scanner types and availability, as well as local regulations, institutional guidelines may be followed upon consultation with, and approval by, the central vendor. Combined PET-CT whole body scans will be acquired from base of skull to mid-thigh, with the CT portion of the scan used only for attenuation correction. CECT anatomical coverage includes the chest, abdomen, and pelvis (and neck, if not visualized with chest), and the acquisition of separate CECT scans is strongly recommended for staging evaluation. Refer to the Imaging Manual for complete details about PET-CT and CECT scanning procedures and instructions.

PET-CT images should be converted to standardized uptake values (SUV) maps to support comparison across timepoints and to standardize viewing conditions.

If PET-CT and CECT are acquired on the same day, it is strongly recommended that PET-CT is performed prior to CECT. If acquired separately, every attempt should be made to complete PET-CT and CECT within 3 days of each other.

Refer to the Imaging Manual for additional details. Findings will be recorded per eCRF guidelines.

33. Section 7.2.11.2 MRI Brain

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7.2.11.2 MRI Brain

For both Part 1 (dose escalation) and Part 2 (dose expansion), all NHL subjects must have MRI or /CT of the brain performed within 21 days prior to enrollment. All brain scans on protocol are required to be MRI unless MRI is contraindicated, then CT with contrast is acceptable. Subsequently, MRI brain can be performed at any time if clinically indicated per standard of care.

34. Section 7.2.14 Blood Samples , Tables 6, 7, and 8

Removed strikethrough text, Added text in BOLD

Table 65.. Approximate Blood Volumes Collected for MM Subjects Only

		No Lead-In Dosing		With Lead-In Dosing	
Test	Volume (mL) per Collection	Approximate Number of Collection	Approximate Total Volume (mL)	Approximate Number of Collection	Approximate Total Volume (mL)
CBC with diff	~~54~~	18	~~7290~~	21	84
~~Laboratory safety (c~~Chemistry • **Pregnancy test (childbearing females only)~~; coagulation)~~	~~8.510~~	~~2514~~	~~212.5140~~	33	280.5
Coagulation	3	18	54	21	63
Serology (HIV, Hepatitis panel)	5	1	5	1	5
Quantitative Immunoglobulin	10	2	20	2	20
~~Serum pregnancy test (female of child bearing potential only)~~	~~3~~	~~5~~	~~15~~		
Blood samples for biomarkers	5	~~12~~169	~~60 4580~~	16	80
Blood samples for PK	5	20	100	32	160
Beta-2 microglobulin, SPEP and SFLC	10	7	70	7	70
Total approximate blood volume			~~5~~2000		762.5

Table 67. Approximate Blood Volumes Collected for NHL Subjects Only

		No Lead-In Dosing		With Lead-In Dosing	
Test	Volume (mL) per Collection	Approximate Number of Collection	Approximate Total Volume (mL)	Approximate Number of Collection	Approximate Total Volume (mL)
CBC with diff	4	18	72	21	84
Chemistry • Pregnancy test (childbearing females only)	8.5	25	212.5	33	280.5
Coagulation	3	18	54	21	63
Serology (HIV, Hepatitis panel)	5	1	5	1	5
Blood samples for biomarkers	5	9	45	16	80
Blood samples for PK	5	20	100	32	160
Total approximate blood volume for dose escalation			488.5		672.5
Whole blood plasma (Dose expansion subjects only)	5	5	25	5	25
Total approximate blood volume for dose expansion			513.5		697.5

Table 78. Approximate Blood Volumes Collected for AML Subjects Only

		No Lead-In Dosing		With Lead-In Dosing	
Test	Volume (mL) per Collection	Approximate Number of Collection	Approximate Total Volume (mL)	Approximate Number of Collection	Approximate Total Volume (mL)
CBC with diff	4	18	72	21	84
Chemistry • Pregnancy test (childbearing females only)	8.5	25	212.5	33	280.5
Coagulation	3	18	54	21	63
Serology (HIV, Hepatitis panel)	5	1	5	1	5
Blood samples for biomarkers	5	9	45	16	80
Blood samples for PK	5	20	100	32	160
Total approximate blood volume			488.5		672.5

