Statistical Analysis Plan

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
Short Protocol Title:	Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 224 in subjects with relapsed or refractory multiple myeloma
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List of Abbreviations and Definition of Terms

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
CI	confidence interval
CL	clearance
Cmax	maximum observed concentration
Cmin	minimum observed concentration
CR	complete response
CRF	case report form
CTCAE	common terminology criteria for adverse events
DLRM	dose level review meeting
DLRT	dose level review team
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
eSAE	electronic serious adverse event
FIH	first in human
GCP	Good Clinical Practice
heart rate / HR	number of cardiac cycles per unit of time
ICH	International Conference on Harmonisation

Abbreviation or Term	Definition/Explanation
Ig	immunoglobulin
IMWG	International myeloma working group
IMWG-URC	International myeloma working group uniform response criteria
MR	minor response
MRD	minimal residual disease
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
N, n	number
ORR	overall response rate
PD	pharmacodynamics or progressive disease
PK	pharmacokinetics
PKDM	pharmacokinetics and data management
PT	prothrombin time
Q3W	once every 3 weeks
QD	once daily
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
QD	once daily
RP2D	recommended phase 2 dose
sCR	stringent complete response
SD	standard deviation / Stable disease
SFLC	serum free light chain
SPEP	serum protein electrophoresis
$T_{1/2}$	half-life
t_{max}	time of maximum observed serum concentration
TPI	toxicity probability interval
TNSr	total neuropathy score-reduced
UPEP	urine protein electrophoresis
VGPR	very good partial response

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the draft protocol amendment 4 for study 20130314, AMG 224 **dated 16 July 2018**. The scope of this plan includes the primary analysis and the final analyses that are planned and will be executed by the **Amgen Global** Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate the safety and tolerability of AMG 224 monotherapy in subjects with relapsed or refractory multiple myeloma	• Safety: Incidence of DLTs, treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, physical examinations, ECGs and clinical laboratory tests
• Determine the maximum tolerated dose (MTD) and/or recommended phase 2 does (RP2D) of AMG 224, if possible	
Secondary	
• Characterize the pharmacokinetics (PK) of AMG 224 when administered intravenously (IV) once every 3 weeks (Q3W)	• 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 ($t_{1/2}$)
• 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).	• 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)

Objectives	Endpoints
Secondary(Continued)	
• Evaluate the preliminary rate of conversion to minimal residual disease (MRD) negativity	• Conversion to MRD negativity
• Evaluate the incidence of anti-AMG 224 antibody formation.	• Incidence of anti-AMG 224 antibody formation

Exploratory	
• Correlate clinical response with B-cell maturation antigen (BCMA) expression in pre-dose bone marrow biopsies /and or bone-marrow aspirates.	• Quantification of BCMA expression in pre-dose bone marrow biopsy and bone-marrow aspirates
• Evaluate gene expression profiling by sequencing in pre-dose biopsies/plasma to identify gene signatures for response	• Pre-dose bone marrow biopsy and/or plasma DNA gene expression profiles.
• 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	• Serum level of BCMA, BCMA ligands, APRIL and BAFF
• Assess multiple myeloma blood samples for the relevant circulating tumor cells.	• Quantification of circulating tumor cells, plasma cells and/or BCMA specific tumor cells

2.2 Hypotheses and/or Estimations

- 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.
- 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. Study Overview

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 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 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 protocol 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 enrolment 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**	**Enrol 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 protocol 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 CD 38-targeting antibody (at least 10 subjects).**
- **Group B will consist of subjects who are naïve to CD 38-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. Criteria for adjustment in dosing based on stages of thrombocytopenia will be implemented as explained in the protocol.

In the Part 1of 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 in protocol.

The study endpoints are defined in protocol Section 10.1.1.

3.2 Sample Size

Participants in this clinical investigation shall be referred to as “subjects”. It is anticipated that approximately **60 subjects** will be enrolled in this study.

In the dose exploration cohorts, approximately 40 subjects will be enrolled and 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 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%.

4. Covariates and Subgroups

4.1 Planned Covariates

The relationship of covariates to efficacy endpoints will be explored if appropriate.

4.2 Subgroups

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.

