Title: A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 224 in Subjects With Relapsed or Refractory Multiple Myeloma

Amgen Protocol Number 20130314

Clinical Study Sponsor: Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320
Phone: +1-805-447-1000

Key Sponsor Contacts: [redacted], MD, PhD
Medical Monitor
One Amgen Center Drive
Thousand Oaks, CA 91320
Phone: [redacted]
Email: [redacted]

[redacted]
Clinical Research Study Manager
One Amgen Center Drive
Thousand Oaks, CA 91320
Email: [redacted]

Date:	09 June 2015
Amendment 1 Date:	07 October 2015
Amendment 2 Date:	12 July 2017
Amendment 3 Date:	02 March 2018
Amendment 4 Date:	16 July 2018

Note added in posting: Discrepant dates in some headers are from a clerical error in the original protocol. For correct dates please refer to this cover page.

Confidentiality Notice

NCT Number: NCT02561962
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

Investigator's Agreement

I have read the attached protocol entitled A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 224 in Subjects with Relapsed or Refractory Multiple Myeloma, dated 16 July 2018, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization (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 sub-investigators (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 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 224 in Subjects with Relapsed or Refractory Multiple Myeloma

Study Phase: 1

Indication: Multiple Myeloma

Primary Objectives:

- Evaluate the safety and tolerability of AMG 224 monotherapy in subjects with relapsed or refractory multiple myeloma
- Determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of AMG 224, if possible

Secondary Objectives:

- Characterize the pharmacokinetics (PK) of AMG 224 when administered intravenously (IV) once every 3 weeks (Q3W)
- Evaluate preliminary efficacy of AMG 224 when given as monotherapy in relapsed or refractory multiple myeloma according to International Myeloma Working Group (IMWG) uniform response criteria.
- Evaluate the preliminary rate of conversion to minimal residual disease (MRD) negativity
- Evaluate the incidence of anti-AMG 224 antibody formation.

Exploratory Objectives:

- Correlate clinical response with B-cell maturation antigen (BCMA) expression in pre-dose bone marrow biopsies and/or bone-marrow aspirates
- Evaluate gene expression profiling by sequencing in pre-dose biopsies/plasma to identify gene signatures for response
- Determine prognostic and predictive value of serum BCMA and BCMA ligands, a proliferation inducing ligand (APRIL)/B-cell activating factor (BAFF), from multiple myeloma serum samples
- Assessment of multiple myeloma samples for relevant circulating tumor cells

Hypotheses:

- AMG 224 administered by IV infusion at (or one dose level below) the preliminary MTD identified during the dose exploration part of the study is expected to achieve acceptable safety and tolerability in subjects with relapsed or refractory multiple myeloma. A favorable PK profile will be achieved with AMG 224 administered by IV infusion Q3W.
- Objective responses by IMWG uniform response criteria will be observed at a dose level that achieves acceptable safety and tolerability

Primary Endpoints:

- Safety: Incidence of dose limiting toxicities (DLTs), treatment-related, treatment-emergent adverse events, and clinically significant changes in vital signs, physical examinations, electrocardiograms (ECG)s and clinical laboratory tests

Secondary Endpoints:

- PK profile: PK parameters for AMG 224 conjugated antibody (anti-BCMA antibody with at least one DM1 molecule conjugated to the antibody), total anti-BCMA antibody (sum of unconjugated anti-BCMA antibody and AMG 224 conjugated antibody), and DM1 (total unconjugated DM1) including, but not limited to maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), area under the concentration-time curve (AUC), clearance (CL), and if feasible half-life ($t_{1/2}$)

- Overall response according to International Myeloma Working Group (IMWG) uniform response criteria, relative reduction in M-component, time to progression (TTP), duration of response (DOR)
- Conversion to MRD negativity
- Incidence of anti-AMG 224 antibody formation

Exploratory Endpoints:

- Quantification of BCMA expression in pre-dose bone marrow biopsy and bone-marrow aspirates
- Pre-dose bone marrow biopsy and/or plasma DNA gene expression profiles
- Serum level of BCMA, BCMA ligands, APRIL and BAFF
- Quantification of circulating tumor cells, plasma cells and/or BCMA specific tumor cells

Study Design:

This is a phase 1, first-in-human, multicenter; non-randomized, open-label, dose-exploration and dose-expansion study of AMG 224 administered by IV infusion Q3W in subjects with relapsed or refractory multiple myeloma. The study will be conducted in two parts: Part 1 - Dose Exploration to define the MTD and/or RP2D followed by Part 2 - Dose Expansion to obtain further safety and efficacy data. Eligible subjects enrolled in the study will receive AMG 224 by IV infusion Q3W beginning at study Day 1. During the initial DLT window (Day 1 through Day 28), subjects will be assessed for DLTs (see Section 6.2.1.6 for DLT definition). Dosing with AMG 224 may continue Q3W unless there is evidence of progressive disease (PD) defined by IMWG, the subject becomes intolerant to the study medication, signs and symptoms of clinical progression are evident as determined by the principal investigator or the subject withdraws consent.

Part 1 – Dose Exploration:

In Part 1 for the first dose level and at each new higher dose level, the first enrolled subject will be treated, and then after a period of 24 hours, subsequent subjects will be treated, provided that there are no safety concerns relating to the treatment of the first subject. The dose-exploration cohorts will define the preliminary MTD, safety, tolerability, PK, and PD of AMG 224. A standard 3+3 design will be used to make a preliminary estimate of MTD. The preliminary MTD is defined as the maximum dose at which fewer than one-third of subjects experience a DLT. A final estimate of the MTD will be made using data from Dose Exploration and Dose Expansion. Planned dose levels for the dose-exploration cohorts are as follows: 30, [redacted] mg of AMG 224 (IV; Q3W).

Part 2 – Dose Expansion:

In Part 2 of the study, up to 20 subjects with relapsed or refractory multiple myeloma will be treated. Subjects will be divided into the following 2 groups based on the status of prior treatment with CD38 targeting antibody (eg, Daratumumab):

- Group A will consist of subjects who had prior treatment with a CD38 targeting antibody (at least 10 subjects).
- Group B will consist of subjects who is naïve to CD38 targeting antibody treatment (approximately 10 subjects).

In the Part 1 of the study, a fixed dosing (ie, dose not adjusted for individual subject's body weight) will be evaluated and in Part 2 of study body weight-based dosing will be evaluated. Subjects will be treated with preliminary MTD identified from the Dose Exploration part of the study [redacted] adjusted for their body weight. Subjects with grade 2 thrombocytopenia at baseline (ie, platelet count < 75 to 50 x 10^9/L) should be started at a reduce dose of [redacted]. The subsequent doses of AMG 224 could be further reduced to [redacted] if the criteria for dose reduction for thrombocytopenia are met as per sections 6.2.5.1 and 6.3.1. For therapeutic monoclonal antibody based therapies a full assessment of body weight effect on the PK/PD should be conducted to determine the optimal dosing approach prior to conducting the registration trial and a recommendation for adjustment or lack of adjustment of dose based on body weight be made once sufficient clinical data is available (Bai, 2012 and Wang, 2009). When

sufficient AMG 224 clinical data becomes available, a full assessment of body size effect on PK/PD will be conducted to determine the optimal dosing approach prior to conducting the registration trial for AMG 224 in multiple myeloma patients.

During dose-expansion, after 5 subjects have enrolled (combining Group A and B subjects) and completed 28 days on study, a toxicity probability interval (TPI) Bayesian model utilizing all current DLT-evaluable subjects will be fit to evaluate the appropriateness of the preliminary MTD from dose exploration. The subsequent subjects to be enrolled in dose expansion may be dosed with the updated dose level. A final estimate of the MTD will be made based on a toxicity probability interval (TPI) Bayesian model utilizing all DLT evaluable subjects from the dose exploration and dose expansion cohorts.

An end of study (EOS) visit will be performed 30 to 37 days after the last dose of AMG 224.

Sample Size: It is anticipated that approximately 60 subjects will be enrolled in this study. Approximately 40 subjects will be enrolled in the dose exploration cohorts and up to 20 additional subjects will be enrolled in the dose expansion cohort.

The sample size in the dose exploration is based on practical consideration and it is consistent with conventional oncology studies with the objective to identify the MTD. With 3 subjects per cohort, there is a 27 to 70% probability of observing at least one DLT if the true DLT rate is 10 to 33% and with 6 subjects per cohort, there is a 47 to 91% probability.

In the dose expansion cohort, a subject number of 20 will provide a 64% probability of observing at least one adverse event with 5% incidence rate and 88% probability of observing at least one adverse event with 10% incidence rate. An exact 80% binomial confidence interval (CI) will be provided for overall response rate (ORR). With the 20 subjects and 20% ORR, the 80% CI would be 9% to 36%.

Summary of Subject Eligibility Criteria:

Subjects ≥ 18 years of age with pathologically documented, definitively diagnosed, multiple myeloma relapse or refractory progressive disease after at least 3 lines of therapy for multiple myeloma. Once consented to the study, subjects will undergo safety tests and provide a medical history to confirm they meet all requirements of the study. For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

Amgen Investigational Product Dosage and Administration:

AMG 224 will be supplied as 5 mL deliverable volume in a single use 8cc glass vial stored at liquid temperatures of [redacted] at 10 mg/mL protein concentration formulated with [redacted] mM sodium acetate, [redacted] (w/v) sucrose, [redacted] (w/v) polysorbate 20, pH [redacted].

AMG 224 will be administered as an IV infusion given over 60 ± 10 minutes once Q3W in the first 2 cycles. The dose of AMG 224 will vary by study part:

- Part 1 – Dose Exploration: The doses range from 30 to 300 mg
- Part 2 Dose Expansion: The starting dose is [redacted]. Subjects with grade 2 thrombocytopenia at baseline (ie, platelet count < 75 to 50 x 10^9/L) should be started at a reduced dose of [redacted] The subsequent doses of AMG 224 could be further reduced to [redacted] if the criteria for dose reduction for thrombocytopenia are met as per sections 6.2.5.1 and 6.3.1.

During the Dose Expansion Phase all doses are to be based on the subject's actual body weight on the day of dosing (Day 1 of each cycle). For cycles 2 and beyond, weight should be re-checked, and dosing adjusted accordingly, unless body weight is changed by 5% or less compared to the cycle 1 weight. The dose of AMG 224 should not exceed [redacted] (based on available nonclinical toxicology information on maximum sucrose allowance limit).

For each subject, the infusion time may be shortened to 30 ± 5 minutes in the later cycles if subjects experience no infusion reaction or lengthened up to 120 ± 10 minutes if subjects experience an infusion reaction.

Control Group:

The study does not incorporate a control group.

Procedures:

After written informed consent has been obtained, all screening tests and procedures will be performed within 14 days of administration of the first dose of AMG 224 (day 1), unless otherwise noted. Subjects will be seen in clinic where critical clinical safety and study evaluations will be performed including physical examination, vital signs, clinical laboratory tests, ECGs, PK, and biomarker sample collections.

For a full list of study procedures, including the timing of each procedure and the Schedule of Assessments, please refer to Section 7.

Statistical Considerations:

All subjects who are enrolled and receive at least one administration of the investigational product (AMG 224) will be included in the analysis, unless otherwise specified. The primary analysis will occur when target enrollment is complete and each subject either completes 6 months on study or withdraws from the study. Descriptive statistics will be provided for selected demographics, safety, PK, PD 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. The number and percentage of subjects reporting any treatment-emergent adverse events will be tabulated.

Summaries of positive anti-AMG 224 antibody test results over time will be provided. The preliminary estimate of the MTD will be identified using the 3+3 design. A final estimate of the MTD will be made based on a toxicity probability interval (TPI) Bayesian model utilizing all DLT evaluable subjects from the dose exploration and dose expansion cohorts.

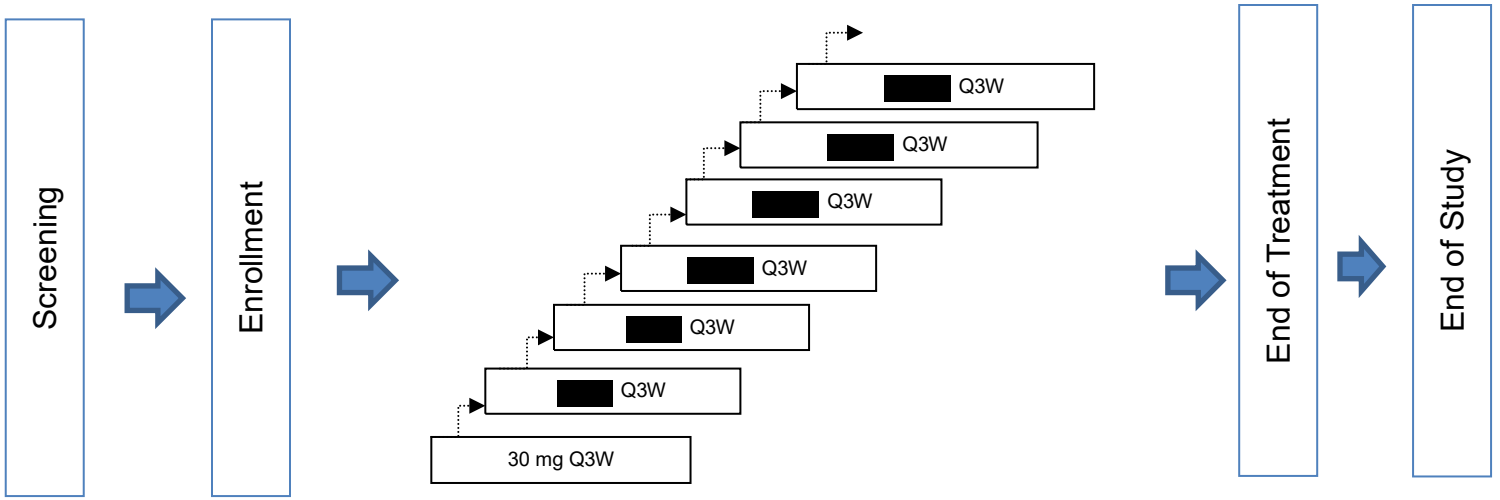
The proportion of subjects with objective response (PR or better) per IMWG criteria with corresponding exact 80% CI will be calculated using the Clopper-Person method and tabulated for subjects treated at the MTD.

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

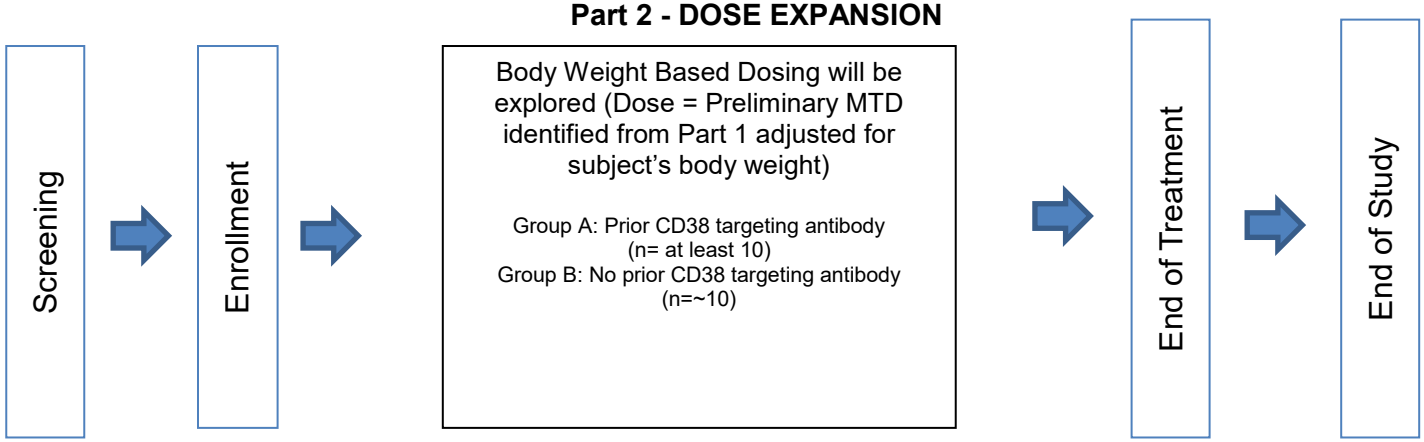
Sponsor: Amgen Inc.

Study Design and Treatment Schema

Part 1 - DOSE EXPLORATION



Part 2 - DOSE EXPANSION



Study Glossary

Abbreviation or Term	Definition/Explanation
ADC	antibody drug conjugates
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
ANC	absolute neutrophil count
APRIL	A proliferation inducing ligand
AST	aspartate aminotransferase (SGOT)
AUC	area under the concentration-time curve
BAFF	B-cell activating factor
BAFF-R	B-cell activating factor receptor
BCMA	B-cell maturation antigen
BP	blood pressure
CBC	complete blood count
CI	confidence interval
CL	clearance
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CR	complete response
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DAR	drug-to-antibody ratio
DILI	drug-induced liver injury
DLRM	dose level review meeting
DLRT	dose level review team
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	Duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture

Abbreviation or Term	Definition/Explanation
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject.
End of Treatment	defined as the last assessment for the protocol specified treatment phase of the study for an individual subject
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 (end of trial)	defined as when the last subject completes the safety follow-up assessments (30 to 37 days after last dose of AMG 224)
End of Safety Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
eSAE	electronic serious adverse event
ESR	erythrocyte sedimentation rate
FIH	first in human
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
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
ICF	informed consent form
ICH	International Conference on Harmonization
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
LVEF	left ventricular ejection fraction
MAD	maximum administered dose

Abbreviation or Term	Definition/Explanation
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mg	milligrams
MM	multiple myeloma
MR	minor response
MRD	minimal residual disease
MTD	maximum tolerated dose
MUGA	multi-gated acquisition scan
N, n	number
ORR	overall response rate
PD	pharmacodynamics or progressive disease
PG	pharmacogenetic
PK	pharmacokinetics
PKDM	pharmacokinetics and data management
Pre	pre-dose
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
Q3W	once every 3 weeks
QD	once daily
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
RBC	red blood cells
RF	rheumatoid factor
RP2D	recommended phase 2 dose
sCR	stringent complete response
SD	standard deviation
SFLC	serum free light chain

Abbreviation or Term	Definition/Explanation
SPEP	serum protein electrophoresis
$T_{1/2}$	half-life
TACI	trans-membrane activator and calcium modulator
TBL	total bilirubin
t_{max}	time of maximum observed serum concentration
TPI	toxicity probability interval
ULN	upper limit of normal
UPEP	urine protein electrophoresis
VGPR	very good partial response
w/v	weight/volume
WBC	White blood cell

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1. OBJECTIVES

1.1 Primary

- Evaluate the safety and tolerability of AMG 224 monotherapy in subjects with relapsed or refractory multiple myeloma.
- Determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of AMG 224, if possible.

1.2 Secondary

- Characterize the pharmacokinetics (PK) of AMG 224 when administered intravenously (IV) once every 3 weeks (Q3W).
- Evaluate preliminary efficacy of AMG 224 when given as monotherapy in relapsed and refractory multiple myeloma according to International Myeloma Working Group (IMWG) uniform response criteria (Durie, 2006 and Rajkumar 2011).
- Evaluate the preliminary rate of conversion to minimal residual disease (MRD) negativity.
- Evaluate the incidence of anti-AMG 224 antibody formation.