35. Section 7.3.1 Blood Samples , Tables 6, 7, and 8

Removed strikethrough text, Added text in BOLD

~~7.2.~~17.3.1 **Blood Samples**

Whole blood samples are to be collected for biomarker measurement at several time points as listed in the schedule of assessments. The first set of samples will be collected ~~for~~on Cycle 1 pre-dose on Days 1 and 2, 5 hours post-dose on Days 1 and 2, as well as Day 3, 24 hours after the second dose. This set of samples will be collected in 2 tubes at each time point and undergo 2 separate tests: 1) CBC with differential to monitor cell counts (tested locally); 2) Flow cytometric analysis to measure the increase in BAX and Caspase 3 activity in circulating monocytes (MM, NHL) or peripheral blasts (AML) following treatment with AMG 397.

Initially, these blood samples will be collected on Cycle 1 pre-dose on day 1, 3 and 5 hours post-dose on day 1, as well as pre-dose on day 2 according to Table 4. If Lead-in dosing is initiated due to TLS symptoms, additional samples will be collected for remaining subjects according to Table 5 as follows: Cycle 1 pre-dose on Days 1 and 2, 3 and 5 hours post-dose on Day 1, as well as pre-dose on Days 8 and 9, 3 and 5 hours post-dose on Day 8.

In AML subjects, these whole blood samples may also be used to measure pro-survival family members (such as MCL1, BCL2, and BCL2L1 expression) in peripheral leukemic blasts. ~~In Part 1, a second set of whole blood samples will be collected during Cycle 1 on day 1 and 2 pre-dose, day 3, day 4, and day 8 pre-dose. These~~ **A second set of biomarker** blood collections will be used to monitor cell counts of immune cell subsets, including T cells, B cells, NK cells, monocytes, and Myeloid Derived Suppressor Cells (MDSCs) following treatment with AMG 397. **Initially, these samples will be collected on Cycle 1 pre-dose on days 1, 2, 3, 4, and 8 according to Table 4 above. If Lead-in dosing is initiated due to TLS symptoms, additional samples will be collected for remaining subjects according to Table 5 as follows: Cycle 1 pre-dose on days 1, 2, 3, 4, 8, 9, 10, and 15.**

For ~~DLBCL~~ **NHL** subjects in Part 2 **during dose expansion**, additional whole blood samples may be taken to assess clinical responses through depth of minimal residual disease status as indicated in schedule of assessments.

36. Section 7.4.1 Screening

Added text in BOLD

- **Bone marrow aspirate or biopsy as applicable**
- Biopsy Assessments, as applicable
- Imaging Assessments, as applicable
- ECG
- ECHO/MUGA
- **For NHL subjects, MRI brain (See Section 7.2.11.2)**
- Serious Adverse Event reporting
- Documentation of concomitant and rescue medications

Subjects may be rescreened at the discretion of the investigator after consultation with the Amgen Medical Monitor. Refer to Section 5 for instructions on rescreening and enrolling subjects.

37. Section 7.4.2 Treatment

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~~7.3.27.4.2~~ **Treatment**

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Section 7.1). Administration of AMG 397 is to be administered as applicable during each visit that it is required.

Treatment visits to include the following:

- **Hospitalization (See Section 6.5.7)**
- **TLS prophylaxis (See Section 6.5.7)**
- Clinical evaluations will be collected pre-dose on dosing days and include: physical exam, ECOG status, and weight.
- AMG 397 dosing
- Dosing diary review
- PK (including intensive PK assessments)
- ECG
- Vital signs (eg, blood pressure, heart rate, respiratory rate, temperature)
- Laboratory assessments including local and central laboratories, as applicable
- Pregnancy tests, as applicable
- **Bone marrow aspirate or biopsy as applicable**
- Biopsy Assessments, as applicable
- Imaging Assessments, as applicable
- Disease assessments, as applicable
- Serious Adverse Event reporting
- Adverse Event reporting
- Documentation of concomitant medications

38. Section 7.4.3 End of Treatment Visit

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~~7.3.37.4.3~~ End of Treatment Visit

The end of treatment (EOT) visit will occur after the last dose of AMG 397. The end of treatment (EOT) visit will occur upon the decision to end the treatment, disease progression, intolerable adverse event, documented clinical progression or consent withdrawal.