5. Definitions

Age at Enrollment

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

$AUC_{0\text{-}3\ week} = AUC_{\mathbf{0\text{-}504\ hrs}}$

It is defined as the area under the concentration-time curve from time 0 to 504 hours.

Baseline

Unless otherwise specified the baseline value for parameters/assessments scheduled to be performed on the same day as the first administration of AMG 224 (Q3W), is the last value measured before the first administration of AMG 224 on that day. For parameters/assessments not scheduled to be performed (or scheduled but not performed) on the same day as the first administration of AMG 224, the baseline value is the value from the screening period measured closest to the day of first administration of AMG 224. In the event that multiple assessments are done on the same day as the first administration of AMG 224 and there is no time associated with the assessments, the value associated with the last clinically planned event before the first administration of AMG 224 will be used as the baseline value.

For baseline ECG, three triplicate ECGs to be collected ≥ 30 minutes apart, with each ECG in triplicate approximately 30 seconds apart (3 set collected predose on day 1 with total of 9 ECGs]) planned to be taken predose. Mean value will be calculated and used in the analysis. The mean of the values within a triplicate should be calculated before taking the mean of the triplicate averages. Where an ECG is missing within a triplicate, all available data will be averaged for that time point.

Best Overall Response

Best overall response for a subject is the best observed post baseline disease response per the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma (IMWG-URC).

Best Overall Response/Progression CRF will be employed to determine the response.

Every effort should be made to document the objective progression even after discontinuation of treatment.

Body Mass Index (BMI)

Body Mass Index should be calculated using the following formula

BMI (kg/m^2) = weight (kg) / [height (cm)/100]^2

Change From Baseline

Change from Baseline is the arithmetic difference between post-dose assessments and Baseline.

C_{max}

Maximum observed serum AMG 224 concentration during a treatment cycle.

C_{min}

Minimum observed serum AMG 224 concentration during a treatment cycle.

Death Date

Death Date for each subject is defined as the date collected on the End of Study CRF where the reason for ending the study is equal to Death.

Dose Limiting Toxicity (DLT):

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. DLTs do not include fatigue, nausea, diarrhea, vomiting, neutropenia, anemia, thrombocytopenia and lymphopenia, increased serum creatinine or electrolytes abnormalities that are **not** clinical significant and require no treatment unless the following criteria are met:

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
- 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

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.

Duration of Response (DOR)

Duration of response is defined as the number of days between the date of the first observation indicating an objective response as PR (or better) through to the subsequent date of disease progression as classified by per the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma or death or where applicable date of censoring [date of first progressive disease assessment or death or date of censoring – date of the first observation indicating PR (or better) as an objective response +1]. Subjects who respond (PR or better) and have not progressed while on study or not died will be censored at the date of assessment of the last evaluable response as documented on International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma CRF. Subjects who do not achieve an objective response will be excluded from the analysis of duration of response.

End of IP Administration Date

End of IP Admin for each subject is defined as the date the decision was made to end IP as recorded on the End of Investigational Product Administration CRF page.

End of Study (Individual Subject)

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

Enrollment Date

Enrollment Date is defined as the date collected on 'Subject Enrollment' CRF.

Fridericia-corrected QT Interval (QTcF)

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

Use above definition for derivation only if QTcF is not collected in the CRF.

Investigational Product

The term 'investigational product' is used in reference to AMG 224.

Last Investigational Product Dose Date

The last IP dose date for each subject is defined as the latest date IP is administered.

Measurable Plasmacytoma

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.

Maximum Tolerated Dose (MTD)

The dose exploration part of study is aimed at determining preliminary maximum tolerated dose (MTD). The preliminary MTD is defined as the maximum dose at which fewer than one third (< 33%) of subjects enrolled in a cohort dose level experience a DLT. 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. Based on the TPI model, the MTD is defined as the dose with the highest probability of a DLT rate between (0.20 and 0.35) while controlling the probability of excessive and unacceptable toxicity.

Minimal Residual Disease (MRD) Negativity

Tumor load of 10^{-5} target cutoff level is considered for the definition of MRD negativity ie, less than 1 clonal cell in 10^5 normal cells is defined as MRD negative.
(Paiva B, 2015)

Objective Response

Objective response is defined as a tumor response assessment of either stringent complete response, complete response, very good partial response or partial response per the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma (IMWG-URC) and will be determined only for subjects with measurable disease at baseline as per IMWG-URC for Multiple Myeloma.