1.3 Exploratory

- Correlate clinical response with B-cell maturation antigen (BCMA) expression in pre-dose bone marrow biopsies.
- Evaluate gene expression profiling by sequencing in pre-dose biopsies/plasma to identify gene signatures for response.
- Determine prognostic and predictive value of serum BCMA and BCMA ligands a proliferation inducing ligand (APRIL)/B-cell activation factor (BAFF) from multiple myeloma serum samples.
- Assess multiple myeloma blood samples for the relevant circulating tumor cell.

2. BACKGROUND AND RATIONALE

2.1 Multiple Myeloma Background

Multiple myeloma is a neoplastic plasma-cell disorder that is characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine and associated organ dysfunction (Palumbo and Anderson, 2011). Multiple myeloma accounts for almost 2% of all cancers and 20% of hematologic malignancies. The disease is slightly more common in males and African Americans (Siegel, 2015). Multiple myeloma remains an incurable cancer, although recent improved understanding of pathogenesis of myeloma has led to the development of new treatments and improved survival (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 benefit. 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 patients 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 patients or those with coexisting conditions. Conventional therapy combined with thalidomide, lenalidomide, or bortezomib should be administered in patients 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 patients over 75 years of age or in younger patients 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 relapsed or refractory multiple myeloma (RRMM) 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 Carfilzomib and Pomalidomide that were granted approval by US FDA in 2012 and 2013 respectively for

RRMM, 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.

The first monoclonal antibodies targeting SLAMF7 (elotuzumab) and CD38 (daratumumab) have recently been granted approval. Emplicity™ (elotuzumab) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies. The 1 and 2-year rates of PFS for elotuzumab in combination with lenalidomide and dexamethasone treatment were 68% and 41%, respectively, compared with 57% and 27%, respectively, for lenalidomide and dexamethasone treatment in the corresponding phase 3 trial (Lonial et al, 2015). Darzalex® (daratumumab) approval was based on the pivotal phase III POLLUX and CASTOR clinical studies. Daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, substantially improved progression-free survival and overall response rates for previously treated patients with multiple myeloma, regardless of prior treatment exposure or cytogenetic risk. Daratumumab with lenalidomide and dexamethasone lowered the risk of disease progression or death by 64 percent, compared with lenalidomide and dexamethasone alone, in patients with multiple myeloma who had received 1 to 3 prior lines of therapy. Daratumumab with bortezomib and dexamethasone reduced the risk of disease progression or death by 61 percent in similar patients, compared with bortezomib and dexamethasone alone (Dimopoulos et al, 2016; Palumbo et al, 2016). Even newer approaches such as chimeric antigen-receptor (CAR) T-cells, antibody-drug conjugates and bispecific antibodies targeting BCMA have also demonstrated first promising anti-myeloma activity (Cohen, 2016; Berdeja, 2016; Panowski, 2016).

Despite advances in the management of multiple myeloma as described, relapse is inevitable in almost all patients. 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, 2014). More treatment options are still warranted.

2.2 AMG 224 Background

AMG 224 is an antibody drug conjugate (ADC) comprised of anti-BCMA-MCC-DM1 where anti-BCMA is an anti-human BCMA IgG1 antibody; MCC is the non-cleavable

linker 4-[N-maleimidomethyl] cyclohexane-1-carboxylate conjugated to lysine residues in the antibody; and DM1 is a semi-synthetic derivative of the ansamycin antibiotic, maytansine conjugated to MCC. There is an average of 3.5 DM1 molecules per antibody.

The antibody portion of AMG 224 consists of anti-human BCMA Xenomouse IgG1 antibody that selectively binds to native BCMA, does not cross-react to B-cell activating factor receptor (BAFF-R) or Trans-membrane activator and calcium modulator (TACI), and is internalized rapidly into BCMA-expressing myeloma cell lines.

The anti-tubulin warhead is a maytansinoid. Maytansine, an ansamycin antibiotic, was originally isolated from an Ethiopian shrub, Maytenus serrata. DM1 is reported to bind to tubulin in the vinca alkaloid binding site and to inhibit tubulin polymerization (Sackett, 1995).

Upon internalization of an antibody drug conjugate, with a “non-cleavable” linker, the antibody was catabolized into individual amino acids, including amino acids with warhead still attached (Erickson, 2006). The amino acid-linker-drug, Lysine-MCC-DM1, was identified in the cytoplasm of cells. Once internalized, this warhead was capable of killing target-expressing tumor cells in vitro and in vivo. The amino acid-linker-drug is considerably less potent on cells than the free warhead. The highly restricted normal tissue BCMA expression, the robust antibody internalization of BCMA specific antibodies into BCMA expressing tumor cells and the ability of the anti BCMA conjugated to DM1 with a non-cleavable linker to deliver a level of warhead capable of mediating tumor cell kill combine to create a promising impactful therapy for BCMA-expressing malignancies.

2.2.1 AMG 224 Preclinical Pharmacology

Amgen pre-clinical pharmacology studies have shown that AMG 224 binds with high affinity to human BCMA. Flow cytometry indicates that anti-BCMA antibody binds to recombinant BCMA from cynomolgus monkey and humans with similar affinity, but does not bind to rat BCMA.

The activity of AMG 224 against human multiple myeloma cells has been investigated both *in vitro and in vivo*. Upon binding to BCMA-expressing H929 or KMS26 human multiple myeloma cells in culture, AMG 224 has been shown to internalize into the cells where it is catabolized into its individual amino acids, thereby releasing the lysine-MCC-DM1 warhead into the cytoplasm. It can then associate with tubulin during mitosis thereby inhibiting cell division resulting in cell death.

The activity in animals was investigated using KMS26 (express 3,000 BCMA sites/cell on average) human multiple myeloma tumors grown as orthotopic xenografts in murine model. In the KMS26 model, significant anti-tumor activity was still observed at a single dose of AMG 224 as low as 62.5 µg/kg DM1 equivalents. KMS26 tumors that grew back post initial low dose AMG 224 therapy maintained their sensitivity to AMG 224 upon re-treatment. Administration of AMG 224 at 62.5, 150 and 250µg DM1/kg resulted in a protection against KMS26-luc mediated osteolytic bone lesions.

2.2.2 Pharmacokinetics

The pharmacokinetics (PK) of AMG 224 was characterized in cynomolgus monkeys following single dose intravenous (IV) administration and following multiple-dose IV administration.

Single dose IV PK of AMG 224 was studied at [redacted] and [redacted] dose levels. After single dose IV administration of AMG 224 the plasma exposures for AMG 224 conjugated antibody (anti-BCMA antibody with at least one DM1 molecule conjugated to the antibody), total anti-BCMA antibody (sum of unconjugated anti-BCMA antibody and AMG 224 conjugated antibody), and DM1 (total unconjugated DM1) increased in an approximately dose proportional manner over the studied doses [redacted]) in cynomolgus monkeys. Relatively similar plasma concentration profiles for AMG 224 conjugated antibody and total anti-BCMA antibody were observed indicating low plasma exposure for unconjugated antibody. In addition, low plasma exposures were observed for DM1.

The multiple-dose PK of AMG 224 was characterized in the GLP toxicology study following multiple once every 2 weeks (Q2W) IV administration of AMG 224 at [redacted], [redacted] and [redacted] dose levels in cynomolgus monkeys. Following multiple dosing the plasma exposures for AMG 224 conjugated antibody, total anti-BCMA antibody, and DM1 increased in an approximately dose proportional manner over the studied dose range ([redacted]). No significant plasma accumulation (accumulation ratio < 2) was observed for any of the PK analytes upon multiple Q2W dosing with AMG 224 in cynomolgus monkeys. Following multiple dosing relatively similar plasma concentration profiles for AMG 224 conjugated antibody and total anti-BCMA antibody were observed indicating low plasma exposure for unconjugated antibody. In addition, low plasma exposures were observed for DM1.

A 2-compartment model best described the PK of AMG 224 conjugated antibody in cynomolgus monkey. The half-life of AMG 224 conjugated antibody in cynomolgus

monkey from this model was estimated to be approximately 8 days. A 2-compartment model identical in structure to the one used to fit the cynomolgus monkey PK data was used to simulate human PK for AMG 224 conjugated antibody. Human PK parameters were predicted allometrically from the cynomolgus monkey PK parameters. The predicted half-life of AMG 224 conjugated antibody in humans is approximately 15 days.

2.2.3 AMG 224 Preclinical Toxicology

The potential toxicity of AMG 224 was evaluated in a 28-day intravenous study in the cynomolgus monkey at [redacted] administered every 2 weeks for a total of 3 doses. Scheduled necropsy was on Day 36, one week after the last dose. One animal at [redacted] was euthanized on Day 35 after being found in a moribund condition that was attributed to bacteremia secondary to marked bone marrow hypocellularity of all cell lineages. Heart rate was increased at [redacted] at the end of the study. Clinical pathology changes included decreased lymphocytes, platelets and red cell mass, increased liver enzymes, and indicators of an acute phase response. Light microscopic changes attributed to expected DM1 pharmacology included degeneration/regeneration in epithelial cells of the choroid plexus, liver, adrenal gland and salivary gland, axonal degeneration of the spinal cord and sciatic nerve, and lymphocyte depletion of lymphoid organs. The effects in this study were largely consistent with those of other ADC's containing the same DM1 warhead (Poon, 2013, Saber and Leighton, 2015) and are expected to be reversible. Based on the AMG 224-related decreased bone marrow cellularity with secondary bacteremia that resulted in the early euthanasia of one animal at [redacted], the highest non-severely toxic dose (HNSTD) was [redacted]

2.3 Risk Assessment

The target cell populations of AMG 224 are plasma cells, mature and activated B cells shown to express BCMA; hence the potential on-target toxicity is depletion of these hematologic cell types and depleting immunoglobulin level which could result in an increased risk of infection. In a recent review of antibody-drug conjugates by the FDA, it was revealed that the small molecule appears to dictate the dose limiting adverse events. For ADCs sharing the small molecule (SM) drug, the same linker, and the same SM:Ab ratio, available prior clinical data can inform the design of a safe yet efficient Phase 1 clinical trial design (Saber, 2015). Based on experiences with an approved ADC Trastuzumab emtansine (T-DM1 [Kadcyla®]) and Amgen past experiences (AMG 595) with antibody drug conjugates utilizing MCC-DM1 as a linker warhead and the same drug-to-antibody ratio (DAR), the anticipated toxicities include

thrombocytopenia and hepatotoxicity. Clinical signs and symptoms of infection, bleeding and liver dysfunction, platelet counts and liver enzymes, along with other safety labs, will be monitored during the study and at the appropriate time points to ensure subjects' safety. Refer to the Investigator's Brochure for the full details of the potential and identified risks of AMG 224.

2.4 Rationale

2.4.1 Target Rationale

B-cell Maturation Antigen (BCMA, TNFRSF17, CD269) is a TNF receptor superfamily member and a type III integral membrane protein (Madry, 1998). BCMA expression on normal tissues is highly restricted to the B-cell lineage where it is predominately expressed in the secondary follicle/germinal center of tonsils/lymph nodes (Chiu, 2007), on plasmablasts (Avery, 2003) and on differentiated plasma cells (O'Connor, 2004). Analysis of BCMA mRNA and protein expression in human tissues indicated that, except for plasma cells, BCMA is not detectably expressed in normal human tissues (Carpenter, 2013). The biological function of BCMA, promoting the survival of plasma cells, is mediated via binding to its ligands APRIL and BAFF (Yu et al, 2000). In addition to BCMA, APRIL binds to Trans-membrane activator and calcium modulator (TACI) and BAFF binds to B-cell activating factor receptor (BAFF-R) (Gross, 2000) and (Thompson, 2001). Both APRIL and BAFF are expressed predominately by myeloid-derived cells including macrophages, DCs and neutrophils that form part of the bone marrow stroma and also reside in lymphoid organs. Disruption of the BCMA/BAFF-APRIL interaction in mice deficient for BCMA results in decreased survival of long-lived plasma cells (Avery, 2003).

BCMA is expressed at relatively higher levels on malignant plasma cells (multiple myeloma) than the level observed on normal plasma cells (Zhao et al, 2008). Multiple independent analyses of mRNA in primary human MM samples indicate that all MM patients' samples have high levels of BCMA (Moreaux, 2004 and Tai et al, 2006). The high prevalence of BCMA expression in MM has been confirmed at the protein level by immunohistochemistry or flow cytometry, which demonstrated cell-surface BCMA expression in neoplastic plasma cells from all MM patients tested (Novak, 2004 and Carpenter, 2013).

For this phase I trial, relapsed or refractory multiple myeloma has been chosen as the indication to pursue with the anti BCMA ADC because of the near 100% incidence of BCMA expression in this patient population.

2.4.2 Dose Selection Rationale

Dose Exploration Phase (Part 1)

In this first-in-human (FIH) study of AMG 224 in subjects with relapsed or refractory multiple myeloma the dose exploration phase dose levels 30, [redacted] administered intravenously (IV) once every 3 week (Q3W) are selected based on toxicology, pharmacology, and pharmacokinetic (PK) data of AMG 224 as well as prior clinical safety and tolerability experience in cancer patients following administration of antibody drug conjugates (ADCs) with same cytotoxin, linker, and drug-to-antibody ratio (DAR) as AMG 224.

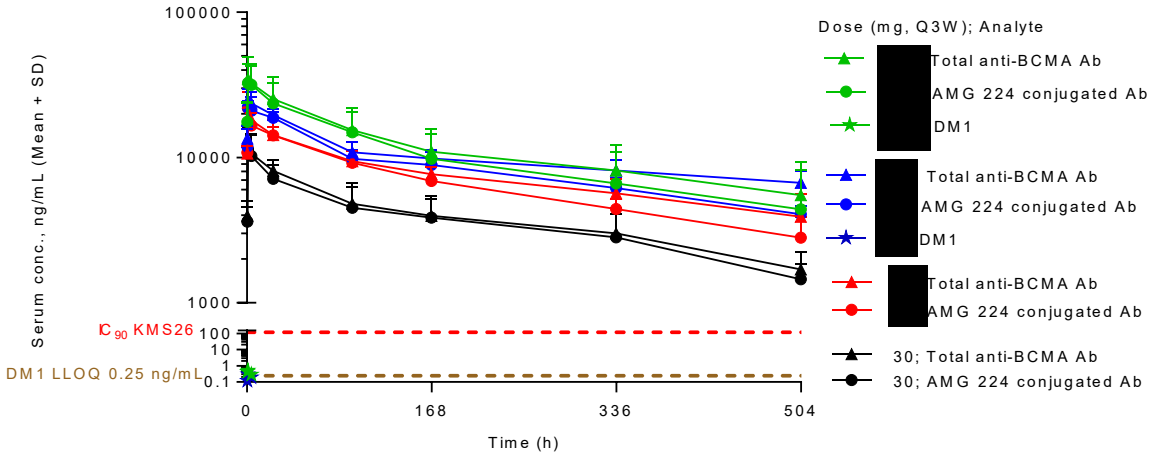
ADCs AMG 595 and Trastuzumab emtansine (T-DM1 [Kadcyla®]) share with AMG 224 the same cytotoxin (DM1), the same linker (MCC), and the same DAR (~3.5). Based on a retrospective analysis of ADCs, prior clinical data from ADCs sharing the same cytotoxin, linker, and DAR can be used to inform the design of FIH study of a new ADC with the same cytotoxin, linker, and DAR (Saber and Leighton, 2015). Accordingly, a dosing interval of Q3W has been selected for AMG 224 based on the recovery profile observed from the primary safety concern thrombocytopenia, following administration of ADCs like AMG 595 and T-DM1 to cancer patients as single agents.

The AMG 224 starting dose of 30 mg is based on the ICH S9 guidance for the maximum recommended starting dose in patients for novel therapeutics for advanced cancer indications. A retrospective analysis of ADCs also indicates that this approach provides a safe FIH starting dose for ADCs (Saber and Leighton, 2015). For AMG 224 in the repeat-dose GLP toxicology study in cynomolgus monkey the HNSTD was [redacted] 1/6th of the HNSTD and scaling for difference in body surface area between cynomolgus monkeys and humans yields a dose of 32 mg for humans. Accordingly, a conservative estimate of 30 mg has been selected as the starting dose. The planned dose exploration steps at lower dose levels are followed by more conservative dose exploration steps at higher dose levels in the study. The planned dose explorations and planned nominal highest dose for AMG 224 are also based on the thrombocytopenia dose limiting toxicity for ADCs like T-DM1 in cancer patients and will be guided by observed safety and tolerability of AMG 224.

Preliminary PK results of AMG 224 following administration as an IV infusion Q3W to adult subjects with relapsed or refractory multiple myeloma in ongoing FIH study are available for 12 subjects after the first dose of 30 mg (3 subjects), [redacted] (3 subjects), [redacted] (3 subjects), and [redacted] (3 subjects). Mean serum concentration-time profiles

for AMG 224 conjugated antibody, total anti-BCMA antibody, and DM1 are shown in Figure 1.

Figure 1. Preliminary Serum Concentration-time Profiles of AMG 224 Conjugated Antibody, Total Anti-BCMA Antibody, and DM1 in Subjects With Relapsed or Refractory Multiple Myeloma Following Q3W Administration of AMG 224 as IV Infusion



Ab = antibody; BCMA = B cell maturation antigen; IV = intravenous(ly); LLOQ = lower limit of quantitation; Q3W = once every 3 weeks

Mean (+ SD) concentration-time profiles: n = 3 subjects each dose cohort (30 mg Q3W, [redacted] Q3W; [redacted] Q3W; [redacted] Q3W

Analytes:

- AMG 224 conjugated Ab = anti-BCMA Ab with at least 1 DM1 molecule conjugated to the Ab
- Total anti-BCMA Ab = sum of unconjugated anti-BCMA Ab plus AMG 224 conjugated Ab
- DM1 = unconjugated total DM1

DM1 LLOQ 0.25 ng/mL: DM1 levels following administration of 30 mg and [redacted] doses were below LLOQ.

IC_{90}KMS26: AMG 224 conjugated Ab concentration expected to result in 90% killing of tumor cells estimated from the pharmacokinetic/pharmacodynamic modeling of AMG 224-mediated tumor burden reduction observed in orthotopic xenograft (BCMA-expressing human multiple myeloma [KMS26]) mice.

Source: Pharsight Knowledgebase Server: http://uslv-pweb-pks02/pks/WebUI Study: 20130314_BSMLIMSPLUS_Clinical_v1

Following Q3W IV administration of AMG 224 to subjects with relapsed or refractory multiple myeloma, similar pharmacokinetic profiles were observed over the 3-week dosing interval for AMG 224 (anti-BCMA antibody with at least 1 DM1 molecule conjugated to the antibody) and total anti-BCMA antibody (sum of AMG 224 plus unconjugated anti-BCMA antibody), indicating low levels of circulating unconjugated antibody. In addition, low plasma levels were observed for DM1 (total unconjugated DM1). The DM1 levels following administration of AMG 224 30 mg or [redacted] doses were below the lower limit of quantitation (LLOQ) (0.25 ng/mL); and following administration of

[redacted] dose were close to the LLOQ, with mean maximum observed concentrations of 0.31 ng/mL and 0.52 ng/mL, respectively.