For subjects who choose to discontinue investigational product treatment, the EOT visit should occur as soon as possible after the last dose of investigational product is administered. Serious adverse events considered related to the investigational product, by the Investigator, or Amgen will be followed until resolved or considered stable.

EOT visits to include the following:

- Clinical evaluations include: physical exam, ECOG status, and weight.
- Dosing diary review
- PK
- ECG
- Vital signs (eg, blood pressure, heart rate, respiratory rate, temperature)
- Laboratory assessments including local and central laboratories, as applicable
- Pregnancy tests, as applicable
- **Bone marrow aspirate or biopsy as applicable**
- Biopsy Assessments, as applicable
- Imaging Assessments, as applicable
- Disease assessments, as applicable
- Serious Adverse Event reporting
- Adverse Event reporting
- Documentation of concomitant medications

39. Section 10.4, Adaptive Design, 3rd paragraph

Removed strikethrough text, Added text in BOLD, Added Table 10 and 11

Operating characteristics for this **BLRM** design are described in **Appendix D**~~Appendix D~~.

During dose expansion, Amgen will conduct evaluations of the ongoing grade 4 or higher adverse event rate to assess if the threshold for early trial termination has been reached. The stopping rules use a Bayesian approach proposed by Thall, et al (1995) to terminate the study if the posterior probability that the grade 4 or higher adverse event rate is greater than 20% is > 90%. The stopping boundaries assuming a prior distribution of Beta(0.40, 1.60) are presented in Table 10 and the operating characteristics with pre-specified batch size of 10 new subjects per batch are presented in Table 2. Subjects including in a batch may come from different tumor types. The evaluations could occur more frequently if necessary to address emerging safety concerns. The operating characteristics in Table 11 provide the probability of stopping the study early for given hypothetical true rate of grade 4 or higher adverse events, whereas the stopping criteria in Table 10 are based on situations where the empirical evidence would result in a posterior probability of ≥ 90% that the true grade 4 or higher adverse event rate is ≥ 20%.

Table 10. Stopping Boundary for Dose Expansion with Posterior Probability of 90% and Grade 4 or Higher Adverse Event Limit of 20%

Number of subjects	Stop study if observing these many grade 4 or higher adverse events
10	≥5
20	≥7
30	Study Complete

Table 11. Operating Characteristics with Batch Size of 10 Subjects

True grade 4 or higher adverse event rate	Probability of early stopping of dose expansion	Average dose expansion sample size
0.10	0.4%	29.9
0.15	2.7%	29.6
0.20	9.7%	28.7
0.25	22.9%	26.9
0.30	40.8%	24.4

40. Section 13, References

Added text in BOLD, Removed strikethrough text

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41. Added Appendix K. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

Complication	Grade 0	1	2	3	4	5
Creatinine*,†	≤ 1.5 × ULN	1.5 × ULN	1.5 – 3.0 × ULN	> 3.0 – 6.0 × ULN	> 6.0 × ULN	Death
Cardiac Arrhythmia*	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Seizure*	None	--	One brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death

ULN = upper limit of normal; CHF = congestive heart failure; ADL = activities of daily living

* Not directly or probably attributable to therapeutic agent.

† If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading.

Note: Laboratory tumor lysis syndrome and at least one clinical complication.

42. Added Appendix L. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Element	Value		Change from Baseline
Uric Acid	≥ 476 µmol/L (8 mg/dL)	-OR-	25% increase from baseline
Potassium	≥ 6.0 mmol/L (6 mg/L)	-OR-	25% increase from baseline
Inorganic phosphorus	≥ 1.45 mmol/L (4.5 mg/dL)	-OR-	25% increase from baseline
Calcium	≤ 1.75 mmol/L (7.0 mg/dL)	-OR-	25% decrease from baseline

Note: Two or more elements with laboratory values out of range or changes from baseline.