Objective response will be determined based on the responses collected using Best Overall Response/Progression CRF.

Objective Response Rate (ORR)

Incidence of either PR or better (sCR, CR, VGPR) while on study as defined by the IMWG-URC. All subjects that do not meet the criteria for objective response by the analysis cutoff date will be considered non-responders.

Percent Change From Baseline

Percent change from Baseline is the arithmetic difference between post-Baseline and Baseline divided by Baseline values times 100.

Study Day

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

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

Study Day 1

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

Serious TEAE

Serious adverse events (SAEs) are events categorized as AEs that are starting on or after first dose of investigational product as determined by the flag indicating if the adverse event started prior to the first dose on the Events CRF and up to and including 37 days after the end of investigational product.

Time to Response (TTR)

Time to response is calculated as the number of days from the first administration of AMG 224 to the first response as per IMWG-URC. It is calculated for subjects with PR or better.

Treatment-Emergent Adverse Event (TEAE)

A treatment-emergent adverse event is any adverse event starting on or after the first administration of investigational product, as determined by the flag indicating if the adverse event started prior to the first dose on the Events CRF, and up to and including 37 days after the end of investigational product. The severity of each adverse event will be graded using the CTCAE version 4.0. Adverse events will be coded using MedDRA.

Treatment-Related AE

A treatment-related AE is any treatment-emergent AE that per investigator review has a reasonable possibility of being caused by the investigational product.

Time to Progression (TTP)

Time to progression is calculated as the number of days from the first administration of AMG 224 to the first objective assessment of disease progression as per IMWG-URC or deaths or if applicable date of censoring (date of progressive disease / death or censoring – date of first administration of AMG 224 +1).

If a subject's disease has not progressed and the subject is alive, time to progression will be censored at the last date they are known to be progression-free (ie, date of assessment of the last evaluable response as documented on International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma CRF).

If a subject has no evaluation related to assessment of response criteria of Multiple Myeloma (IMWG-URC) in the study, time of response will be censored at the date of the first administration of AMG 224.

Subjects who withdraw consent to participate in the study prior to disease progression will be censored at their last evaluable assessment of response documented on IMWG-URC for Multiple Myeloma CRF.

6. Analysis Sets

6.1 Safety Analysis Set

Safety Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 224.

6.2 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

6.2.1 Pharmacokinetic Concentration Analyses Set

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.

6.3 Dose Limiting Toxicity Evaluable Analysis Set

The analysis of DLT will be restricted to DLT-evaluable subjects. A subject is not DLT-evaluable if he / she 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.

7. Planned Analyses

The Planned analysis is described in following sections.

7.1 Interim Analysis and Early Stopping Guidelines

Safety data will be reviewed on an ongoing basis. **The Dose Level Review Team (DLRT, see protocol 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 protocol 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.

Early stopping guidelines will be implemented as explained in the protocol Sections 6.2.1.2-1.4.

7.2 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. 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.

7.3 Primary Analysis

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

7.4 Final Analysis

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

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

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

Incomplete adverse event and concomitant medication dates missing data will be imputed as described in Appendix A.

Non-pharmacokinetic measurements (eg, biomarker data) that are below the lower limit of quantification will be considered equal to half of the lower limit of quantification for all analyses unless specified otherwise.

8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations in each cohort. The clinical study team will identify and document the criteria for important protocol deviations.

8.5 Outliers

Outlier data will not be excluded unless scientifically justified.

Pharmacokinetic (PK) serum concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard pharmacokinetic evaluation practice.

8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. If required data transformations or alternative non-parametric methods of analyses will be utilized.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later, **East 6.4 or later.**

9. Statistical Methods of Analysis

9.1 General Considerations

Descriptive statistics will be provided for selected demographic, safety, PK, PD and biomarker data. Unless otherwise stated, the data analysis will be conducted using subjects in the Safety analysis set. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented. When data are summarized by time, the values recorded

against the scheduled time points listed in the protocol will be used. When assessing minimum/maximum increases or decreases over the study, all assessments, including unscheduled assessments will be used. Data listings will include all available data from all enrolled subjects unless specified otherwise.