Based on preliminary observed PK profile for AMG 224 conjugated antibody (Figure 1), trough serum concentrations following AMG 224 doses ≥ 30 mg Q3W exceed the 90% tumor cell killing concentration (IC_{90}) estimated from the pharmacokinetic/ pharmacodynamic modeling of AMG 224-mediated tumor burden reduction observed in orthotopic xenograft (BCMA-expressing human multiple myeloma [KMS26]) in mice. Hence, AMG 224 doses ≥ 30 mg Q3W are expected to be potentially efficacious, which is in line with preliminary response observed at AMG 224 doses ≥ 30 mg Q3W doses in the ongoing FIH study. The starting dose of 30 mg Q3W is selected not only to be a safe starting dose (as per the ICH S9 guidance for novel therapeutics for advanced cancer indications) but also potentially efficacious. Also higher trough concentrations in patients have been associated with improved efficacy based on a recent exposure-response analysis by the FDA for the ADC T-DM1 (Wang, 2014). Accordingly, the design of the dose selection strategy for the AMG 224 FIH study is to minimize treating subjects with relapsed or refractory multiple myeloma in the study with sub-efficacious doses of AMG 224.

Preliminary pharmacokinetics results indicated dose-related increase in serum exposure for AMG 224 conjugated antibody and lack of any significant accumulation upon multiple dosing following the Q3W dosing regimen with mean serum accumulation ratio of ≤ 1.4 for AMG 224 conjugated antibody following the Day 22 dose.

Safety margins were calculated based on the observed exposures for the AMG 224 conjugated antibody in subjects with relapsed or refractory multiple myeloma and at the HNSTD in cynomolgus monkey from the GLP toxicology study. At the starting dose of 30 mg the observed safety margins were 24 and 21 based on the maximum plasma concentration (C_{max}) and area under the plasma concentration time curve over the dosing interval of 3 weeks ($AUC_{0\text{-}3\ week}$), respectively relative to observed exposure at the HNSTD in cynomolgus monkey. At the proposed highest planned dose of [redacted] safety margins are expected to be approximately 2.8 and 2.7 based on C_{max} and $AUC_{0\text{-}3week}$, respectively relative to observed exposure at the HNSTD in cynomolgus monkey. Overall, preliminary results indicate that AMG 224 exhibits a favorable PK profile in its target patient population of subjects with relapsed or refractory multiple myeloma. The primary safety concern thrombocytopenia is monitor-able and expected to be reversible, and the safety and tolerability data from prior dose levels will guide the dose escalations

and the planned top dose for AMG 224 in the dose exploration phase (see Section 6.2.1.2 Study Dose Exploration and Stopping Rules).

Dose Expansion Phase (Part 2)

In the Part 1 of the study a fixed dosing (ie, dose not adjusted for individual subject's body weight) will be evaluated and in the Part 2 of study body weight based dosing will be evaluated. Subjects will be treated with preliminary MTD identified from the Dose Exploration part of the study adjusted for their body weight, which is [redacted] Q3W. An integrated preliminary analysis of dose exploration phase data for the primary safety concern of thrombocytopenia indicates that a dose of [redacted] Q3W is not associated with concerning platelet count decreases (greater than Grade 3) during the DLT evaluation period. A dose of [redacted] is also expected to be efficacious based on patients' serum trough coverage of the projected efficacious exposures (90% tumor cell killing concentration (IC_{90})) estimated from the pharmacokinetic/pharmacodynamics modeling of AMG 224-mediated tumor burden reduction observed in orthotopic xenograft (BCMA-expressing human multiple myeloma [KMS26]) in mice, which is also in line with preliminary response observed in the study. Additionally, higher trough concentrations in patients have been associated with improved efficacy based on a recent exposure-response analysis by the FDA for the ADC T-DM1 (Wang, 2014), with same cytotoxin, linker and DAR as AMG 224. Hence, a dose of [redacted] is expected to be well tolerated, as well as efficacious, and is recommended for the dose expansion phase. For therapeutic monoclonal antibody-based therapies a full assessment of body weight effect on the PK/PD should be conducted to determine the optimal dosing approach prior to conducting the registration trial and a recommendation for adjustment or lack of adjustment of dose based on body weight be made once sufficient clinical data is available (Bai, 2012 and Wang, 2009). When sufficient AMG 224 clinical data becomes available, a full assessment of body size effect on PK/PD will be conducted to determine the optimal dosing approach prior to conducting the registration trial for AMG 224 in multiple myeloma patients.

2.5 Clinical Hypotheses

- AMG 224 administered by IV infusion at (or one dose level below) the preliminary MTD identified during the dose exploration part of the study is expected to achieve acceptable safety and tolerability in subjects with relapsed or refractory multiple myeloma.
- A favorable PK profile will be achieved with AMG 224 administered by IV infusion Q3W.
- Objective responses by IMWG uniform response criteria will be observed at a dose level that achieves acceptable safety and tolerability.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 1, first-in-human, multicenter; non-randomized, open-label, dose-exploration and dose expansion study of AMG 224 IV Q3W for subjects with relapsed or refractory multiple myeloma. The study will be conducted in two parts: Part 1 - Dose Exploration and Part 2 - Dose Expansion.

Eligible subjects enrolled in the study will receive AMG 224 IV once Q3W beginning at study Day 1. During the initial DLT window (Day 1 through Day 28) subjects will be assessed for DLT. DLTs are defined in Section 6.2.1.6. Dosing with AMG 224 may continue Q3W unless there is evidence of progressive disease (PD) defined by IMWG, the subject becomes intolerant to the study medication, signs and symptoms of clinical progression are evident as determined by the principal investigator, or the subject withdraws consent.

Part 1 – Dose Exploration

In Part 1 for the first dose level and at each new higher dose level, the first enrolled subject will be treated, and then after a period of 24 hours, subsequent subjects will be treated, provided that there are no safety concerns relating to the treatment of the first subject.

The dose-exploration cohorts will define the preliminary MTD, safety, tolerability, PK, and PD of AMG 224. A 3+3 design will be used to make a preliminary estimate of MTD. The preliminary MTD is defined as the maximum dose at which fewer than 33% of subjects experience a DLT. A final estimate of the MTD will be made using data from Dose Exploration and Dose Expansion. Planned dose levels for the dose-exploration cohorts are as follows: 30, [redacted] of AMG 224 (IV; Q3W).

Dose exploration decisions will be made by the Dose Level Review Team (DLRT). All cumulative safety and laboratory data will be reviewed prior to making dose exploration decisions. Safety data from all enrolled subjects in preceding cohorts and dose levels will also be considered. Additionally, the DLRT may stop enrollment into a cohort at any time to evaluate safety.

3+3 Design:

Dose escalation decisions will be made in accordance with a 3+3 design modified to allow flexibility in the initial cohort size (decision rules noted in Table 1). Dose escalation will occur at the planned dose levels until the MTD is determined or until the highest dose level is tested. The MTD is defined as the highest dose level with an observed incidence of DLT in < 33% of subjects enrolled in a cohort dose level. At least 6 subjects will be treated at the MTD or highest tested dose.

Table 1. 3+3 Dose Level Decision Rules

#Subjects[a]	#Subjects with DLT	Decision
3-4	1	Enroll 2-3 additional subjects at same dose level
3-4	0	Escalate[b]
3-4	≥ 2	De-escalate[c]
6	1	Escalate[b]
6	≥ 2	De-escalate[c]

[a] Subjects who are not DLT-evaluable (see Section 3.4) are excluded from the count of subjects
[b] If final dose level has been reached, accrual will be suspended.
[c] If 6 subjects already entered at next lower dose level, the estimated MTD has been established.

Part 2 – Dose Expansion:

In the Part 2 of the study up to 20 subjects with relapsed or refractory multiple myeloma will be treated. Subjects will be divided into the following 2 groups based on the status of prior treatment with CD38 targeting antibody (eg, Daratumumab):

- Group A will consist of subjects who had prior treatment with a CD38 targeting antibody (at least 10 subjects).
- Group B will consist of subjects who are naïve to CD38 targeting antibody treatment (approximately 10 subjects).

A body weight-based dosing will be evaluated in the Dose Expansion part of the study. Subjects will be treated with preliminary MTD identified from the Dose Exploration part of the study [redacted] adjusted for their body weight. Subjects with grade 2 thrombocytopenia at baseline (ie, platelet count < 75 to 50 x 10^9/L) should be started at

a reduced dose of [redacted]. The subsequent doses of AMG 224 could be further reduced to [redacted] if the criteria for dose reduction for thrombocytopenia are met as per sections 6.2.1.5 and 6.3.1. For therapeutic monoclonal antibody-based therapies a full assessment of body weight effect on the PK/PD should be conducted to determine the optimal dosing approach prior to conducting the registration trial and a recommendation for adjustment or lack of adjustment of dose based on body weight be made once sufficient clinical data is available (Bai, 2012 and Wang, 2009). In the Part 1 of the study a fixed dosing (ie, dose not adjusted for individual subject's body weight) will be evaluated and in the Part 2 of study body weight-based dosing will be evaluated. When sufficient AMG 224 clinical data becomes available, a full assessment of body size effect on PK/PD will be conducted to determine the optimal dosing approach prior to conducting the registration trial for AMG 224 in multiple myeloma patients.

During dose-expansion, after 5 subjects have enrolled (combining Group A and B subjects) and completed 28 days on study. A toxicity probability interval (TPI) Bayesian model utilizing all current DLT-evaluable subjects will be fit to evaluate the appropriateness of the preliminary MTD from dose exploration. The subsequent subjects to be enrolled in dose expansion may be dosed with the updated dose level. A final estimate of the MTD will be made based on a toxicity probability interval (TPI) Bayesian model utilizing all DLT evaluable subjects from the dose exploration and dose expansion cohorts.

The DLRT will review safety after 5 subjects have enrolled and completed 28 days on study. The review will include all available safety data. If concerns arise from either planned or unplanned safety reviews, the DLRT may request additional review or recommend modifying or suspending the study

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 10.1.1.

3.2 Number of Sites

The study will be conducted at approximately 4 to 6 sites in the United States and Australia. Sites that do not enroll subjects into an open cohort within 4 months of site initiation may be terminated and replaced.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. Subjects with relapsed or refractory multiple myeloma is eligible for this study. Up to 60 evaluable subjects will be enrolled at approximately 4-6 clinical centers in the US and Australia. In the dose exploration cohorts, approximately 40 subjects will be enrolled. Up to 6 subjects will be enrolled at the MTD or highest tested dose to gain additional safety and PK information. In the expansion cohorts, up to 20 subjects will be enrolled and treated with MTD or highest tested dose of AMG 224. The rationale for the number of subjects required is detailed in Section 10.

3.4 Replacement of Subjects

During dose exploration, subjects that are not DLT-evaluable will be replaced. A subject is not DLT-evaluable if the subject discontinues treatment for any reason other than a DLT prior to completing the first 28 days of AMG 224 treatment or does not receive 2 doses of AMG 224 during the 28-day DLT window. Additional subjects may be enrolled if Amgen’s medical monitor determines that the minimum required numbers of subjects with evaluable tissue samples have not been enrolled.

3.5 Estimated Study Duration

The duration of the study will be approximately 30 months which includes 24 months of enrollment and 6 months of protocol treatment period.

3.5.1 Study Duration for Subjects

It is anticipated that each subject will be on study for approximately 2 weeks for screening and 6 months of treatment period. Approximately 30 to 37 days after the last dose of AMG 224, the subject will return to the clinic for a safety follow-up (EOS) visit. The estimated study duration for participant is 7.5 months but this may be longer or shorter depending on the subject’s disease, ability to tolerate AMG 224 and/or willingness to participate in the study.

3.5.2 End of Study

The end of study occurs when a subject discontinues treatment with AMG 224 and completes the EOS visit. The date the final safety assessment or procedure is performed is considered the end of study. The safety follow-up or EOS visit will occur 30 to 37 days after the last administration of AMG 224.

Primary Completion is defined as the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the 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. Subjects who are still active at the time of the primary analysis may continue on study until disease progression, study withdrawal, death, or investigational product intolerance is observed

End of Trial is defined as the time when the last subject is assessed or receives an intervention for evaluation in the study. Once achieved, the final analysis will occur.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). Before any study-specific procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion Criteria

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

102 Age ≥ 18 years old at the time of signing the informed consent.

103 Subject must have a pathologically documented, definitively diagnosed, multiple myeloma relapsed or refractory progressive disease after at least 3 lines of therapy for multiple myeloma (see Appendix D and Appendix G for further details). Prior therapeutic treatment or regimens must include proteasome inhibitors (eg, bortezomib) and immunomodulatory drugs (eg, lenalidomide).

a. For group A expansion cohort prior therapy for multiple myeloma must include a CD38 targeting antibody.

b. For group B expansion cohort prior therapy for multiple myeloma must not include a CD38 targeting antibody.

104 Subject must be willing and able to undergo bone marrow aspirate per protocol (with or without bone marrow biopsy per institutional guidelines).

105 Measurable disease per the IMWG response criteria (assessed within 28 days prior to day 1), as indicated by one or more of the following:

- Serum M-protein ≥ 1 g/dL
- Urine M-protein ≥ 200 mg/24 hours
- 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

106 Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2

107 Life expectancy of > 3 months, in the opinion of the investigator.

108 Hematological function, as follows, without transfusion support:

- Absolute neutrophil count ≥ 1.0 X 10^9/L,

- Platelet count ≥ 75 X 10^9/L (in patients with < 50% of bone marrow nucleated cells were plasma cells) or ≥ 50 X 10^9/L (in patients with ≥ 50% of bone marrow nucleated cells were plasma cells) without transfusion or growth factor support
- Hemoglobin > 8 g/dL (> 80 g/L)

109 Coagulation function, as follows: PT/INR and PTT < 1.5 x Institutional Upper Limit of Normal (ULN).

110 Renal function as follows; estimated Glomerular filtration rate based on MDRD (Modification of Diet in Renal Disease) calculation > 45 mL/min/1.73 m^2

111 Hepatic function, as follows; AST and ALT < 3 x ULN, Total bilirubin < 1.5 x ULN (except subjects with Gilbert's syndrome)

112 Cardiac function, as follows; left ventricular ejection fraction (LVEF) > 50%. 2-D transthoracic echocardiogram (ECHO) is the preferred method of evaluation. Multi-gated Acquisition Scan (MUGA) is acceptable if ECHO is not available.

4.2 Exclusion Criteria

201 Currently receiving treatment in another investigational device or drug study, or less than 28 days since ending treatment on another investigational device or drug study(s).

202 Previously received an allogeneic stem cell transplant and the occurrence of one or more of the following:

- received the transplant within 1 year prior to study day 1
- received immunosuppressive therapy within the last 3 months prior to study day 1
- having signs or symptoms of acute or chronic graft-versus-host disease

203 Autologous stem cell transplant less than 90 days prior to study day 1

204 Multiple myeloma with IgM subtype

205 POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

206 Plasma cell leukemia (>2.0 X10^9/L circulating plasma cells by standard differential).

207 Waldenstrom's macroglobulinemia

208 Amyloidosis

209 Glucocorticoid therapy (prednisone > 30 mg/day or equivalent) within 7 days prior to study day 1.

210 History of other malignancy, except:

- Malignancy treated with curative intent and with no known active disease present for ≥ 2 years before study day 1 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

211 Evidence of a bleeding diathesis

212 Current use of anticoagulationagents. Note: Use of therapeutic anti-coagulation agents may be permitted if there is no bleeding and in the opinion of the investigator and in consultation with Amgen's medical monitor the use of these agents is medically necessary. Subjects with thrombocytopenia (platelet count < 100 x 10^9/L) and on anti-coagulant treatment should be closely monitored during treatment with AMG 224.

213 Myocardial infarction within 6 months of study day 1, symptomatic congestive heart failure (New York Heart Association > class II).

214 History of arterial thrombosis (eg, stroke or transient ischemic attack) within 6 months prior to study day 1.

215 Infection requiring intravenous anti-infective treatments within 1 week of study day 1.

216 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

217 Known positive results for Human Immunodeficiency Virus (HIV)

218 Unresolved toxicities from prior anti-tumor therapy, defined as not having resolved to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 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 may be allowed if they are not otherwise described in the exclusion criteria AND there is agreement to allow by both the investigator and Amgen medical monitor).

219 Treatment with medications known to cause QTc interval prolongation (see Appendix F) within 7 days of study day 1 unless approved by the Amgen medical monitor.

220 A baseline ECG QTcF > 470 msec

221 Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy, or investigational agent) within 28 days prior to study day 1.

222 Prior systemic radiation therapy must have been completed at least 28 days before study day 1. Prior focal radiotherapy completed at least 14 days before study day 1.

223 Major surgery within 28 days prior to study day 1.

224 Male and female of reproductive potential who are unwilling to practice a highly effective method(s) of birth control while on study through 3 months (female) or 6 months (male) after receiving the last dose of study drug. Acceptable highly effective methods of birth control are defined as those which result in a low failure rate (ie, less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, intrauterine devices (IUDs), sexual abstinence or vasectomized partner. Barrier methods of contraception are acceptable if a condom with spermicide (male) is used in combination with diaphragm, cervical cap or cervical sponge (female).

225 Female who are breastfeeding or who plan to breastfeed while on study through 3 months after receiving the last dose of study drug.

226 Female with a positive pregnancy test.

227 Female planning to become pregnant while on study through 3 months after receiving the last dose of study drug.

228 Subject has known sensitivity to any components of the investigational product.

229 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

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific 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 (see Section 11.2).

All subjects must personally sign and date the IRB/IEC approved ICF before commencement of study-specific procedures. Each subject who signs the inform consent enters into the screening period for the study and 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 study identification number will consist of 11 digits. The first 3 digits will represent the last 3 digits of the protocol number (eg, 314). The next 5 digits will represent the country code and site number (eg, 66001) and will be identical for all subjects at the site. The next 3 digits will be assigned in sequential order as subjects

are screened (eg, 001, 002, 003). For example, the first subject to enter screening at site 66001 will receive the number 31466001001, and the second subject at the same site will be 31466001002.The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

All screening tests and procedures should be performed within 14 days prior to study day 1, unless otherwise indicated. All blood and urine samples collected for screening assessments will be submitted and analyzed by the local laboratory. Time permitting, screening laboratory assessments used to determine subject eligibility may be repeated once (up to a total of 2 times during the 14-day screening period), if necessary.

Subjects who do not meet eligibility criteria within the 14-day screening period will not be eligible for enrollment. Subjects may be re-screened up to 2 additional times at the discretion of the Investigator. The subject must be re-consented if a re-screening attempt occurs outside of the 14-day screening period. Subjects who are deemed ineligible will be documented as screen failures.

Subjects may be eligible to enroll once all screening tests and procedures are completed and results indicate that all eligibility criteria are met. A site representative will complete and send the enrollment eligibility worksheet to Amgen along with the lab results and any requested supporting documentation for review of eligibility criteria. The Eligibility Worksheet should be completed and emailed to the Amgen representative at least 3 days prior to the planned day of first dose. The Amgen representative will acknowledge receipt of the paperwork and send confirmation of the cohort and dose level assignment for the subject.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in the enrollment eCRF.

5.1 Treatment Assignment

An Amgen representative will notify the site in writing when a cohort is open to screen and enroll subjects. The notification will include the cohort number 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 224.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 224.