Data analysis will occur at the following time points:

- Dose decision analyses will occur in the dose exploration cohorts and **also after enrolling 5 subjects from Cohort A and Cohort B (combined) in dose expansion cohort.**
- The primary analysis will occur when target enrollment is complete and each subject either completes 6 months on study or withdraws from the study.
- A final analysis is planned after all dose-escalation cohorts and dose-expansion subjects have ended the study.

9.2 Subject Accountability

The number and percent of subjects who were enrolled, received investigational product, completed investigational product, discontinued from investigational product (including reasons for discontinuing, completed study, discontinued the study (including reasons for discontinuing) will be summarized by cohort.

Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will be presented.

A subject listing and summary noting inclusion in each analysis subset will be provided for all subjects enrolled. A subject listing noting duration of AMG 224 administration, reason for discontinuation of treatment, and reason for discontinuing the study will be provided. A list of subjects screened but not enrolled (screen failures) will be provided.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first patient visit and updated during the IPD reviews throughout the study prior to database lock. If a snapshot is being taken during the study rather than a database lock at the end of the study, categories should be updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes and descriptions will be used during the course of the study. The final IPD list is used to produce the Summary of IPDs table and the List of Subjects with IPDs. In addition, a separate listing of all inclusion and exclusion deviations will be provided.

9.4 Demographic and Baseline Characteristics

The following descriptive summaries of the demographic and baseline characteristics will be produced: Demographic (ie, age, age groups [< 65, >= 65 and >= 75], sex, race, ethnicity), prior line of therapies (median, range) and baseline characteristics (height, weight, Eastern Cooperative Oncology Group (ECOG) Performance Status, ECHO or MUGA, refractory status, neurological evaluation status and % of subjects exposed to duratumumab) will be summarized using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple.

A listing of the demographic and baseline characteristics will be provided. In addition listings of medical history, hepatic history, prior anti-cancer therapy and prior radiotherapy usage will be provided.

9.5 Efficacy Analyses

9.5.1 Analyses of Primary Efficacy Endpoint(s)

No efficacy parameter is considered in primary endpoints.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

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 and duration of response with estimates for rates and 80% CI at selected weeks.

9.5.2.1 Best Overall Response Rate

The number and percent of subjects with objective response as determined by the IMWG-URC will be calculated using the Clopper-Pearson method and it will be tabulated for subjects treated at the MTD. If the preliminary MTD and the final MTD are different then a preliminary BOR, final BOR and combined BOR rate will be presented.

BOR will be calculated for subjects with prior CD38 treatment in expansion phase.

BOR will also be calculated per refractory status.

The number and percentage of subjects with a best overall response of stringent complete response, complete response, very good partial response, partial response, minor response, stable disease and progressive disease will be presented by dose.

9.5.2.2 Minimal Residual Disease Conversion Rate

The proportion of subjects with negative minimal residual disease with corresponding exact 80% CI will be calculated using the Clopper-Pearson method.

Rate of conversion of MRD negativity will be calculated as,

= (No of subjects with MRD negativity / Total person months of subjects in safety analysis set) * 100.

It would be calculated only if no. of subjects with MRD negativity >=1.

9.5.2.3 Progression Free Subject Rate

The proportion of subjects who are progression free (IMWG-URC) at 6 months with corresponding exact 80% CI will be calculated using the Clopper-Pearson method.

9.5.2.4 Time to progression

Time to progression (IMWG-URC) will be analyzed using the Kaplan-Meier method. Kaplan-Meier survival curves and median time to progression along with 80% CI will be presented.

9.5.2.5 Time to Response (TTR)

Time to response will be descriptively analyzed, summary statistics of the number, percentage will be reported.

9.5.2.6 Duration of Response (DOR)

Duration of response will be conducted based on the subset of subjects having objective response. Kaplan-Meier estimates of median DOR, and their 80% confidence intervals may also be estimated.

9.5.2.7 Anti-AMG224 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.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

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.

9.6.1.1 Adverse Events and Disease-related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version version 13.0 or later will be used to code all adverse events to a system organ class and a preferred term.