6.2 Investigational Product

All investigational products will be administered at the research facility by a qualified staff member. A physician must be available at the time of administration of Investigational Product.

6.2.1 AMG 224 Investigational Product

AMG 224 will be manufactured by BSP Pharmaceuticals, Italy and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. AMG 224 will be presented as 10 mg/mL protein concentration formulated with [redacted] mM sodium acetate, [redacted] % (w/v) sucrose, [redacted]% (w/v) polysorbate 20, pH [redacted]. AMG 224 will be supplied as 5 mL deliverable volume in a single use 8cc glass vial stored at liquid temperatures of [redacted] C to [redacted]°C. AMG 224 will be administrated as an IV infusion.

6.2.1.1 Dosage, Administration, and Schedule

AMG 224 will be administered as an intravenous (IV) infusion Q3W. In Part 1 of the study, the pre-specified nominal AMG 224 (mg) doses are 30, [redacted] (non-weight-based dosing).

In part 2 of the study, AMG 224 will be also administered as per weight-based dosing at [redacted] with a cap of [redacted] based on available nonclinical toxicology information on maximum sucrose allowance limit. It is estimated that 3 g sucrose ([redacted] AMG 224) per injection with a total dose not exceeding 1.8 g/dose/week is safe.

AMG 224 will be administered as an IV infusion given over 60 ± 10 minutes Q3W in the first 2 cycles. The dose of AMG 224 will vary by study part:

- Part 1 - Dose Exploration: The doses range from 30 to 300 mg.
- Part 2 - Dose Expansion: The starting dose is [redacted]. Subjects with grade 2 thrombocytopenia at baseline (ie, platelet count < 75 to 50 x 10^9/L) should be started at a reduced dose of [redacted]. The subsequent doses of AMG 224 could be further reduced to [redacted] if the criteria for dose reduction for thrombocytopenia are met as per sections 6.2.1.5 and 6.3.1.

The dose of AMG 224 should not exceed [redacted] (based on available nonclinical toxicology information on maximum sucrose allowance limit).

During the Dose Expansion Phase all doses are to be based on the subject's actual body weight on the day of dosing (Day 1 of each cycle). For cycles 2 and beyond, weight should be re-checked and dosing adjusted accordingly, unless body weight is changed by 5% or less compared to the cycle 1 weight. The dose of AMG 224 should not exceed [redacted] (based on available nonclinical toxicology information on maximum sucrose allowance limit).

For each subject, the infusion time may be shortened to 30 minutes ± 5 in the later cycles if the subject did not experience an infusion reaction or lengthened up to 120 ± 10 minutes if the subject experienced an infusion reaction. The dose, start date/time, stop date/time and lot number is to be recorded for each subject in the eCRF. No other investigational product will be used or provided in this study.

The effects of overdose of this product are not known.

Pre-medication for AMG 224

No routine pre-medication should be administered prior to the first AMG 224 infusion. If a subject develops an infusion reaction, subjects should acutely be treated according to best clinical practice. The infusion should be either interrupted or slowed depending upon the severity of the symptoms. Reduce the infusion rate by 50% in subjects who experience Grade 1 or 2 AMG 224-related infusion reaction. Terminate the infusion in subjects who experience ≥ Grade 3 AMG 224-related infusion reaction. Medication may be administered as deemed appropriate by the investigator to control any infusion 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 an infusion reaction of Grade 3 or greater severity.

Premedication with antihistamines and/or corticosteroids may be considered for subsequent doses in subjects who experience an infusion reaction, at the discretion of the investigator. Any subject experiencing ≥ Grade 2 bronchospasm or generalized urticaria, significant hypotension and/or wheezing despite maximal medical management should receive no additional doses of AMG 224.

6.2.1.2 Study Dose Exploration and Stopping Rules

For the dose exploration, a 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 the Investigators, 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, Global Safety Officer or designee, and study investigators. 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.

All available study data, including data collected after the initial DLT window, and including 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 decisions will be made in accordance with a modified 3+3 design using the rules noted below (refer to Table 1) and in Section 3.1.

- If no dose limiting toxicity (DLT) is observed within the DLT window in the initial 3-4 subjects of a cohort, then dose escalation to the next higher dose level cohort will occur.
- If 1 DLT is observed within the DLT window in the initial 3-4 subjects of a cohort, then the cohort will be expanded to 6 subjects. If no further DLT(s) are observed in the 6 subjects, then dose escalation to the next higher dose level cohort will occur. If ≥ 2 subjects among the initial 3-4 evaluable subject or among the expanded cohort of 6 evaluable subjects experience a DLT in a cohort, then the dose will be declared not safe and enrollment will be stopped.
- If a subject permanently ended the study treatment before completion of DLT evaluation period for a reason other than experiencing a DLT, then another subject will be recruited to replace this subject for the evaluation of the MTD.

Dose escalation will occur at the planned dose levels until the MTD is determined or until the highest dose level is tested. The MTD is defined as the highest dose level with an observed incidence of DLT in < 33% of subjects enrolled in a cohort dose level. At least 6 subjects will be treated at the MTD or highest tested dose.

A DLT will be defined as any of the events described under (Section 6.2.1.6), occurring in a subject during the DLT window, and regarded by the investigators and/or Amgen medical monitor to be related to AMG 224. The DLT window will be the initial 28 days of treatment with AMG 224. The DLT window may also be extended to assess events starting within the window in case the DLT definition is time dependent (neutropenia or thrombocytopenia, see below). Any adverse event occurring outside the DLT window that is determined by the investigator to be possibly related to the investigational product, which is seen more frequently or is more severe than expected or is persistent despite appropriate management, can be determined to be a DLT upon unanimous decision by the DLRT after review of the adverse event and all available safety data. The CTCAE version 4.0 will be used to assess the severity of toxicities/adverse events.

The DLRT may request additional reviews or recommend modifying or suspending the study if safety concerns arise during the study. In the event that a need to modify or suspend the study is identified, this information will be communicated to investigators immediately, in accordance with Amgen procedures, and in compliance with prevailing guidance, including EMEA/CHMP/SWP/28367/07 (Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products). Refer to Section 10.3.2 for additional details regarding the DLRT.

Dose Exploration Stopping Rules

The DLRT may consider part 1 dose exploration complete if one of the following rules is met:

- The highest planned dose level is evaluated, MTD has not been defined and no DLTs occur at any dose level, in this case the maximum administrated dose (MAD) may be used for part 2.
- A total of 40 DLT-evaluable subjects have been enrolled.
- An MTD is identified.

Table 2. Cohort and Dose Exploration Schema

Dose Exploration Schema		
Cohort	Number of Subjects	Dose IV Q3W
1	3-6	30 mg
2	3-6	[redacted]
3	3-6	
4	3-6	
5	3-6	
6	3-6	
7	3-6	
8	3-6	

6.2.1.3 Study Dose Expansion and Stopping Rules

For the dose-expansion phase, a safety review will be held after 5 subjects have enrolled and completed 2 cycles of therapy regardless of group.

The dosing schedule is described in schema in the protocol synopsis.

6.2.1.4 Other Stopping Rules During Enrollment

Enrollment will be held at any time during the study if any of the following events occurs:

- DLTs in the first 2 subjects in cohort 1
- Any other study drug-related Grade 5 toxicity

In this case, enrollment and dosing at that particular dose level will be discontinued immediately. Subjects in that dosing cohort will have their treatment dose immediately reduced to the next lower dose level or have study treatment discontinued if the event occurs in Cohort 1 at the starting dose level.

The investigator must discuss the safety findings with all ongoing subjects before continuing AMG 224 to ensure that the subjects understand the risks of continuing AMG 224 therapy.

The sponsor will discuss such cases with the DLRT, Regulatory Authority and the study Investigators as appropriate to decide whether to resume enrollment. IRBs/IEs will be notified by the Investigators of all cases and decisions regarding continued enrollment.

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

Dosage Adjustments

The subject should continue on the same dose of AMG 224 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 (ie Dose Level -1 as outlined in Table 3 or a further lower dose level (ie Dose Level -2 as outlined in Table 3).
- The study drug can be resumed once the adverse events recover to baseline or Grade 1 and the reintroduction of AMG 224 is deemed safe by the Investigator, Amgen's Medical Monitor, and Global Safety Officer.
- Subjects must be informed of the risk of continuing on therapy. Each subject is only allowed a single dose reduction.
- For subjects experiencing thrombocytopenia after the DLT-window, there will be an option to reduce the dose to the immediate next lower dose level (ie, Dose Level -1 as outlined in Table 3) or a further lower dose level (ie Dose Level -2 as outlined in Table 3 in the dose expansion part of the study (as described in section 6.3.1).

The investigator should notify Amgen immediately before administration of the lower dose of AMG 224.

Subject who have been dose-reduced will have an option to receive the higher dose (ie, Dose Level -1 or Dose Level 1) at the next planned cycle if the adverse event resolves to ≤ grade 1 or baseline and the reintroduction of AMG 224 at the higher dose is deemed safe by the Investigator.

For dose reduction level, refer to Table 3:

Table 3. Dose Reduction of AMG 224 for Toxicity (Only in Dose Expansion)

Dose level	Dose IV Q3W
Dose Level 1 Dose Level -1 Dose Level -2	[redacted]

Subjects should not be rechallenged with AMG 224 if the following AMG 224-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. Any treatment-related adverse event meeting DLT-criteria that recurs

Dosage Delays

During the DLT-window, if the dosing is delayed for more than 7 days the subject will be removed from the study and will be replaced. After DLT-window, if the dosing is delayed for ≤ 3 weeks, the subject should resume the treatment as soon as possible if deemed safe by the investigator. The investigator should inform the Amgen Clinical team as soon as the unexpected dosing interruption occurs. If the dosing of AMG 224 is delayed more than 3 weeks (missing 1 cycle) due to treatment-related adverse events, the subject will be removed from the study. If the dosing delay occurred under conditions other than those associated with AMG 224 related toxicities, the case will be reviewed by Amgen medical monitor to determine whether the subject will be allowed to resume AMG 224 treatment.

Rules for Withholding or Restarting

AMG 224 should be withheld for any of the following:

- Suspected DLT (including AE that meet DLT definition outside DLT window)
- Grade 3 thrombocytopenia (follow the thrombocytopenia management in Section 6.3.1)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3x ULN or total bilirubin greater than 1.5x ULN

AMG 224 dosing can be resumed if the toxicities resolve to grade ≤ 1 or return to subjects' baseline values. The restarting of therapy should be 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 224 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 224, may have the option to continue therapy once the adverse events recover to baseline or Grade 1 and the re-introduction of AMG 224 is deemed safe by the investigator, Amgen's medical monitor, and Global Safety Officer. The subject should

restart at a reduced dose (see Section 6.2.1.4) subsection Dose Adjustments).

- Intolerability of the study treatment
- The dosing is delayed > 3 weeks due to AMG 224-related adverse events
- Disease progression according to IMWG response criteria
- Clinical significant deterioration of health status
- Withdrawal of informed consent
- Subjects become pregnant or is breastfeeding

6.2.1.6 Dosage Limiting Toxicities

The grading of adverse events will be based on the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (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 4.0. 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 224.

A DLT is defined as a Grade 3 or higher non-hematological or a Grade 4 hematologic adverse event that occurs during the DLT window (day 1 through day 28 after the administration of the first dose of AMG 224) in Part 1 Dose Exploration unless clearly attributable to causes other than AMG 224 treatment. DLT toxicities do not include fatigue, nausea, diarrhea, vomiting, neutropenia, anemia, thrombocytopenia and lymphopenia, increased serum creatinine or electrolytes abnormalities that are not clinically significant and require no treatment unless the following criteria are met:

<u>Hematological toxicity:</u>

- Grade 4 neutropenia lasting > 7 days
- Grade 3 or 4 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
- Lymphopenia of any grade is not considered a DLT

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 > 4.0 mg/dL) lasting > 3 days
- Elevation of either AST or ALT according to the following criteria:
  - > 8x ULN;
  - > 5x ULN but < 8x ULN for ≥ 2 weeks;
  - > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule; or
  - > 3x ULN with clinical signs or symptoms that is consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice, rash or eosinophilia (> 5%).
- TBIL > 3x ULN

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 6.4 for hepatotoxicity management and Appendix A for further explanation of Hy's law case and Management of Hepatic Function).

6.3 Management of Adverse Events

6.3.1 Management of Thrombocytopenia

Increased monitoring should be implemented in subjects whose platelet counts are < 100 x 10^9/L and subjects on anti-coagulant or anti-platelet treatment. Hematology panels should be repeated on days 5, 6, or 7, or as clinically indicated, following each dose, if platelet counts are < 75 x 10^9/L, until platelet counts are ≥ 75 x 10^9/L (Grade 1).

Subjects should not receive anti-coagulant therapy or anti-platelet therapy while treated with AMG 224 unless in the opinion of the investigator and in consultation with Amgen's medical monitor the use of these agents is medically necessary. Use caution with these agents and consider additional monitoring as described above when concomitant of these agents is medically necessary.

Details of dose modification based on pre-dose platelet count are described in Table 4.

The investigator should notify Amgen immediately before administration of the lower dose of AMG 224.

Subjects who have been dose-reduced will have an option to receive the higher dose (ie Dose Level -1 or Dose Level 1 as outlined in Table 3, Section 6.2.1.5) at the next planned cycle if the adverse event resolves ≤ grade 1 or baseline and the reintroduction of AMG 224 at the higher dose is deemed safe by the Investigator. The investigator should notify Amgen immediately before administration of the higher dose of AMG 224.

Treatment for thrombocytopenia should be initiated per standard of care as clinically indicated. Any subject who experiences a Grade 3 or 4 thrombocytopenia that cannot be managed per standard of care, will be permanently discontinued from AMG 224 treatment.

Table 4. Dosing Guideline Based on Platelet Count After 2nd Cycle

Grade of Platelet Count Decrease	Withhold Dose	Previous dose [redacted]	Previous dose [redacted]	Dose Discontinuation
Grade 0 or 1 (PLT LLN to ≥ 75 10^9/L)	No	Continue to administer AMG 224 at Dose Level 1 [redacted] Q3W)	Escalate to one higher Dose Level ([redacted] Q3W)	N/A
Grade 2 (PLT 75 to ≥ 50 10^9/L)	No	Continue to administer AMG 224 at Dose Level 1 [redacted] Q3W)	Continue to administer AMG 224 at the same dose level	N/A
Grade 3 (PLT <50 to ≥ 25 10^9/L)	Yes, don't administer AMG 224 until platelet count recovers to ≤ Grade 2 (≥ 50K)	Upon recovery, administer AMG 224 at Dose Level 1 ([redacted] Q3W)	Upon recovery, administer AMG 224 at the same dose level	Yes, if grade 3 platelet count decrease did not recover to at least grade 2
Grade 4 (PLT < 25 10^9/L) and last ≤ 7 days	Yes, don't administer AMG 224 until platelet count recovers to ≤ Grade 2 (≥ 50K)	Upon recovery, administer AMG 224 at Dose Level -1 ([redacted] Q3W) if deemed safe by the investigator	Upon recovery, administer AMG 224 at one lower Dose Level (minimum [redacted] Q3W) if deemed safe by the investigator	Yes, if grade 4 platelet count decrease did not recover to at least grade 2 OR subsequent drops in platelet count to Grade 4 after dose reduction

Table 4. Dosing Guideline Based on Platelet Count After 2nd Cycle

Grade of Platelet Count Decrease	Withhold Dose	Previous dose [redacted]	Previous dose [redacted]	Dose Discontinuation
Grade 3 or 4 PLT count decreased associated with < grade 2 bleeding	Yes, don't administer AMG 224 until platelet count recovers to ≤ Grade 2 (≥ 50K) and bleeding is controlled	Upon recovery, administer AMG 224 at Dose Level -1 ([redacted] Q3W) if deemed safe by the investigator	Upon recovery, administer AMG 224 at one lower Dose Level (minimum [redacted] Q3W) if deemed safe by the investigator	Yes, if grade 3 or 4 platelet count decrease did not recover to at least grade 2 and bleeding is not controlled OR subsequent episode of Grade 3 or 4 thrombocytopenia associated with < grade 2 bleeding
Grade 4 (PLT < 25 10^9/L) and last > 7 days or Grade 3 or 4 (PLT<50 10^9/L) with ≥G2 bleeding	N/A	N/A	N/A	Yes

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6.3.2 Management of Anemia

Anemia is one of the multiple myeloma-related organ/tissue dysfunction and is generally related to bone marrow infiltration or renal dysfunction. Subject should be monitored for changes in hemoglobin as described in the schedule of assessments (see Table 5.). Increased monitoring should be implemented in subjects whose hemoglobin < 8 g/dL. Subjects should have anemia corrected in accordance with the local practice and institutional guidelines. Hemoglobin parameters of grade 3 but not considered as clinically relevant (ie, without symptoms of anemia and not leading to a clinical intervention including withdrawal of investigational product treatment, transfusion, or significant additional concomitant therapy) will not require discontinuation of AMG 224. However, treatment should be discontinued for persistent (ie, ongoing > 3 weeks after the end of a treatment cycle) grade 3 or 4 anemia in the absence of detectable multiple myeloma which may reflect a prolonged marrow toxic effect of AMG 224.

6.3.3 Management of Infections

Subjects with evidence of existing infection should be closely monitored while being treated with AMG 224. Subjects with active systemic infections requiring IV antibiotics, antivirals, or antifungals should not be dosed with AMG 224 until infection has resolved

and if being treated with an anti-infectious therapy, the course of such therapy should have been completed. 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.

6.3.4 Management of Peripheral Neuropathy

Peripheral neuropathy is a common side effect of multiple myeloma standard of care therapy. Thorough assessment of baseline peripheral neuropathy is required at screening (see Appendix H). Subjects should be clinically monitored on ongoing basis for signs and symptoms of peripheral neurotoxicity according to the schedule of assessments (see Table 5.). AMG 224 should be temporarily withheld in subjects experiencing Grade 3 or 4 peripheral neuropathy until resolution to grade 1 or baseline. Peripheral neuropathy should be managed according to the local standard of care and institutional guidelines.

6.3.5 Management of Cardiac Arrhythmia

Subjects with risk factors for, or evidence of, existing heart disease should be closely monitored throughout their treatment with AMG 224. Subjects should be clinically monitored on ongoing basis for cardiac function (blood pressure, heart rate, and ECG) according to the schedule of assessments (see Table 5.). The administration of AMG 224 should be withheld if grade 3 or 4 arrhythmias (including tachycardia) develop or appear to be exacerbated by AMG 224 treatment. Treatment may be resumed once the signs and symptoms resolve to baseline value or grade 1. Management should be tailored to the appropriate treatment for the underlying cardiac disorder according to the local standard of care and institutional guidelines.

6.3.6 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 224. Serum chemistry values, including BUN, serum creatinine, and urine for urinalysis and microscopic exam (microscopic exam only needed for positive dipstick), must be obtained and reviewed prior to each dose of AMG 224 per the schedule of assessments (see Table 5.). AMG 224 must be held for subjects with CrCl or eGFR <30 ml/min/1.73m^2 or any other grade 3 or 4 renal toxicity any time during study treatment participation. Management should be tailored to the appropriate treatment for the underlying renal disorder according to the local standard of care and institutional guidelines.

6.4 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 Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009).