Treatment-emergent adverse events are events with an onset after the administration of the first dose of investigational product.

The subject incidence of adverse events will be summarized for all treatment-emergent, serious treatment emergent, treatment related, serious treatment related, those leading to withdrawal of investigational product, fatal, and of special interest (if applicable). The identification of adverse events of special interest is a continuous process. Events may be identified and documented as the safety profile of the drug is characterized. The severity of each adverse event will be graded using CTCAE version 4.0 criteria.

Subject incidence of all treatment-emergent, serious, treatment-related, serious treatment related, those leading to withdrawal of investigational product, events of special interest (if applicable) and fatal adverse events will be tabulated by system organ class and preferred term in descending order of frequency. Where appropriate the tables will also be presented by worst grade. The above adverse event tables will not be created if two or fewer subjects experience the adverse event.

Summaries of treatment-emergent and serious AEs occurring in all subjects by preferred term in any cohort will be provided in descending order of frequency.

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

9.6.1.2 Dose Limiting Toxicities

The analysis of the probability of DLT will be based on the DLT Evaluable Analysis Set. A listing and summary of the subject incidence of DLT will be provided.

A final estimate of the MTD will be estimated from the TPI Bayesian model utilizing all DLT-evaluable subjects. A sensitivity analysis may also be performed where DLTs

occurring outside of the specified time interval are included. A listing of DLTs occurring outside of the specified time interval will be produced to aid in determining if the sensitivity analysis should be conducted.

The planned doses for dose exploration cohort are 30, [redacted] of AMG 224. It will use a standard 3+3 design to guide dose escalation decisions and to make a preliminary estimate of the MTD. Dose level decision rules are specified in Table 1.

In the dose expansion cohort, up to 20 subjects would be treated at the preliminary MTD. After 5 subjects (combining Group A and B) have completed 28 days on study, there will be a safety review by the DLRT. A TPI Bayesian model utilizing all current DLT evaluable subjects will be fit to evaluate appropriateness of preliminary MTD from dose exploration phase. As more subjects are treated, there may be a higher than expected incidence of DLTs or a higher than expected tolerance of treatment. If these scenarios (either with higher toxicity or tolerance) occur during expansion cohort the additional data will be used to refine the estimate of MTD established during the dose escalation phase. (Iasonos A and O'Quigley J, 2013).

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 dose 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.

The TPI design seeks to identify a dose most likely to have a DLT rate in the target TPI, but with overdose control that limits the possibility that the dose has an excessive or unacceptable DLT rate (Babb et al, 1998).The probability of a DLT at dose level d_i is assumed to follow a Bernoulli distribution with probability p_i where the logit of p_i increases linearly with the log of the standardized dose in the following 2-parameter logistic model:

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

where a and b are random variables and d_{max} is the maximum planned dose.

The probability of each TPI and of a DLT will be summarized by dose along with the estimated dose-toxicity curve. A final estimate of the MTD will be estimated from the TPI Bayesian model utilizing all DLT-evaluable subjects. Please refer to Appendix A (Toxicity Probability Interval (TPI) Bayesian Design section) for more details on the TPI model.

9.6.1.3 Laboratory Test Results

9.6.1.3.1 Chemistry, Hematology and Coagulation

Individual chemistry, hematology and coagulation laboratory data will be listed and other selected laboratory parameters of interests may be plotted. The selected laboratory parameters of interest include: platelets, white blood cell, hemoglobin, hematocrit, absolute neutrophil count, lymphocyte, AST, ALT, total bilirubin, and alkaline phosphatase, serum creatinine, PT, PTT, and INR. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings. CTCAE grades will also be highlighted where appropriate. Unscheduled assessments will be incorporated in the laboratory analyses where possible.

The number and percentage of subjects experiencing treatment emergent laboratory toxicities with worst post dose CTCAE grades of ≥ 1, ≥ 2, ≥ 3 and 4 will be presented. The direction of the laboratory worsening will be denoted. The summary will be presented for all laboratory parameters for which at least one subject experienced a treatment emergent toxicity with a worst grade ≥ 3.

Additionally, the number and percentage of subjects experiencing 1, 2, 3 and 4 worsening CTCAE grade shifts from baseline will be presented. The direction of the laboratory worsening will again be denoted.