6.4.1 Criteria for Permanent Withholding of AMG 224 due to Potential Hepatotoxicity

AMG 224 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 > 2 x 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 Steatohepatitis (NASH) or other "fatty liver disease"
- Non-hepatic causes (eg, rhabdomyolisis, hemolysis)

6.4.2 Criteria for Conditional Withholding of AMG 224 due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent withholding of AMG 224 outline above and with 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 conditional withholding of AMG 224 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 is consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice, rash or eosinophilia (> 5%).

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

AMG 224 should be withheld pending investigation into alternative causes of DILI. If investigational product 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.

6.4.3 Criteria for Rechallenge of AMG 224 After Potential Hepatotoxicity

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, Principal Investigator, and Amgen. Subjects who clearly meet the criteria for permanent discontinuation (ie, no definite alternative cause for the laboratory abnormalities was discovered) (as described in Section 6.2.1.4) should never be rechallenged. If signs or symptoms recur with rechallenge, then AMG 224 should be permanently discontinued.

6.5 Concomitant Therapy

Throughout the study, Investigators may prescribe any concomitant medications or treatments, including red blood cell (RBC) and platelet transfusions as deemed necessary to provide adequate supportive care except for those listed in Appendix F.

Concomitant therapies are to be collected from informed consent through the EOS. Collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

6.6 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 drugs or devices 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 drugs or devices provisioned and/or repackaged/modified by Amgen. Drugs or devices includes investigational product.

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

6.7 Excluded Treatments, Medical Device Use, and/or 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 below):

- Treatment with immune modulators including, but not limited to, immunosuppressive dose of corticosteroid (>10 mg/day prednisone or equivalent), cyclosporine, and tacrolimus
- Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy, or investigational agent); concurrent use of bisphosphonates or denosumab for bone loss are permitted
- Treatment with medications known to cause QTc interval prolongation unless approved by the Amgen Medical Team
- Concurrent use of warfarin, factor Xa inhibitors, and direct thrombin inhibitors unless agreed upon by Amgen and investigator (eg, use of agents such as low-dose aspirin and low-dose warfarin may be allowed)
- Any live vaccine therapies used for the prevention of infectious disease
- Any surgery or radiotherapy unless agree upon by Amgen and investigator

There are no prohibited therapies and procedures during the post-treatment follow-up.

7. STUDY PROCEDURES

7.1 Schedule of Assessments Dose Exploration and Dose Expansion

Table 5. Schedule of Assessments – Dose Exploration and Dose Expansion

	Screen	Treatment																							
Cycles		I									II									Cycle III and IV					
Weeks		1					2	3		4							5	6		7 and 10				8 &11	9 &12
Days	-14	1				2	5	8	15	22					23	26	29	36		43 and 64				50 & 71	57 & 78
Hours (relative to start of dosing)		Pre-dose	0	0.5	EOI	4	24	96	168	336	Pre-dose	0	0.5	EOI	4	24	96	168	336	Pre-dose	0	0.5	EOI		
GENERAL AND SAFETY ASSESSMENT																									
Informed consent	x																								
Clinical evaluation [1]	x	x					x	x	x	x	x					x	x	x	x	x				x	x
Vital signs [2]	x	x			x		x	x	x	x	x			x		x	x	x	x	x		x	x	x	x
12-lead ECG [3]	x1	3x 3			x3	x3	x 3	x3	x3	x3	x3			x3	x3	x3	x3	x3	x3	x3		x3	x3	x3	x3
Echocardiogram [4]	x																								
Peripheral Neuropathy Assessment [5]	x	x									x									x					
Prior/concomitant medication review	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→
Adverse events review	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→
LABORATORY ASSESSMENTS AND DOSING																									
AMG 224 dosing [6]			x								x									x					
AMG 224 PK [7] [9]		x		x	x	x	x	x	x	x		x	x	x	x	x	x	x	x		x		x	x	x
DM1 PK [8] [9]		x		x	x	x	x	x		x		x	x	x	x	x									
Anti-AMG 224 antibody collection (Immunogenicity)		x																	Cycle 3 only						
Safety lab tests [10]	x	x					x	x	x	x	x					x	x	x	x	x				x	x
Pregnancy test [11]	x	x																							x [11]
Hepatitis serology [12]	x																								
SPEP/UPEP/ Immunofixation [13]	x									x									x						
SFLC [14]	x									x									x						
Quantitative Ig [15]	x																								
Beta-2 microglobulin	x																								
Bone marrow, FISH [16]	x																								
Biomarker Bone Marrow Biopsy	x																								
Biomarker Bone Marrow Aspirate	x																								
Biomarker Blood Samples collection [17]	Plasma	x								x									x						
	Serum	x								x									x						
	Whole Blood CTC	x																							
	Cell Pellet (PG sample)	x								x									x						
PAXgene RNA [18]	x																								
IMAGING ASSESSMENTS																									
Plasmacytoma [19]	x																								
Skeletal survey [20]	x																								

Footnotes defined on last page of this table.

Table 5. Schedule of Assessments – Dose Exploration and Dose Expansion

		Treatment					EOT[21]	EOS[21]
Cycle		V and Beyond						
Weeks		Q3W			Q6W	Q9W		
Days								
Hours (relative to start of dosing)		Pre-dose	0	EOI	Pre-dose	Pre-dose		
GENERAL AND SAFETY ASSESSMENT								
Informed consent								
Clinical evaluation [1]		x					x	x
Vital signs [2]		x		x			x	x
12-lead ECG [3]					x3		x3	x3
Echocardiogram [4]								
Peripheral Neuropathy Assessment [5]					x		x	x
Prior/concomitant medication review								
Adverse events review								
LABORATORY ASSESSMENTS AND DOSING								
AMG 224 dosing [6]			x					
AMG 224 PK [7] [9]		x					x	x
DM1 PK [8] [9]								
Anti-AMG 224 antibody collection (Immunogenicity)						x	x	x
Safety lab tests [10]		x					x	x
Pregnancy test [11]						x	x	x
Hepatitis serology [12]								
SPEP/UPEP/Immunofixation [13]		x					x	x
SFLC [14]		x					x	x
Quantitative Ig [15]								
Beta-2 microglobulin								
Bone marrow, FISH [16]								
Biomarker Bone Marrow Biopsy		<	—	—	—	—	—	>
Biomarker Bone Marrow Aspirate		<	—	—	—	—	—	>
Biomarker Blood Sample Collection [17]	Plasma				x		x	x
	Serum				x		x	x
	Cell Pellet				x		x	x
IMAGING ASSESSMENTS								
Plasmacytoma [19]								
Skeletal survey [20]						x		

Footnotes defined on the next page.

1. Clinical evaluation will include: physical exam with a neurologic assessment, ECOG status, and weight. Screening only - medical and surgical history, weight and height.
2. Vitals signs (blood pressure, respiratory rate, heart rate, temperature) will be collected (pre-dose on dosing days) after subject has rested for at least 5 minutes.
3. ECG will be performed after subject has rested for approximately 5 minutes; X1 = single ECG; X3 = triplicate ECG (tracings one minute apart), reporting PR, QRS, QT, QTc, RR interval. If interval prolongation > 480 msec occurs (and is a 30 msec increase above baseline), subject's serum potassium, magnesium, calcium and phosphorus should be measured immediately and replaced if needed. On day 1 predose only, triplicate ECGs to be completed at approximately 90, 60 and 30 minutes prior to dosing.
4. Echocardiogram (or MUGA; a consistent method will be used throughout the study) will be performed at screening only.
5. Refer to Appendix H for the evaluation tool and document in the eCRF. The site will enter the score to each question and the total score will be derived in RAVE.
6. Each complete cycle will be of 3 weeks duration comprising 1 dose administration of AMG 224. The subsequent cycle will start 3 weeks after the dose administration of the prior cycle
7. AMG 224 PK = samples collected and analyzed for AMG 224 conjugated antibody and Total anti-BCMA antibody. The PK of AMG 224 conjugated antibody and total anti-BCMA antibody will be assessed using the same samples.
8. DM1 PK = samples collected and analyzed for Total unconjugated DM1 PK. Samples for total DM1 PK will be collected on Day 1: predose, 0.5hr, EOI, 4hr, 24hr (Day 2), 96hr (Day 5); Day 22: predose, 0.5hr, EOI , 4hr, 24hr (Day 23), 96hr (Day 26). Refer to Laboratory Manual for procedure.
9. 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 to the nominal time point and record the actual collection time. PK samples not collected at exact nominal time point will not be considered protocol deviations.
10. Safety lab tests will include: chemistry (sodium, potassium, chloride, bicarbonate, albumin, calcium, magnesium, phosphorus, glucose, total protein, BUN or urea, creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, uric acid and LDH (LDH required at Screening only); Hematology includes CBC and platelets with differential; coagulation includes PT, PTT and INR; and urinalysis includes specific gravity, pH, blood, leucocyte esterase (WBC), protein, ketones, glucose, bilirubin (microscopic is needed only for positive dipstick for the following test): WBC, RBC, epithelial cells, bacteria, casts and crystals. Abnormal electrolytes should be corrected prior to administration of AMG 224 and consideration should be given to monitoring electrolytes (eg, magnesium and potassium) in symptomatic subjects (eg, subjects with nausea, vomiting, diarrhea, fluid imbalance or cardiac symptoms). Day 5, 8 and 15 can be +/- 1 day, CBC, LFT or renal function test should be repeated within 24-48 hour if labs if the subject experiences Grade 2 to 3 thrombocytopenia or transaminitis or grade 3 acute kidney injury.
11. Serum pregnancy test performed at screening; urine or serum pregnancy test at all other timepoints (day 1, week 9 and Q9W thereafter, EOT) for female of child bearing potential.
12. Hepatitis Serology, all subjects will be tested for HBsAg, antiHBcAb, HCVAb. If HBsAg is negative and HBcAb positive, test HBV DNA by PCR. If HCVAb positive, test HCV RNA by PCR.
13. 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.
14. Serum free light chain (SFLC) assay and ratio will be performed at each time point.
15. 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).
16. Bone marrow sample will be collected from all subjects during screening to quantify percent myeloma involvement and for fluorescent in situ hybridization (FISH). An additional bone marrow sample will only be required to confirm a complete response (CR).
17. Biomarker samples will be collect at pre-dose for cycle 1 through cycle 5 then every 6 weeks (odd cycles) thereafter, EOT and EOS.
18. Signed informed consent specifically allowing pharmacogenetic testing must be obtained ssssbefore obtaining samples.

19. 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 Q9W if clinically indicated ie.; new symptoms (bone pain) arises. Consider obtaining MRI for subjects with bone pain but skeletal survey is normal.
21. In any case of premature treatment discontinuation, the investigator should make every effort to perform all examinations scheduled for the EOT and EOS visits. These data should be recorded, as they comprise an essential evaluation that should be performed prior to discharging any subject from the study and to allow for the evaluation of the study endpoints. 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. The end of study (EOS) visit will occur 30 to 37 days after last treatment of AMG 224.

7.2 General Study Procedures

A signed and dated IRB-approved informed consent must be obtained before any study-specific procedures are performed. Procedures that are part of routine care are not considered study-specific procedures and may be used at screening to determine eligibility. All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the study.

7.2.1 Informed Consent

A signed informed consent must be obtained from each subject prior to any study mandated procedures.

7.2.2 Medical History

The Investigator or designee will collect a complete medical and surgical history that started prior to enrollment through the time of consent. Medical history will include information on the subject's concurrent medical health conditions, relevant past medical conditions, and surgical history.

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.

7.2.3 Prior Therapy

The Investigator or designee will collect relevant prior therapy which includes previous chemotherapy or radiotherapy, anticancer therapies (eg,stem cell transplant).

7.2.4 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).

7.2.5 Peripheral Neuropathy Assessment

The peripheral neuropathy assessment should be done at screening and time points specified in the Schedule of Assessments (Section 7.1). All assessments must be reported on the corresponding eCRF page (see Appendix H for peripheral neuropathy assessment tool).

7.2.6 Height Measurements

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

7.2.7 Weight Measurements

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

7.2.8 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 designated site physician 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.

7.2.9 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group Performance Status (Appendix E) assessments will occur at time points specified in the Schedule of Assessments (see Section 7.1).

7.2.10 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, and run consecutively (approximately 1 minute apart), 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 will be collected ≥ 30 minutes apart, with each ECG in triplicate approximately 30 seconds apart (3 set collected pre-dose on day 1 [ie, total = 9 ECGs])
- Triplicate ECGs, with each ECG approximately 30 seconds apart, at all other time points except for screening when this is only required once

When ECGs, vital signs, blood for laboratory tests and PK are to be collected at the same time points, the ECGs and vital signs will be collected prior to blood collections.

The principal investigator or designated site physician will review all ECGs. Electrocardiograms will be transferred electronically to an ECG central reader for analysis per Amgen instructions. Once signed, 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 transited to the selected vendor.

7.2.11 Echocardiogram (ECHO) / Multi-gated Acquisition (MUGA) Scan

ECHO or MUGA will be performed to assess cardiac ejection fraction and cardiac valve abnormalities and will occur at screening only. The test can be repeated if clinically indicated by the investigator.

7.2.12 Tumor Assessments

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. 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

Bone marrow sample will be collected from all subjects during the screening to quantify percent myeloma involvement and for fluorescent in situ hybridization (FISH); FISH will be performed locally. An additional bone marrow sample will only be required to confirm a complete response (CR).

7.2.13 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.

7.2.14 Quantitative Immunoglobulin

Quantitative Immunoglobulin (Ig) will be performed at screening. Quantitative Immunoglobulin will be repeated only if clinically indicated, ie, frequent infection despite multiple myeloma disease control or deemed clinically indicated by the investigator.

7.2.15 Beta-2 Microglobulin

Beta-2 microglobulin will be performed only at baseline as part of risk stratification.

7.2.16 Skeletal Survey

Skeletal survey will be performed at the time points as specified in the schedule of assessments (Table 5.). Skeletal survey is defined by X-rays or PET/CT scans of lateral view of the skull, anteroposterior and lateral views of the spine and anteroposterior views of the pelvis, ribs, femora, and humeri. MRI should be performed in subjects with bone pain but skeletal survey is normal.

7.2.17 Pharmacokinetic Blood Sampling

For pharmacokinetic assessment blood samples for quantitative determination of AMG 224 conjugated antibody, Total anti-BCMA antibody, and DM-1 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. The pharmacokinetics of AMG 224 conjugated antibody and total anti-BCMA antibody will be assessed using the same samples.

7.2.18 Blood Samples

Approximate blood volumes expected to be collected during 6 months for Part 1 and Part 2 of study participation are presented in Table 6

Table 6. Approximate Blood Volumes for Part 1 and Part 2

Test	Volume (mL) per Collection	Approximate Number of Collection	Approximate Total Volume (mL)
Laboratory safety (chemistry, hematology, coagulation)	15 mL	17	255 mL
Serology	5 mL	1	5 mL
Quantitative Immunoglobulin	10 mL	1	10 mL
Serum pregnancy test (female of child bearing potential only)	3 mL	5	15 mL
Blood for Anti-AMG 224 (Immunogenicity)	5 mL	4	20 mL
Blood samples for PK (DM1)	3 mL	16	48 mL
[redacted]	10 mL	5	50 mL
Blood samples for PK (AMG 224, conjugated Antibody and Total anti-BCMA antibody)	3 mL	25	75 mL
PaxGene RNA sample	2.5 mL	1	2.5 mL
Total blood volume assumes 6 cycles for study participation plus EOT and EOS (if applicable)			~480.5 mL

7.2.19 Clinical Laboratory Assessments

Blood samples for clinical chemistry, hematology, and urine samples for urinalysis, will be collected at screening, and at time points specified in the Schedule of Assessments (Table 5.). All tests (except for PK, antibodies and biomarkers) are to be performed at a local laboratory and test results are to be recorded in the eCRF. Blood samples will be obtained by venipuncture before study drug administration. All laboratory tests must be reviewed by the investigator or qualified designee. Additional safety laboratory assessments may be performed if clinically indicated at the discretion of the investigator. The following tests listed in Table 7 will be conducted on samples collected by standard laboratory procedures.

Table 7. Clinical Laboratory Assessments

Chemistry	Hematology	Urinalysis	Coagulation
Albumin	ANC	Specific gravity	PT
ALP	Hematocrit	pH	PTT
ALT	Hemoglobin	Blood	INR
AST	MCH	Protein	
Bicarbonate	MCHC	Ketones	Other Labs:
BUN or Urea	MCV	Bilirubin	Pregnancy
Calcium	Platelets	Glucose	Hep B surface antigen
Chloride	RBCs	Leucocytes esterase (WBC)	Hep B antibody
Creatinine	WBCs	Microscopic exam (only needed for positive dipstick and should include the following):	Hep C antibody
Direct bilirubin	▪ Differential:	Epithelial, Bacteria, Casts, Crystal, RBCs, WBCs	HCV PCR (if applicable)
Glucose	▪ Neutrophils		HBV PCR (if applicable)
LDH	▪ Lymphocytes		PK
Magnesium	▪ Monocytes		Biomarker
Phosphorus	▪ Eosinophils		Anti-AMG 224
Potassium	▪ Basophils		Anti-BCMA
Sodium			SPEP
Total bilirubin			UPEP
Total protein			SFLC
Uric acid			Quantitative Immunoglobulin
			Beta-2 microglobulin
			PG

7.2.20 Screening

After obtaining informed consent, all screening procedures and tests establishing eligibility will be performed within a period of 28 days before dosing and 14 days for laboratory assessments. If acceptable screening laboratory assessments are within

48 hours of study day 1, the pre-dose laboratory assessments do not need to be obtained. The following procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 5.) (Section 7.1).

7.2.21 Screening Procedures to Determine Eligibility

Confirmation that the Informed Consent Form has been signed and dated

Review of inclusion and exclusion criteria to determine eligibility

Demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact biomarker variability and pharmacokinetics.

- Review of medical and surgical history including:
  - concomitant medication
  - documentation of diagnosis including history of current and prior cancers
  - prior anticancer treatments
- Clinical evaluation includes the following:
  - physical examination with neurological assessment, ECOG performance status, height and weight
  - assessment according to CTCAE version 4.0 for prior and continuing diagnosis, disease complications and toxicities
- Peripheral neuropathy assessment
- Vital signs (blood pressure, respiratory rate, heart rate, temperature)
- 12-lead ECG
  - Collected after subject has rested for 5 minutes.
  - Record QRS, QT, QTc, RR and PR intervals.
- Echocardiogram
- Safety Laboratory Assessments (locally tested) within 14 days of study day 1
  - Chemistry
  - Hematology
  - Coagulation
  - Urinalysis
- Serum pregnancy test (only females of childbearing-potential)
- Determination of HIV status (via medical history)

- Determination of HBV and HCV status
    - HBsAg and total HBc
        - If results are HBc positive and HBsAg positive, no additional testing is necessary
        - If results are HBc positive and HBsAg negative, additional testing for hepatitis B virus DNA by PCR is necessary
    - HepCAb
        - If results are HepCAb positive, additional testing for hepatitis C virus RNA by PCR is necessary.
- Serum protein electrophoresis (SPEP) and 24-hour urine protein electrophoresis (UPEP)
- Serum free light chain (SFLC)
- Beta-2 macroglobulin
- Quantitative Immunoglobulin
- Bone marrow, bone marrow biopsy and bone marrow aspirate
- Pharmacogenetic blood collection (optional)
- Imaging Assessments (plasmacytoma and skeletal survey)
- Adverse event assessment is preformed throughout the study at every visit
    - Serious adverse events are collected from the time the subject signs the ICF
    - Adverse events are collected from the time the subject is dosed on day 1

Subjects can be rescreened at the discretion of the investigator after consultation with Amgen. The investigator must provide appropriate rationale prior to repeating any screening procedures or tests during the screening period. A new consent must be signed unless it has been < 30 days since the last consent was signed.

7.2.22 Treatment

The following procedures will be completed during each cohort treatment period at the times designated in the Schedule of Assessments (Table 5.). Administration of AMG 224 is to be administered after all protocol-specific pre-dose assessments has been performed during each visit that it is required.

Clinical evaluation to include the following:

- Physical examination with neurological assessment and ECOG performance status
- Peripheral neuropathy assessment
- Vital signs (blood pressure, respiratory rate, heart rate, temperature)
- 12-lead ECG
    - collected after subject has rested for 5 minutes.
    - record QRS, QT, QTc, RR and PR intervals.

- Pregnancy test – serum or urine (only females of childbearing-potential)
- Safety Laboratory Assessments (locally tested)
  - Chemistry
  - Hematology
  - Coagulation
  - Urinalysis
- Blood collection
  - PK (DM1 & AMG 224 conjugated antibody and Total anti-BCMA antibody PK)
  - Anti-AMG 224 antibody
  - Biomarker
- Serum protein electrophoresis (SPEP) and 24-hour urine protein electrophoresis (UPEP)
- Serum free light chain (SFLC)
- Imaging Assessments (plasmacytoma and skeletal survey)
- Adverse event assessment is preformed throughout the study at every visit
  - Serious adverse events are collected from the time the subject signs the ICF.
  - Adverse events are collected from the time the subject is dosed on day 1.
- Documentation of concomitant medications

7.2.23 End of Treatment

The end of treatment (EOT) visit will occur after the last dose of AMG 224. 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.

Clinical evaluation to include the following:

- Physical examination with neurological assessment and ECOG performance status
- Vital signs (blood pressure, respiratory rate, heart rate, temperature)
- Peripheral neuropathy assessment
- 12-lead ECG
  - collected after subject has rested for 5 minutes.
  - record QRS, QT, QTc, RR and PR intervals.
- Safety Laboratory Assessments (locally tested)
  - Chemistry
  - Hematology

  - Coagulation
  - Urinalysis
- Blood collection
  - Anti-AMG 224 antibody
  - Biomarker
- Serum protein electrophoresis (SPEP) and 24-hour urine protein electrophoresis (UPEP)
- Serum free light chain (SFLC)
- Adverse event assessment is preformed throughout the study at every visit
  - Serious adverse events are collected from the time the subject signs the ICF.
  - Adverse events are collected from the time the subject is dosed on day 1.
- Documentation of concomitant medications

7.2.24 End of Study Visit

The EOS visit must be performed 30 to 37 days after the last dose of AMG 224. All efforts should be made to conduct this visit. If it is not possible to conduct the EOS 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 to include the following:

- Physical examination with neurological assessment and ECOG performance status
- Vital signs (blood pressure, respiratory rate, heart rate, temperature)
- Peripheral neuropathy assessment
- 12-lead ECG
  - collected after subject has rested for 5 minutes.
  - record QRS, QT, QTc, RR and PR intervals.
- Safety Laboratory Assessments (locally tested)
  - Chemistry
  - Hematology
  - Coagulation
  - Urinalysis
- Blood collection
  - Biomarker
  - Anti-AMG 224 antibody
- Serum protein electrophoresis (SPEP) and 24-hour urine protein electrophoresis (UPEP)
- Serum free light chain (SFLC)

- Adverse event assessment is preformed throughout the study at every visit
  - Serious adverse events are collected from the time the subject signs the ICF.
  - Adverse events are collected from the time the subject is dosed on day 1.
- Documentation of concomitant medications

7.3 Antibody Testing Procedures

Blood samples for anti-drug antibody (ADA) testing are to be collected at the time points as specified in the table of assessment (Table 5.). Samples testing positive for binding anti-AMG 224 antibodies may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Additional blood samples may be obtained to rule out anti-AMG 224 antibodies during the study. The incidence of binding anti-AMG 224 antibodies will be reported, and the impact of ADA on pharmacokinetics, pharmacodynamics, safety and efficacy will be evaluated.

Samples testing positive for binding anti-AMG 224 antibodies will be banked and may be analyzed in a validated in-vitro neutralizing assay during late-stage clinical development.

7.4 Biomarker Development

In addition to testing the safety and effectiveness of the experimental drug AMG 224 in this study, Amgen will attempt to develop tests from blood and/or tumor tissue that will identify subjects most likely to benefit from AMG 224. 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 224 or protocol required therapies.

Biomarker development may be pursued by use of advanced biochemical analyses, such as proteomic methods or ribonucleic acid transcript profiling. Some of the biomarkers to be explored include but are not limited to, BCMA and BCMA ligand expression, mutation status, analysis of BCMA RNA transcripts in tumors, enumeration and/or signaling activity of CTCs levels of soluble BCMA and BCMA ligands.

Blood Samples

Blood samples are to be collected for biomarker development at the time points as listed in the schedule of assessments. Plasma samples may also be used to explore whether

expression or mutation of specific commonly occurring mutations found in tumors tissues (and other genes based on emerging data) correlates with response to AMG 224.

7.5 Bone Marrow

During screening, bone marrow sample is required for all subjects. Samples will be sent to the central laboratory along with the corresponding pathology report. The tumor block is to be carefully selected by a pathologist or a skilled experienced histology associate to include generous tumor tissue using the Pathology Report as a guide. In lieu of a block, 20 unstained sections on charged slides from the same block can be submitted within 4 weeks of study day 1 to allow time to evaluate the samples, and to ask for additional samples if the initial samples are not appropriate. Analyses of tumor specific mutations or epigenetic changes may be performed (eg, somatic mutations) when the samples of tumor tissues become available. Minimal residual disease will be evaluated on the bone marrow specimen of the patients that achieve complete remission per IMWG.

7.6 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be 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 multiple myeloma and/or to identify subjects who may have positive or negative response to AMG 224. No additional samples are collected for this part of the study however for subjects who consent to this/these analysis/analyses, DNA may be extracted from the blood samples collected for the biomarker studies will be used for this purpose.

7.7 Sample Storage and Destruction

Any remaining blood and tumor samples collected according to the Schedule of Assessments (Table 5.) 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, the dose response and/or prediction of response to AMG 224 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 pharmacogenetic, 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 Amgen with the required study and subject number so that any remaining blood 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 (or a legally acceptable representative) 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 or other protocol required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 5.) and collection of data, including endpoints and adverse events. The Investigator must document the change to the Schedule of Assessments (Table 5.) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

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, publicly 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 Amgen can decide to withdraw subjects 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 the investigational product include any of the following:

- subject request
- safety concern (eg, due to an adverse event)
- ineligibility determined
- protocol deviation
- non-compliance (eg, procedural or dosing as defined in Section 6.2.1.1)
- requirement for alternative therapy
- pregnancy

- decision by Amgen (other than subject request, safety concern, or lost to follow-up)
- decision by investigator (other than subject request, safety concern, or lost to follow-up)
- death
- lost to follow-up
- Confirmed Disease Progression per IMWG (Appendix D)

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by Amgen
- 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 expected by the investigator's assessment. 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.

If the severity of an adverse event worsens from the date of onset to the date of resolution, 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 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 therapy 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 therapy 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 study 30 to 37 days after the last dose of investigational product 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 4.0. 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 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 and/or procedure (including any screening procedures). 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, 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 to 37 days after the last dose 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.

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.

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

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. The investigator may be asked to provide additional follow up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the Event eCRF.

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.

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapies report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through 3 months after the last dose of investigational product.

The pregnancy should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of the event of a 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 lactation case occurs while the female subject is 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 monitor for lactation cases that occur after the last dose of protocol-required therapies through 3 months after the last dose of investigational product.

Any lactation case should be reported to Amgen's 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, Analysis Sets, and Covariates

10.1.1 Study Endpoints

Primary Endpoints

- Safety: Incidence of DLTs, treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, physical examinations, ECGs and clinical laboratory tests

Secondary Endpoints

- PK profile: PK parameters for AMG 224 conjugated antibody, Total anti-BCMA antibody, and total unconjugated DM1including, but not limited to maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), area under the concentration-time curve (AUC), clearance (CL), and if feasible half-life ($t_{1/2}$)
- Overall response according to International Myeloma Working Group (IMWG) uniform response criteria, relative reduction in M-component, time to progression (TTP), duration of response (DOR)
- Conversion to MRD negativity
- Incidence of anti-AMG 224 antibody formation

Exploratory Endpoints

- Quantification of BCMA expression in pre-dose bone marrow biopsy and bone-marrow aspirates
- Pre-dose bone marrow biopsy and/or plasma DNA gene expression profiles.
- Serum level of BCMA, BCMA ligands, APRIL and BAFF
- Quantification of circulating tumor cells, plasma cells and/or BCMA specific tumor cells

10.1.2 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 224. The analysis of DLT will be restricted to DLT-evaluable subjects (see Section 3.4). The PK Analysis Set will contain all subjects who have received at least 1 dose of the investigational product 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.

10.1.3 Covariates and Subgroups

The relationship of covariates to efficacy endpoints will be explored if appropriate. Biomarker data may be incorporated in additional exploratory subgroup or multivariate analyses. The analyses of biomarkers may be performed after collection of all samples during the conduct of the study and therefore may be reported after the primary analysis of efficacy endpoints.

10.2 Sample Size Considerations

It is anticipated that approximately 60 subjects will be enrolled in this study. Approximately 40 subjects will be enrolled in the dose exploration cohorts and up to 20 additional subjects will be enrolled in the dose expansion cohort.

The sample size in the dose exploration is based on practical consideration and it is consistent with conventional oncology studies with the objective to identify the MTD. With 3 subjects per cohort, there is a 27 to 70% probability of observing at least one DLT if the true DLT rate is 10 to 33% and with 6 subjects per cohort, there is a 47 to 91% probability.

In the dose expansion cohort, a subject number of 20 (regardless of group) will provide a 64% probability of observing at least one adverse event with 5% incidence rate and 88% probability of observing at least one adverse event with 10% incidence rate. An exact 80% binomial confidence interval (CI) will be provided for overall response rate (ORR). With the 20 subjects and 20% ORR, the 80% CI would be 9% to 36%.

10.3 Planned Analyses

The following data analyses are planned: (1) dose decision analyses in the dose-exploration cohorts, (2) the primary analysis when target enrollment is complete 6 months on study or withdraws from the study, and (3) the final analysis after all subjects have ended the study.

10.3.1 Interim Analyses

Safety data will be reviewed on an ongoing basis. The Dose Level Review Team (DLRT, see Section 10.3.2) will review all available cumulative data by cohort prior to making dose escalation decisions. Adverse events and DLTs observed in all subjects will be evaluated continually and considered in all enrollment and dosing decisions.

During dose-expansion, the DLRT will review safety after 5 subjects have enrolled (combining Group A and Group B subjects) and completed 28 days on study. A TPI Bayesian model (see Section 10.4.2.3) utilizing all current DLT-evaluable subjects will be

fit to evaluate the appropriateness of the preliminary MTD from dose exploration. The subsequent subjects to be enrolled in dose expansion may be dosed with the updated dose level, determined by the DLRT.

10.3.2 Data Monitoring Committee (DMC), Data Review Team (DRT) or Dose Level Review Team (DLRT)

Dose Level Review Meetings (DLRMs) will be held to review data, monitor safety, and make decisions on dose escalation / change. The DLRT will be composed of the investigators or designees, and the following Amgen representatives: medical monitor, global safety officer or designee, clinical study manager, biostatistician, additional members may be added as needed (eg, clinical pharmacologist). The following members are responsible for DLRT decisions: investigators, Amgen medical monitor, and global safety officer or designee. All available study data, including data collected after the initial DLT window, and including demographics, IP administration, medical history, concomitant medications, adverse events, ECGs, vital signs, laboratory data, 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.

10.3.3 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.

10.3.4 Final Analysis

A final analysis is planned after all dose-exploration cohorts and dose-expansion subjects have ended the study.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, PD 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. Graphical summaries of the data may also be presented.

10.4.2 Primary Endpoints

10.4.2.1 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 224.

10.4.2.2 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 fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product, and significant treatment emergent adverse events will also be provided.

10.4.2.3 Dose Limiting Toxicities

The analysis of the probability of dose limiting toxicities (DLT) will include data from DLT-evaluable subjects, both from dose-exploration and dose-expansion (see section 3.4 for definition of DLT-evaluable). The primary analysis will only include DLTs that occur within the protocol defined DLT evaluation interval. If DLTs occur outside the specified evaluation interval, a sensitivity analysis will be performed where DLTs occurring outside of the specified time interval are included. The preliminary estimate of the MTD will be identified using the 3+3 design. A final estimate of the MTD will be made based on a toxicity probability interval (TPI) Bayesian model utilizing all DLT evaluable subjects from the dose exploration and dose expansion cohorts (Babb, 1998). A minimally informative prior distribution will be used for the model parameters (Neuenschwander, 2008). The MTD target probability interval is (0.20, 0.35) and TPIs of (0.35, 0.60) and (0.60, 1.00) are defined as excessive and unacceptable, respectively. The model's predicted MTD is the dose with the highest probability of the target TPI, but with a less than 0.25 probability of an excessive or unacceptable TPI.

10.4.2.4 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.

10.4.2.5 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.

10.4.2.6 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.

10.4.3 Pharmacokinetic Endpoints

The analysis of pharmacokinetic endpoints will include data from all subjects who have received at least 1 dose of the investigational product and have at least 1 pharmacokinetic sample collected.

The PK parameters for AMG 224 conjugated antibody (anti-BCMA antibody with at least one DM1 molecule conjugated to the antibody), Total anti-BCMA antibody (sum of unconjugated anti-BCMA antibody and AMG 224 conjugated antibody), and DM1 (total unconjugated DM1), including, but not limited to maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), area under the concentration-time curve (AUC), clearance (CL), and if feasible half-life ($t_{1/2}$) will be estimated using standard non-compartmental PK methods and summarized by dose groups using means, standard deviations, medians, minimums and maximums for intensive and peak/trough determinations. AMG 224 conjugated antibody, total anti-BCMA antibody and DM1 concentrations at each time point along with PK parameter values may be listed for each subject. Individual AMG 224 conjugated antibody, total anti-BCMA antibody and DM1 concentration/time profiles will be plotted by dose groups. Summary statistics will be computed for each sampling time and parameter as appropriate. Analysis of the relationship between AMG 224 dose and exposure parameters (AUC and C_{max}) will be conducted and plots of the relationship between AMG 224 dose and exposure parameters along with dose proportionality assessment will be provided. Analysis of the

relationship between AMG 224 conjugated antibody concentrations and change from baseline in QTc will be conducted and plots of the relationship between AMG 224 conjugated antibody concentrations and change from baseline in QTc will be provided. Additional analyses to explore relationship between exposure and safety and exposure and efficacy may also be performed.

10.4.4 Secondary Endpoint(s)

10.4.4.1 Efficacy Endpoint Analyses

Listings will be produced for all subjects in the dose-exploration cohorts and the dose-expansion cohorts indicating the time to progression, time to response, and duration of response. The proportion of subjects with a partial response to treatment or better per the IMWG with corresponding exact 80% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) and tabulated for subjects treated at the MTD. The proportion of subjects with minimal residual disease and the proportion of subjects' progression-free at 6 months with corresponding exact 80% CI will be calculated using the Clopper-Pearson method. Kaplan Meier curve will be presented for time to progression and duration of response with estimates for rates and 80% CI at selected weeks.

10.4.4.2 Anti-AMG 224 Antibodies

The incidence and percentage of subjects who develop anti-AMG 224 antibodies (binding) at any time will be tabulated by treatment group. If greater than 10% of subjects have a positive anti-AMG 224 antibody test, then summaries of results over time will be provided.

10.4.5 Exploratory Endpoints

Details of analyses on exploratory endpoints will be provided in either a data analysis plan or a supplemental statistical analysis plan.

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 Clinical Study Manager to the investigator. The written informed consent document 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 or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or AMG 224 is administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

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 or a legally acceptable representative and by the person who conducted the informed consent discussion (not necessarily an Investigator). 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 or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, 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 Federal regulations/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

If Amgen amends the protocol, agreement from the Investigator must be obtained. 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 to Amgen.

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 study contract. 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 pre-study 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.

No study document should be destroyed without prior written agreement between Amgen and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify Amgen in writing of the new responsible person and/or the new location.

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 Amgen'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 eCRFs must be maintained and readily available.
- Updates to eCRFs 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 to obvious data errors in the clinical trial database, as documented in the Study Specific Self-Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit-week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects who are 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 (Table 5.), the investigator can search publicly 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

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 encourages 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 Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), 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. Authors should meet conditions 1, 2, and 3.
- 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.

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 4.0 is available at the following location:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/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 6.4 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 eCRF (eg, Event eCRF) 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 9.2.1.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product is withheld (either permanently or conditionally) due to potential DILI as specified in Sections 6.4.2 and 6.4.3 or who experience AST or ALT elevations > 3 x ULN 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 has been discontinued AND the subject is asymptomatic.
- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count (CBC) with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis

  - Obtain serum acetaminophen (paracetamol) levels
  - Obtain 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
  - Obtain viral serologies
  - Obtain CPK, haptoglobin, LDH, and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain 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. 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 eCRFs.

Appendix B. Sample Serious Adverse Event Form

AMGEN Study 20130314 AMG 224	Electronic 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

[If the protocol provides instructions to submit certain types of events ONLY to Amgen Safety and not to the Clinical Trial Database, state that reason below and remove these instructions. If no protocol-specific reasons, remove these instructions and the following bullet.]

Protocol specific reason(s):

☐ *<<Note protocol instruction/reason here and change text from italics to standard.>>*

<<For completion by Amgen prior to providing to sites: SELECT OR TYPE IN A FAX#>>

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. ADVERSE EVENT

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

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/drug under study	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/drug under study or an Amgen device used to administer the IP/drug under study? AMG 224 No / Yes; <Route> No / Yes; <Route> No / Yes; <Route> 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; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 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

AMGEN
Study 20130314
AMG 224

Electronic Adverse Event Contingency Report Form

For Restricted Use

Site Number	Subject ID Number

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

IP/Drug/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 224	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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 20130314 AMG 224	Electronic 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 - _____ *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.*	Title	Date

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

US: +888 814 8853

1. Case Administrative Information

Protocol/Study Number: AMG 224 / 20130314

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 maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011 Page 1 of 1

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 224 / 20130314

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:** _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2. Page 1 of 1

Appendix D. 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 last page of this table

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 E. ECOG Performance Status and NYHA Classification

Eastern Cooperative Oncology Group (ECOG) Performance Status

0. Fully active, able to carry out 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 F. Medications That May Cause QTc Prolongation

List of medications known to cause QTc interval prolongation is available at the following link: https://crediblemeds.org/index.php/login/dlcheckIf participant in this study does not have access to the internet, they can contact the institution investigational pharmacy or contact their study physician to obtain a list.