Shift tables indicating the change between the baseline and the maximum post dose CTCAE grades for an increased value, and the maximum post dose grade for a decreased value will be provided for selected laboratory parameters of interest.

A listing of CTCAE grade 3 or higher laboratory toxicities will be provided. This listing will include all laboratory data for the subject and laboratory parameter of interest in order to provide proper context. A flag will indicate the grade 3 or higher toxicity.

Summaries of the absolute value and/or changes from baseline at each scheduled assessment will be provided for selected laboratory parameters of interest (such as platelets, white blood cell, hemoglobin, hematocrit, absolute neutrophil count, lymphocyte ,AST, ALT, total bilirubin, alkaline phosphatase, serum creatinine, PT, PTT, and INR).

A summary of the change from baseline to the post dose maximum, time to post-dose maximum, change from baseline to the post dose minimum, and the time to the post dose minimum may also be provided for selected parameters of interest (such as platelets, white blood cell, hemoglobin, hematocrit, absolute neutrophil count,

lymphocyte, AST, ALT, total bilirubin, alkaline phosphatase, serum creatinine, PT, PTT, and INR).

Potential Hy's law cases will be listed and may also be summarized per cohort and overall. A listing of AST, ALT, Total Bilirubin values at each time point will be produced for the subjects suspected of fulfilling the criteria for Hy's law.

9.6.1.3.2 Urinalysis

Individual urinalysis data will be listed.

9.6.1.4 Vital Signs

Vital signs data (systolic / diastolic blood pressure, heart rate, respiratory rate, and temperature) 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.

9.6.1.5 Electrocardiogram

All on-study electrocardiogram (ECG) data will be listed. All on-study electrocardiogram (ECG) data will be listed and QTcF will be plotted.

Where multiple 12-lead ECG measurements are taken at the same assessment (they are planned to be recorded in triplicate 30 seconds apart) the mean value will be calculated and used in the analysis. For baseline ECG, three triplicate ECGs to be collected ≥ 30 minutes apart, with each ECG in triplicate approximately 30 seconds apart (3 set collected predose on day 1 with total of 9 ECGs]). Mean value will be calculated and used in the analysis. The mean of the values within a triplicate should be calculated before taking the mean of the triplicate averages.

For pre and post dose ECG measurements, unscheduled ECG measurements taken up to 5 minutes after the last assessment of a triplicate will be included in the average for a time point. Where an ECG is missing within a triplicate, all available data will be averaged for that time point.

Summaries over time and/or changes from baseline over time will be provided for all 12-lead ECG parameters.

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

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

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

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

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

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

In addition, the relationship between PK concentration of AMG 224 and change from baseline in QTcF may be explored graphically.

Analysis of the relationship between AMG 224 serum concentrations and change from baseline in QTcF will be conducted and plots of the relationship between AMG 224 serum concentrations and change from baseline in QTcF will be provided.

In addition, the relationship between drug concentration (AMG 224 conjugated antibody, Total anti-BCMA antibody, and DM-1) and QTcF will be explored graphically.

9.6.2 Exposure to Investigational Product

Details for each AMG 966 administration will be listed for every subject. In addition a listing of the unique manufacturing lot numbers, and a listing of the subjects administered each manufacturing lot number will be provided.

Descriptive statistics will be produced to describe the exposure to investigational product by dosing schedule. Number of cycles, number of doses of investigational product and the total dose by unit will be summarized. Summaries of the number and percentage of subjects with dose modifications and reason for modification will be provided.

9.6.3 Exposure to Concomitant Medication

All medication will be coded using the WHO drug dictionary. A subject listing of all prior and concomitant medications will be presented.

9.7 Exploratory Endpoints

The statistical analysis in this section will be considered exploratory and will be performed only when deemed appropriate. Details of analysis will be provided in supplemental analysis plan for exploratory biomarker analysis. Relationships between the PK and the markers for safety and efficacy may also be explored.

9.8 Other Analyses

All other analyses will be covered in a separate analysis plan.

9.8.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

9.8.1.1 Pharmacokinetic Endpoints

PK parameters will include, but are not limited to maximum observed concentration (Cmax), minimum observed concentration (Cmin) and area under the concentration-time curve over the dosing interval [AUC] and if feasible half-life ($t_{1/2}$).

The PK parameters of AMG 224 conjugated antibody, Total anti-BCMA antibody, and DM1 will be estimated using standard noncompartmental methods and summarized by dose level using means, standard deviations, medians, minimums and maximums.

Serum concentrations below the lower limit of quantifications will be set to zero for the estimation of the pharmacokinetic parameters for each subject and for the calculation of the summary statistic for each time point. Actual dosing and sampling time will be used for all calculations. The reasons for excluding any sample from the analyses will be provided.

Individual concentration-time data will be summarized by dose level. 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 concentration-time data will be tabulated and presented graphically. 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 QTcF will be conducted and plots of the relationship between AMG 224 conjugated antibody concentrations and change from baseline in QTcF will be

provided. The above analysis will also be conducted for the Total anti-BCMA antibody, and DM1.

Additional analyses to explore relationship between exposure and safety and exposure and efficacy may also be performed.

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

Babb, J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. *Stat Med* 1998;17:1103-1120.

Bailey S, Neuenschwander B, Laird G, Branson M. A Bayesian case study in oncology phase I combination dose-finding using logistic regression with covariates. *J Biopharm Stat*. 2009;19:469-484.

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

Durie BG, Harousseau JL, Miguel JS, et al. International Myeloma Working Group. International uniform response criteria for multiple myeloma. *Leukemia. 2006;20(9):1467–73*. Erratum in: Leukemia. 2006;20(12):2220. *Leukemia. 2007;21(5):1134*.

Durie, B G.M. International Myeloma Foundation. Multiple Myeloma Cancer of the Bone Marrow. Concise Review of the disease and treatment Options. *2011/2012*. Iasonos A and O'Quigley J. Design Considerations for Dose-expansion Cohorts in Phase I Trials. *J Clin Oncol. 2013*

Paiva B, van Dongen J M, Orfao A. New criteria for response assessment: role of minimal residual disease in multiple myeloma. *Blood, 2015;(125)3059-3068.*

Rajkumar VS, Harousseau J, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood. 2011;117(18):4691-4695*.

12. Prioritization of Analyses

No prior analyses planned for this study

13. Data Not Covered by This Plan

Exploratory data not included in this plan may be analyzed at a later date or may be analyzed by a different Amgen Department.

14. Appendices

Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

Imputation Rules for Partial or Missing Stop Dates:

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. If the stop date is entirely missing, assume the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or conmed stopped and the stop date will be imputed, if partial. Imputation Rules for Partial or Missing Start Dates

	Stop Date							
		Complete: yyyymmdd		**Partial: yyyymm**		**Partial: yyyy**		
Start Date		**< 1st Dose**	**≥ 1st Dose**	**< 1st Dose yyyymm**	**≥ 1st Dose yyyymm**	**< 1st Dose yyyy**	**≥ 1st Dose yyyy**	**Missing**
Partial: yyyymm	**=1st Dose yyyymm**	2	1	2	1	N/A	1	1
	≠ 1st Dose yyyymm		2		2	2	2	2
Partial: yyyy	**=1st Dose yyyy**	3	1	3	1	N/A	1	1
	≠ 1st Dose yyyy		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose

2 = Impute the first of the month

3 = Impute January 1 of the year

4 = Impute January 1 of the stop year

Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month.

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Code Fragments:

Provisional Code Fragments for calculating a confidence interval using the Clopper Pearson Method. The following example SAS code will be utilized for the response rate

analysis providing the proportion of subjects responding to treatment with corresponding 80% confidence intervals.

```
data propci (keep = ns p low_ci upp_ci);
n=xx; * total n within the treatment group;
do ns= xx; *number of responders;
p=ns/n; * response rate;
q=1-p;
lowF=FINV(0.1, 2*ns, 2*(n-ns+1)); /* use for 2-sided 80% CI */
UppF=FINV(1-0.1, 2*(ns+1), 2*(n-ns)); /* use for 2-sided 80% CI */
low_ci = 1 / (1+(n-ns+1) / (ns*lowf)); * lower CI for response rate;
upp_ci = 1 / (1+(n-ns) / ((ns+1)*uppf)); *upper CI for response rate;
if p=1 then upp_ci=1;
if p=0 then low_ci =0;
output;
end;run;
```

Toxicity Probability Interval (TPI) Bayesian Design:

Expansion phase of the study will use a TPI Bayesian model utilizing data of all current DLT-evaluable subjects. It will evaluate the appropriateness of the preliminary MTD from dose exploration.