The following table presents a list of drugs that may prolong the QTc. This is not an inclusive list of drugs and is provided for guidance only. The participant is encouraged to follow the list in this link above for the most up-to-date information. These drugs are prohibited during the study. Washout period is based on roughly 5 half-lives and rounded to a convenient interval. This list includes (but is not limited to) the following:

Compounds	Compound Half-Life	Possible Washout Period – Hours	Possible Washout Period - Days
Alfuzosin	~10 hours		7
Amantadine	17 +/- 4 hours (10-25)		4
Amiodarone (cordarone)	58 days (15-142) 36 days (active metabolite)		180
Amitriptyline*	> 24 hours, wide interpatient variability		
Arsenic trioxide	Not characterized		
Azithromycin	40 hours		
Bepridil	42 hours (26-64)		10
Chloral hydrate	Readily converted to Trichloroethanol (active metabolite $T_{1/2}$= 7 -10 hours)	48	
Chloroquine	Prolonged (days to weeks)		
Chlorpromazine	30 +/- 7 hours		
Clarithromycin	Non-linear PK3-4 hr (250mg Q12) 5-7 hr (500 mg Q12)	36	
Chloroquine	6 to 60 days; mean 20 days		
Desipramine*	>24 hours, wide interpatient variability		
Disopyramide	6.7 hr (4-10)	36	
Dofetilide	10 hours	48	
Dolasetron	8.1 hours		
Domperidone	7-8 hours	48	
Doxepin*	> 24 hours, wide interpatient variability		
Droperidol	2.2 hours	10	

Footnotes defined on last page of this table

Compounds	Compound Half-Life	Possible Washout Period – Hours	Possible Washout Period - Days
Erythromycin	*Each salt form has different Half-Life*		
Felbamate	20-23 hours		5
Flecainide	20 hours (12-27)		5
Foscarnet	87.5 +/-41.8 hours *distribution and release from bone*		20
Fosphenytoin	12-29 hours		6
Gatifloxacin	7-14 hours	48	
Gemifloxacin	7 hours	48	
Grepafloxacin	16 hours		3
Halofantrine	6-10 days (variable among individual)		45
Haloperidol	18 +/-5 hours		5
Ibutilide	6 hours (2-12) *variable among subject*	36	
Imipramine*	> 24 hours, wide interpatient variability		
Indapamide	14 hours (biphasic elimination)		3
Isradipine	8 hours (multiple metabolites)	48	
Levofloxacin	6-8 hours	48	
Levomethadyl	Multiple compartment PK with active metabolite 2.6 days for LAAM, 2 day for nor-LAAM, 4 day for dinor-LAAM		20
Lithium	24 hours (10-50)		7
Mesoridazine	24-48 hours (animal study)		10
Methadone	15-30 hours		7
Moexipril/HCTZ	2-9 hour (include active metabolite) for moexipril; 5.6-14.8 hours for HCTZ	48	
Moxifloxacin	12 +/-1.3 hours	72	
Naratriptan	6 hours	36	
Nicardipine	~ 2 hour post IV infusion	12	
Nortriptyline*	> 24 hours, wide interpatient variability		
Octreotide	1.7 hours	12	
Ofloxacin	5 to 7.5 hours		2
Ondansetron	4 hours (IV/IM); 3 hours (PO)		1 to 3
Pentamidine	6.4 +/- 1.3 hours	36	
Pimozide	55 hours		10

Footnotes defined on last page of this table

Compounds	Compound Half-Life	Possible Washout Period – Hours	Possible Washout Period - Days
Procainamide	3-4 hours for PA and NAPA (active metabolite)	24	
Protriptyline*	> 24 hours, wide interpatient variability		
Quetiapine	6 hours	36	
Quinidine	6-8 hours in adult; 3-4 hours in children	36	
Quinine	4-5 hours		
Risperidone	3-20 hours (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) $T_{1/2}$ = 21-30 hours (extensive to poor metabolizer)		4
Salmeterol	5.5 hours (only one datum)	36	
Sotalol	12 hours	72	
Sparfloxacin	20 hours (16-30)		4
Sumatriptan	2.5 hours	12	
Tacrolimus	~34 hours in healthy; ~19 hours in Kidney transplant		7
Tamoxifen	5-7 days (biphasic)		30
Telithromycin	2-3 hours	24	
Thioridazine	20-40 hours (Phenothiazines)		7
Tizanidine	2.5 hours	12	
Vardenafil	4 to 5 hours		
Venlafaxine	5 +/- 2 hours for parent comp. 11 +/- 2 hours for OVD (active metabolite)	60	
Voriconazole	6 hours; dose dependent		
Ziprasidone	7 hours	36	
Zolmitriptan	2.8-3.7 hours (higher in female)	18	

*Weakly associated with Torsades de pointes and/or QT prolongation but that are unlikely to be a risk for Torsades de pointes when used in usual recommended dosages and in patients without other risk factors (eg, concomitant QT prolonged drugs, bradycardia, electrolyte disturbances, congenital long QT syndrome, concomitant drugs that inhibit metabolism).

References:

1. Physician's Desk Reference 2002
2. Facts and Comparison (update to June 2005)
3. The Pharmacological Basis of Therapeutics 9th Edition, 1999.

Appendix G. Definition of Relapsed or Refractory 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.

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).

Appendix H. Peripheral Neuropathy Assessment

TNSr Items	0	1	2	3	4
Symptom extension (tingling, numbness, neuropathic pain)[a]	None	Symptoms limited to fingers or toes	Symptoms extend to ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knees or elbows or functionally Disability
Pin sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced up to above elbow/knee
Vibration sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced up to above elbow/knee
Strength[b]	Normal	Mild weakness	Moderate weakness	Severe Weakness	Paralysis
Tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent/others reduced	All reflexes absent

[a] The worse score of the 3 subcomponents (tingling/paresthesia, numbness, and neuropathic pain proximal extension) was used as the subjective symptom extension score.
[b] The muscle with the worse score is used as the strength score (toe, ankle, wrist and finger extensors and flexors, quadriceps, hamstrings, biceps, and triceps). TNSr and pain items were adapted with permission [Lavoie Smith, 2010]sss

Amendment 4

Title: A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 224 in Subjects With Relapsed or Refractory Multiple Myeloma

Amgen Protocol Number AMG 224 20130314

Amendment Date: 16 July 2018

Rationale:

The purpose of this protocol amendment is to implement changes needed regarding dosage delays, weight-based dosing, maximum dose allowed, and dose adjustments.

These changes were included in protocol amendment 3; however, protocol amendment 3 was not implemented because the FDA did not agree with the plan for frail subjects. To implement these changes without the plan for frail subjects, this new amendment was needed.

Dosing delay changes were made to allow subjects who have a second dose delayed for more than 48 hours but could still have the second dose of IP within the 28-day DLT-window. This change will allow those subjects to still be DLT evaluable.

Weight-based dosing changes were made to provide clarification to sites how subject weight should be taken in preparation for weight-based dosing.

After protocol amendment 2 was approved, the maximum dose allowed was determined to be [redacted]. The maximum dose allowed was added to this protocol to ensure subject safety.

For subject safety, dose adjustments are being implemented for subjects experiencing thrombocytopenia. From available safety data, grade 4 thrombocytopenia was seen with AMG 224 over [redacted] To mitigate the risk, the revised protocol will include two starting doses for all patients along with a dose adjustment schedule based on platelet count prior to dosing.

Description of Changes:

Section: Global

Change: Minor editorial changes have been made to improve overall clarity and consistency of the protocol language.

Section: Global

Change: correcting typographical and formatting errors

Section: Global

Change: added amendment 3 date 16 July 2018

Section: Cover Page

Change: Updated Sponsor Contacts

Section: Synopsis, Hypothesis

Change: Add

AMG 224 administered by IV infusion at (or a dose level below) the MTD identified during the dose escalation part of the study is expected to achieve acceptable safety and tolerability in frail subjects with relapsed or refractory multiple myeloma.

Section: Synopsis, Hypothesis

Change: Remove

~~At least one dose level of AMG 224 administered by IV infusion is expected to achieve acceptable safety and tolerability in subjects with relapsed or refractory multiple myeloma.~~

Section: Synopsis, Study Design, Dose Exploration

Change: Remove

~~If the preliminary MTD is not reached within the pre-planned dose range, Amgen's medical monitor in conjunction with the investigators, after careful consideration of all available safety, laboratory, and PK information, may investigate doses > [redacted] Additionally, dose levels lower than 30 mg may also be explored if required or supported by emerging data. Intermediate doses and alternative dose frequencies may also be explored if required or supported by emerging data.~~

Section: Synopsis, Study Design, Dose Expansion

Change: Replace

In the Part 1 of the study, a fixed dosing (ie, dose not adjusted for individual subject's body weight) will be evaluated and in the Part 2 of study body weight-based dosing will be evaluated. Subjects will be treated with preliminary MTD identified from the Dose Exploration part of the study adjusted for their body weight.

With

In ~~the~~ Part 1 of the study, a fixed dosing (ie, dose not adjusted for individual subject's body weight) will be evaluated, and in ~~the~~ Part 2 of study body weight-based dosing will be evaluated. Subjects will be treated with preliminary MTD identified from the Dose Exploration part of the study ([redacted]) **adjusted for their body weight. Subjects with grade 2 thrombocytopenia at baseline (ie, platelet count < 75 to 50 x 10^9/L) should be started at a reduced dose of** [redacted]**. The subsequent doses of AMG 224 could be further reduced to** [redacted] **if the criteria for dose reduction for thrombocytopenia are met as per sections 6.2.5.1 and 6.3.1.**

Section: Protocol Synopsis, Amgen Investigational Product Dosage and Administration

Change: Replace

AMG 224 will be supplied as 5 mL deliverable volume in a single use 8cc glass vial stored at liquid temperatures of [redacted] at 10 mg/mL protein concentration formulated with [redacted] mM sodium acetate, [redacted] (w/v) sucrose, [redacted] (w/v) polysorbate 20, pH [redacted]

AMG 224 will be administered as an IV infusion given over 60 ± 10 minutes once Q3W in the first 2 cycles. The doses range from 30 to 300 mg. For each subject, the infusion time may be shortened to 30 ± 5 minutes in the later cycles if subjects experience no infusion reaction or lengthened up to 120 ± 10 minutes if subjects experience infusion reaction.

With

AMG 224 will be supplied as 5 mL deliverable volume in a single use 8cc glass vial stored at liquid temperatures of [redacted] at 10 mg/mL protein concentration formulated with [redacted] mM sodium acetate, [redacted] (w/v) sucrose, [redacted] (w/v) polysorbate 20, pH [redacted]

AMG 224 will be administered as an IV infusion given over 60 ± 10 minutes once Q3W in the first 2 cycles. **The dose of AMG 224 will vary by study part:**

- **Part 1 – Dose Exploration:** The doses range from 30 to 300 mg
- **Part 2 Dose Expansion: The starting dose is [redacted] Subjects with grade 2 thrombocytopenia at baseline (ie, platelet count < 75 to 50 x 10^9/L) should be started at a reduced dose of [redacted]. The subsequent doses of AMG 224 could be further reduced to [redacted] if the criteria for dose reduction for thrombocytopenia are met as per sections 6.2.5.1 and 6.3.1.**

During the Dose Expansion Phase all doses are to be based on the subject's actual body weight on the day of dosing (Day 1 of each cycle). For cycles 2 and beyond, weight should be re-checked, and dosing adjusted accordingly, unless body weight is changed by 5% or less compared to the cycle 1 weight. The dose of AMG 224 should not exceed [redacted] (based on available nonclinical toxicology information on maximum sucrose allowance limit).

For each subject, the infusion time may be shortened to 30 ± 5 minutes in the later cycles if subjects experience no infusion reaction or lengthened up to 120 ± 10 minutes if subjects experience an infusion reaction.

Section 2.4.2 Dose Selection Rationale, Dose Exploration Phase (Part 1)

Change: Delete

~~If the preliminary MTD is not reached within the pre-planned dose range, Amgen's medical monitor in conjunction with the investigators, after careful consideration of all available safety, laboratory, and PK information, may also investigate doses > [redacted] Q3W.~~

Section 2.4.2 Dose Selection Rationale, Dose Expansion Phase (Part 2)

Change: Add

…which is [redacted] Q3W. An integrated preliminary analysis of dose exploration phase data for the primary safety concern of thrombocytopenia indicates that a dose of [redacted] Q3W is not associated with concerning platelet count decreases (greater than Grade 3) during the DLT evaluation period. A dose of [redacted] is also expected to be efficacious based on patients' serum trough coverage of the projected efficacious exposure (90% tumor cell killing concentration (IC90)) estimated from the pharmacokinetic/pharmacodynamics modeling of AMG 224-mediated tumor burden reduction observed in orthotopic xenograft

(BCMA-expressing human multiple myeloma [KMS26]) in mice, which is also in line with preliminary response observed in the study. Additionally, higher trough concentrations in patients have been associated with improved efficacy based on a recent exposure-response analysis by the FDA for the ADC T-DM1 (Wang, 2014), with same cytotoxin, linker and DAR as AMG 224. Hence, a dose of [redacted] is expected to be well tolerated, as well as efficacious, and is recommended for the dose expansion phase.

Section 2.5 Clinical Hypotheses

Change: Add

- AMG 224 administered by IV infusion at (or one dose level below) the preliminary MTD identified during the dose escalation part of the study is expected to achieve acceptable safety and tolerability in subjects with relapsed or refractory multiple myeloma and frail subjects with relapsed or refractory multiple myeloma.

Section 2.5 Clinical Hypotheses

Change: Delete

- ~~At least one dose level of AMG 224 administered by IV infusion is expected to achieve acceptable safety and tolerability in subjects with relapsed or refractory multiple myeloma.~~

Section 3.1 Study Design, Part 1 – Dose Exploration

Change: Delete

~~If the preliminary MTD is not reached within the pre-planned dose range, Amgen's medical monitor in conjunction with the investigators, after careful consideration of all available safety, laboratory, and PK information, may investigate doses > [redacted] Additionally, dose levels lower than 30 mg may also be explored if required or supported by emerging data. Intermediate doses and alternative dose frequencies may also be used if required or supported by emerging data.~~

Section 3.1 Study Design, Part 2 – Dose Expansion

Change Add

… Exploration part of the study ([redacted] adjusted for their body weight. **Subjects with grade 2 thrombocytopenia at baseline (ie, platelet count < 75 to 50 x 10^9/L) should be started at a reduced dose of [redacted] The subsequent doses of AMG 224 could be further reduced to [redacted] if the criteria for dose reduction for thrombocytopenia are met as per sections 6.2.1.5 and 6.3.1.**

Section 4.2 Exclusion Criteria

Change: Replace

Current use of anticoagulation unless agreed upon with investigator and Amgen medical monitor (eg, use of agents such as low-dose aspirin and low-dose warfarin may be allowed)

With

Current use of anticoagulation **agents** ~~unless agreed upon with investigator and Amgen medical monitor (eg, use of agents such as low-dose aspirin and low-dose warfarin may be allowed)~~ **Note: Use of therapeutic anti-coagulation agents may be permitted if there is no bleeding and in the opinion of the investigator and in consultation with Amgen's medical monitor the use of these agents is medically necessary. Subjects with thrombocytopenia (platelet count < 100 x 10^9/L) and on anti-coagulant treatment should be closely monitored during treatment with AMG 224.**

Section 6.2.1.1 Dosage, Administration and Schedule

Change: Replace

AMG 224 will be administered as an intravenous (IV) infusion Q3W. The pre-specified nominal AMG 224 (mg) doses are 30, [redacted] (non-weight-base dosing).

AMG 224 will be administered as an IV infusion given over 60 ± 10 minutes Q3W in the first 2 cycles. The doses range from 30 to 300 mg. For each subject, the infusion time may be shortened to 30 minutes ± 5 in the later cycles if the subject did not experience an infusion reaction or lengthened up to 120 ± 10 minutes if the subject experienced an infusion reaction. The dose, start date/time, stop date/time and lot number is to be recorded for each subject in the eCRF. No other investigational product will be used or provided in this study.

The effects of overdose of this product are not known.

With:

AMG 224 will be administered as an intravenous (IV) infusion Q3W. **In Part 1 of the study,** t~~T~~he pre-specified nominal AMG 224 (mg) doses are 30, [redacted] (non-weight-based dosing).

In part 2 of the study, AMG 224 will be also administered as per weight-based dosing at [redacted] with a cap of [redacted] based on available nonclinical toxicology information on maximum sucrose allowance limit.

AMG 224 will be administered as an IV infusion given over 60 ± 10 minutes Q3W in the first 2 cycles.

In part 2 of the study, AMG 224 will be also administered as per weight-based dosing at [redacted] with a cap of [redacted] based on available nonclinical toxicology information on maximum sucrose allowance limit. It is estimated that 3g sucrose ([redacted] AMG 224) per injection with a total dose not exceeding 1.8g/dose/week is safe.

AMG 224 will be administered as an IV infusion given over 60 ± 10 minutes Q3W in the first 2 cycles. **The dose of AMG 224 will vary by study part:**

- **Part 1 - Dose Exploration: The doses range from 30 to 300 mg.**
- **Part 2 - Dose Expansion: The starting dose is [redacted]. Subjects with grade 2 thrombocytopenia at baseline (ie, platelet count < 75 to 50 x 10^9/L) should be started at a reduced dose of [redacted]. The subsequent doses of AMG 224 could be further reduced to [redacted] if the criteria for dose reduction for thrombocytopenia are met as per sections 6.2.1.5 and 6.3.1.**

The dose of AMG 224 should not exceed [redacted] (based on available nonclinical toxicology information on maximum sucrose allowance limit).

During the Dose Expansion Phase all doses are to be based on the subject's actual body weight on the day of dosing (Day 1 of each cycle). For cycles 2 and beyond, weight should be re-checked and dosing adjusted accordingly, unless body weight is changed by 5% or less compared to the cycle 1 weight. The dose of AMG 224 should not exceed [redacted] (based on available nonclinical toxicology information on maximum sucrose allowance limit).

~~The doses range from 30 to 300 mg.~~ For each subject, the infusion time may be shortened to 30 minutes ± 5 in the later cycles if the subject did not experience an infusion reaction or lengthened up to 120 ± 10 minutes if the subject experienced an infusion reaction. The dose, start date/time, stop date/time and lot number is to be recorded for each subject in the eCRF. No other investigational product will be used or provided in this study.

The effects of overdose of this product are not known.

Section 6.2.1.5 Dose Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation, Dose Adjustments

Change: Replace

The subject should continue on the same dose of AMG 224 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 exploration part of the study.

• The study drug can be resumed once the adverse events recover to baseline or Grade 1 and the reintroduction of AMG 224 is deemed safe by the Investigator, Amgen's Medical Monitor, and Global Safety Officer.

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

Subjects should not be rechallenged with AMG 224 if the following AMG 224-related adverse events occur:

o Any life-threatening adverse events

o DILI (Drug Induced Liver Injury) meeting Hy's law

o Persistent grade 3 adverse events that do not recover to baseline or Grade 1 within 4 weeks. Any treatment-related adverse event meeting DLT-criteria that recurs

With

The subject should continue on the same dose of AMG 224 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 (ie **Dose Level -1 as outlined in Table 3 or a further lower dose level (ie Dose Level -2 as outlined in Table 3).**
    - The study drug can be resumed once the adverse events recover to baseline or Grade 1 and the reintroduction of AMG 224 is deemed safe by the Investigator, Amgen's Medical Monitor, and Global Safety Officer.

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

- **For subjects experiencing thrombocytopenia after the DLT-window, there will be an option to reduce the dose to the immediate next lower dose level (ie, Dose Level -1 as outlined in Table 3) or a further lower dose level (ie, Dose Level -2 as outlined in Table 3 in the dose expansion part of the study (as described in section 6.3.1).**

The investigator should notify Amgen immediately before administration of the lower dose of AMG 224.

Subject who have been dose-reduced will have an option to receive the higher dose (ie Dose Level -1 or Dose Level 1) at the next planned cycle if the adverse event resolves to ≤ grade 1 or baseline and the reintroduction of AMG 224 at the higher dose is deemed safe by the Investigator.

For dose reduction level, refer to Table 3:

Table 3: Dose Reduction of AMG 224 for Toxicity (Only in Dose Expansion)

Dose level	Dose IV Q3W
Dose Level 1	[redacted]
Dose Level -1	
Dose Level -2	

- 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. Any treatment-related adverse event meeting DLT-criteria that recurs

Section 6.2.1.5 Dose Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation, Dosage Delays

Change: Replace

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.

With

During the DLT-window, if the dosing is delayed for more than **7 days** the subject will be removed from the study and will be replaced.

Section 6.2.1.6 Dosage Limiting Toxicities

Change: Delete

Hematological toxicity:

- Grade 4 neutropenia lasting > 7 days
- Grade 3 or 4 neutropenia with fever > 38.5°C
- Grade 3 thrombocytopenia with ≥ Grade 2 hemorrhage
- ~~o~~ Grade 4 thrombocytopenia lasting > 7 days ~~or requiring AMG 224 dose reduction is a DLT~~
- Grade 3 anemia with symptoms or required intervention (eg, transfusion)
- Grade 4 anemia

Lymphopenia of any grade is not considered a DLT

Section 6.3.1 Management of Thrombocytopenia

Change: Replace

Increased monitoring should be implemented in subjects whose platelet counts are < 100 x 10^9/L. Hematology panels should be repeated on days 5, 6, or 7, or as clinically indicated, following each dose, if platelet counts are < 75 x 10^9/L, until platelet counts are ≥ 75 x 10^9/L (Grade 1).

Following initiation of treatment, if platelet counts decrease to between 25 to 50 x 10^9/L (Grade 3), AMG 224 will not be administered until platelet counts are ≥ 75 x 10^9/L (Grade 1) or back to baseline before starting therapy with AMG 224 then the subject will be administered AMG 224 at the same dose level.

If platelet counts decrease to < 25 x 10^9/L (Grade 4), AMG 224 will not be administered until platelet counts are ≥ 75 x 10^9/L (Grade 1) or back to baseline before starting therapy with AMG 224, then the subject may be administered AMG 224 at the immediate lower dose level that has been previously investigated in this study.Details of dose modification based on pre-dose platelet count are described in Table 4.

The investigator should notify Amgen immediately before administration of the lower dose of AMG 224.

AMG 224 will not be administered to any subject whose platelet levels are <50 x 10^9/L before subsequent dosing or subjects with any platelet level experiencing grade ≥ 2 bleeding. Treatment for thrombocytopenia should be initiated per standard of care as clinically indicated. Any subject who experiences a Grade 3 or 4 thrombocytopenia that cannot be managed per standard of care, will be discontinued from the study.

With

Increased monitoring should be implemented in subjects whose platelet counts are < 100 x 10^9/L **and subjects on anti-coagulant or anti-platelet treatment.** Hematology panels should be repeated on days 5, 6, or 7, or as clinically indicated, following each dose, if platelet counts are < 75 x 10^9/L, until platelet counts are ≥ 75 x 10^9/L (Grade 1). **Subjects should not receive anti-coagulant therapy or anti-platelet therapy while treated with AMG 224 unless in the opinion of the investigator and in consultation with Amgen's medical monitor the use of these agents is medically necessary. Use caution with these agents and consider additional monitoring as described above when concomitant of these agents is medically necessary.**

Details of dose modification based on platelet count are described in Table 4. The investigator should notify Amgen immediately before administration of the lower dose of AMG 224.

Subjects who have been dose-reduced will have an option to receive the higher dose (ie Dose Level -1 or Dose Level 1 as outlined in Table 3, Section 6.2.1.5) at the next planned cycle if the adverse event resolves ≤ grade 1 or baseline and the reintroduction of AMG 224 at the higher dose is deemed safe by the Investigator. The investigator should notify Amgen immediately before administration of the higher dose of AMG 224.

~~AMG 224 will not be administered to any subject whose platelet levels are <50 x 10^9/L before subsequent dosing or subjects with any platelet level experiencing grade ≥ 2 bleeding.~~

Treatment for thrombocytopenia should be initiated per standard of care as clinically indicated. Any subject who experiences a Grade 3 or 4 thrombocytopenia that cannot be managed per standard of care, will be **permanently** discontinued from AMG 224 treatment ~~the study~~.

Table 4 Dosing Guideline Based on Platelet Count After 2nd Cycle

Grade of Platelet Count Decrease	Withhold Dose	Previous dose [redacted]	Previous dose [redacted]	Dose Discontinuation
Grade 0 or 1 (PLT LLN to ≥ 75 10^9/L)	No	Continue to administer AMG 224 at Dose Level 1 [redacted] Q3W)	Escalate to one higher Dose Level ([redacted] Q3W)	N/A
Grade 2 (PLT 75 to ≥ 50 10^9/L)	No	Continue to administer AMG 224 at Dose Level 1 ([redacted] Q3W)	Continue to administer AMG 224 at the same dose level	N/A
Grade 3 (PLT <50 to ≥ 25 10^9/L)	Yes, don't administer AMG 224 until platelet count recovers to ≤ Grade 2 (≥ 50K)	Upon recovery, administer AMG 224 at Dose Level 1 ([redacted] Q3W)	Upon recovery, administer AMG 224 at the same dose level	Yes, if grade 3 platelet count decrease did not recover to at least grade 2
Grade 4 (PLT < 25 10^9/L) and last ≤ 7 days	Yes, don't administer AMG 224 until platelet count recovers to ≤ Grade 2 (≥ 50K)	Upon recovery, administer AMG 224 at Dose Level -1 ([redacted] Q3W) if deemed safe by the investigator	Upon recover, administer AMG 224 at one lower Dose Level (minimum [redacted] Q3W) if deemed safe by the investigator	Yes, if grade 4 platelet count decrease did not recover to at least grade 2 OR subsequent drops in platelet count to Grade 4 after dose reduction
Grade 3 or 4 PLT count decreased associated with < grade 2 bleeding	Yes, don't administer AMG 224 until platelet count recovers to ≤ Grade 2 (≥ 50K) and bleeding is controlled	Upon recovery, administer AMG 224 at Dose Level -1 ([redacted] Q3W) if deemed safe by the investigator	Upon recovery, administer AMG 224 at one lower Dose Level (minimum [redacted] Q3W) if deemed safe by the investigator	Yes, if grade 3 or 4 platelet count decrease did not recover to at least grade 2 and bleeding is not controlled OR subsequent episode of Grade 3 or 4 thrombocytopenia associated with < grade 2 bleeding
Grade 4 (PLT < 25 10^9/L) and last > 7 days or Grade 3 or 4 (PLT<50 10^9/L) with ≥G2 bleeding	N/A	N/A	N/A	Yes

Section 7.1 Schedule of Assessments Dose Exploration and Dose Expansion

Change: Replace

	Screen	Treatment																							
Cycles		I								II								Cycle III and IV						
Weeks		1					2	3		4						5	6	7 and 10				8 &11	9 &12	
Days	-14	1			2	5	8	15		22				23	26	29	36	43 and 64				50 & 71	57 & 78	
Hours (relative to start of dosing)		Pre-dose	0	0.5	EOI	4	24	96	168	336	Pre-dose	0	0.5	EOI	4	24	96	168	336	Pre-dose	0	0.5	EOI		
GENERAL AND SAFETY ASSESSMENT																									
Informed consent	x																								
Clinical evaluation [7]	x	x					x	x	x	x	x					x	x	x	x	x				x	x
Vital signs [2]	x	x			x		x	x	x	x	x			x		x	x	x	x	x		x	x	x	x
12-lead ECG [3]	x1	3x 3			x3	x3	x 3	x3	x3	x3	x3			x3	x3	x3	x3	x3	x3	x3		x3	x3	x3	x3
Echocardiogram [4]	x																								
Peripheral Neuropathy Assessment [5]	x	x									x									x					
Prior/concomitant medication review		←																							→
Adverse events review		←																							→
LABORATORY ASSESSMENTS AND DOSING																									
AMG 224 dosing [6]			x									x									x				
AMG 224 PK [7] [8]		x		x	x	x	x	x	x	x	x		x	x	x	x	x	x	k	x		x	x	x	x
DM1 PK [8] [9]		x		x	x	x	x	x			x		x	x	x	x	x								
Anti-AMG 224 antibody collection (Immunogenicity)		x																		Cycle 3 only					
Safety lab tests [10]	x	x					x	x	x	x	x					x	x	x	x	x				x	x
Pregnancy test [11]	x	x																							x [11]
Hepatitis serology [12]	x																								
SPEP/UPEP/ Immunofixation [13]	x										x									x					
SFLC [14]	x										x									x					
Quantitative Ig [15]	x																								
Beta-2 microglobulin	x																								
Bone marrow, FISH [16]	x																								
Biomarker Bone Marrow Biopsy	x																								
Biomarker Bone Marrow Aspirate	x																								
Biomarker Blood Samples collection [17]	Plasma	x									x									x					
	Serum	x									x									x					
	Whole Blood CTC	x																							
	Cell Pellet (PG sample)	x									x									x					
PAXgene RNA [18]	x																								
IMAGING ASSESSMENTS																									
Plasmacytoma [19]	x																								
Skeletal survey [20]	x																								

Footnotes defined on last page of this table.

Table 3. Schedule of Assessments – Dose Exploration and Dose Expansion

		Treatment					EOT[21]	EOS[21]
Cycle		V and Beyond						
Weeks		Q3W			Q5W	Q9W		
Days								
Hours (relative to start of dosing)		Pre-dose	0	EOI	Pre-dose	Pre-dose		
GENERAL AND SAFETY ASSESSMENT								
Informed consent								
Clinical evaluation [7]		x					x	X
Vital signs [2]		x		x			x	X
12-lead ECG [3]					x3		x3	x3
Echocardiogram [4]								
Peripheral Neuropathy Assessment [5]					x		x	X
Prior/concomitant medication review		←						→
Adverse events review		←						→
LABORATORY ASSESSMENTS AND DOSING								
AMG 224 dosing [6]			x					
AMG 224 PK [7] [8]		x					x	x
DM1 PK [8] [9]								
Anti-AMG 224 antibody collection (Immunogenicity)						x	x	x
Safety lab tests [10]		x					x	x
Pregnancy test [11]						x	x	x
Hepatitis serology [12]								
SPEP/UPEP/Immunofixation [13]		x					x	x
SFLC [14]		x					x	x
Quantitative Ig [15]								
Beta-2 microglobulin								
Bone marrow, FISH [16]								
Biomarker Bone Marrow Biopsy								
Biomarker Bone Marrow Aspirate								
Biomarker Blood Sample Collection [17]	Plasma				x		x	x
	Serum				x		x	x
	Cell Pellet				x		x	x
IMAGING ASSESSMENTS								
Plasmacytoma [19]								
Skeletal survey [20]						x		

Footnotes defined on the next page.

With

	Screen	Treatment																							
Cycles		I									II									Cycle III and IV					
Weeks		1					2	3			4						5	6		7 and 10				8 &11	9 &12
Days	-14	1				2	5	8	15		22				23	26	29	36		43 and 64				50 & 71	57 & 78
Hours (relative to start of dosing)		Pre-dose	0	0.5	EOI	4	24	96	168	336	Pre-dose	0	0.5	EOI	4	24	96	168	336	Pre-dose	0	0.5	EOI		
GENERAL AND SAFETY ASSESSMENT																									
Informed consent	x																								
Clinical evaluation [1]	x	x					x	x	x	x	x					x	x	x	x	x				x	x
Vital signs [2]	x	x			x		x	x	x	x	x			x		x	x	x	x	x		x	x	x	x
12-lead ECG [3]	x1	3x3			x3	x3	x3	x3	x3	x3	x3			x3	x3	x3	x3	x3	x3	x3		x3	x3	x3	x3
Echocardiogram [4]	x																								
Peripheral Neuropathy Assessment [5]	x	x									x									x					
IMWG Frailty Score	x																								
Prior/concomitant medication review	←																								→
Adverse events review	←																								→
LABORATORY ASSESSMENTS AND DOSING																									
AMG 224 dosing [6]			x									x									x				
AMG 224 PK [7] [9]		x		x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x			x	x	x	x
DM1 PK [8] [9]		x		x	x	x	x	x			x		x	x	x	x	x									
Anti-AMG 224 antibody collection (Immunogenicity)		x																		Cycle 3 only					
Safety lab tests [10]	x	x					x	x	x	x	x					x	x	x	x	x				x	x
Pregnancy test [11]	x	x																							x [11]
Hepatitis serology [12]	x																								
SPEP/UPEP/ Immunofixation [13]	x										x									x					
SFLC [14]	x										x									x					
Quantitative Ig [15]	x																								
Beta-2 microglobulin	x																								
Bone marrow, FISH [16]	x																								
Biomarker Bone Marrow Biopsy	x																								
Biomarker Bone Marrow Aspirate	x																								
Biomarker Blood Samples collection [17]	Plasma	x									x									x					
	Serum	x									x									x					
	Whole Blood CTC	x																							
	Cell Pellet (PG sample)	x									x									x					
PAXgene RNA [18]	x																								
IMAGING ASSESSMENTS																									
Plasmacytoma [19]	x																								
Skeletal survey [20]	x																								

		Treatment					EOT [21]	EOS [21]
Cycle		V and Beyond						
Weeks		Q3W			Q6W	Q9W		
Days								
Hours (relative to start of dosing)		Pre-dose	0	EOI	Pre-dose	Pre-dose		
GENERAL AND SAFETY ASSESSMENT								
Informed consent								
Clinical evaluation [1]		x					x	X
Vital signs [2]		x		x			x	X
12-lead ECG [3]					x3		x3	x3
Echocardiogram [4]								
Peripheral Neuropathy Assessment [5]					x		x	X
Prior/concomitant medication review								
Adverse events review								
LABORATORY ASSESSMENTS AND DOSING								
AMG 224 dosing [6]			x					
AMG 224 PK [7] [9]		x					x	x
DM1 PK [8] [9]								
Anti-AMG 224 antibody collection (Immunogenicity)						x	x	x
Safety lab tests [10]		x					x	x
Pregnancy test [11]						x	x	x
Hepatitis serology [12]								
SPEP/UPEP/Immunofixation [13]		x					x	x
SFLC [14]		x					x	x
Quantitative Ig [15]								
Beta-2 microglobulin								
Bone marrow, FISH [16]								
Biomarker Bone Marrow Biopsy		←						→
Biomarker Bone Marrow Aspirate		←						→
Biomarker Blood Sample Collection [17]	Plasma				x		x	x
	Serum				x		x	x
	Cell Pellet				x		x	x
IMAGING ASSESSMENTS								
Plasmacytoma [19]								
Skeletal survey [20]						x		

Section 9.3 Pregnancy and Lactation Reporting

Change: Add

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 lactation case occurs while the female subject is 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 monitor for lactation cases that occur after the last dose of protocol-required therapies through 3 months after the last dose of investigational product.

Any lactation case should be reported to Amgen's 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.

Section 10.4.4.1 Efficacy Endpoint Analyses

Change: Delete

Listings will be produced for all subjects in the dose-exploration cohorts and the dose-expansion cohorts indicating the time to progression, time to response, and duration of response. The proportion of subjects with a partial response to treatment or better per the ~~International Myeloma Working Group criteria~~ (IMWG) with corresponding exact 80% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) and tabulated for subjects treated at the MTD. The proportion of

subjects with minimal residual disease and the proportion of subjects progression-free at 6 months with corresponding exact 80% CI will be calculated using the Clopper-Pearson method. Kaplan Meier curve will be presented for time to progression~~, time to response (partial response or better)~~ and duration of response with estimates for rates and 80% CI at selected weeks.

Amendment 3

Title: A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 224 in Subjects With Relapsed or Refractory Multiple Myeloma

Amgen Protocol Number AMG 224 20130314

Amendment Date: *02 March 2018*

Rationale:

Approximately one-third of multiple myeloma patients at diagnosis are frail and the number of older adults with myeloma is increasing. Frail patients carry more comorbidities, and are often excluded from clinical trials. Because of high unmet medical needs and safety profile of AMG 224, up to twenty frail patients with relapsed or refractory multiple myeloma will be examined as Group C defined by International Myeloma Working Group (IMWG) frailty score in the dose expansion phase of the study. To enroll frail patients with comorbidities, inclusion and exclusion criteria will be modified.

In addition, to further characterize AMG 224 in terms of safety and efficacy with a weight-based dosing regimen, up to 30 patients (10 additional patients) will be examined in Groups A and B in the dose expansion phase. These additional patients/groups will change our overall sample size from 20 to 50 and frequency of Dose Level Review Meetings (DLRMs).

From available safety data, grade 4 thrombocytopenia was seen with AMG 224 over [redacted] To mitigate the risk, the revised protocol will include two starting doses for all patients along with the dose adjustment schedule based on platelet count prior to dosing.

Amendment 2

Protocol Title: A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 224 in Subjects With Relapsed or Refractory Multiple Myeloma

Amgen Protocol Number AMG 224 20130314

Amendment Date: 12 July 2017

Rationale:

Since an MTD (Maximum Tolerated Dose) for the exploration phase of the 20130314 protocol dated 07 October 2015 has not been reached with Cohort 6 [redacted] Q3W, nor has a DLT (Dose Level Toxicity) occurred, an amendment to include additional cohorts of [redacted] Q3W is supported. Cohort 6 preliminary safety data supports these higher doses.

These additional cohorts will change our overall sample size from 50 to approximately 60. The exploratory phase of the study will include an approximate additional 10 subjects and the dose expansion phase will remain the same at 20 subjects. However the dose expansion phase will be divided into Group A of subjects who had prior treatment with a CD 38-targeting antibody (at least 10 subjects) and Group B subjects who is naïve to CD 38-targeting antibody treatment (approximately 10 subjects).

Amendment 1

Title: A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 224 in Subjects with Relapsed or Refractory Multiple Myeloma

Amgen Protocol Number 20130314

Change Summary Date: 07 October 2015

Rationale:

Protocol was updated based off FDA recommended changes to the AMG 224 IND submission dated 21 August 2015:

1. Recommend a study population of patients with multiple myeloma with relapse or refractory disease after at least 3 therapeutic treatment regimens for multiple myeloma. In addition, patients must have received prior treatment with proteasome inhibitors (eg, bortezomib) and immunomodulatory drugs (eg, lenalidomide).

2. Trial stopping rules should be in the protocol. These criteria would serve as a worst case scenario, such that, if the criteria are met, the trial is halted.

3. Correct typographical errors throughout the document.