The MTD target TPI for DLT 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 design seeks to identify a dose most likely to have a DLT rate in the target TPI, but with overdose control that limits the possibility the dose has an excessive or unacceptable DLT rate (Babb et al, 1998). The probability of a DLT at dose level d_i is assumed to follow a Bernoulli distribution with probability p_i where the logit of p_i increases linearly with the log of the standardized dose in the following 2-parameter logistic model:

$$\log\left(\frac{p_i}{1-p_i}\right) = \text{logit}(p_i) = \log\alpha + \beta\log\left(\frac{d_i}{d_{max}}\right)$$

where α and β are random variables and d_{max} is the maximum planned dose.

A minimally informative prior distribution (Neuenschwander et al, 2008) was selected for $\theta = (\log\alpha, \log\beta)$ where the probability that the true DLT rate is ≤ 0.60 at the lowest dose (30 mg Q3W) is 0.90 and the probability the true DLT rate is ≤ 0.20 at the maximum dose ([redacted] Q3W) is 0.21. These values were selected such that p_i is around *0.275* for 105 mg dose level, which is approximately in the median of the planned dose range.

Median values for p_i were interpolated per the logistic model. For each d_i, 2 quantiles for p_i were selected from a Beta distribution with the target median and a precision less than 2. This set of quantiles fully specified a target prior for theta. A bivariate normal distribution for theta was assumed where $\log \alpha$ has a normal distribution with mean μ_α and standard deviation s_α, and $\log \beta$ has a normal distribution with mean μ_β and standard deviation s_β, and γ is the correlation between $\log \alpha$ and $\log \beta$. Numerical integration with the SAS QUAD function was used to calculate $\Pr[p_i \leq q(d_i)]$, where $q(d_i)$ is a quantile for dose d_i. An optimal bivariate normal distribution was estimated that achieved the minimum sum of squared difference between achieved and specified quantiles across all doses using a non-linear optimization by a quasi-Newton method with the SAS IML NLPQN function. The bivariate normal distribution prior solution has $\mu_\alpha = 0.0536$, $s_\alpha = 1.685$, $\mu_\beta = -0.1469$, $s_\beta = 1.001$ and $\gamma = -0.216$.

The operating characteristics of the TPI Bayesian design will be evaluated at each dose using accumulated data of DLT evaluable subjects. Here, two parameters logistic regression would be fitted to accumulated data of all DLT evaluable subjects from dose exploration and expansion phase. Theta= (log a, log b) ~ BVN with parameters information mentioned above (use of prior). Theta would be estimated and would be used to estimate pi for each of di using 2 parameter logistic model. Pi for each of di would be compared with MTD target TPI for DLT. An “acceptable” final dose was defined as one with the highest or second highest target TPI probability and a less than 0.25 excessive or unacceptable TPI probability.

DLRM Outputs List:

Listings:

1. Subject demographics
2. Date, time, dose of investigational product administration
3. Electrocardiogram (ECG) results, change from baseline
4. ECHO or MUGA results
5. Vital signs
6. Reported adverse events (AEs)
7. Safety laboratory data (chemistry, hematology, urinalysis, coagulation)
8. Current malignancy
9. Medical history
10. Concomitant medications
11. Prior anti-cancer therapy and prior radiotherapy data
12. **Quantification of Immunoglobulins**
13. **SPEP**

Figures

1. Line plot of vital signs by time course
2. Line plot of all safety labs by time course
3. Line plot of ECGs results by time course
4. Plot of the posterior probability of DLT (Expansion phase)
5. Distribution plot of the predicted MTD (Expansion phase)
6. Bar chart of the number of subjects studied per dose in dose exploration phase
7. **Protein_M1 line plot**

Appendix B. Reference Values/Toxicity Grades

Not applicable

Appendix C. Concomitant Medications

Not applicable

Appendix D. Clinical Outcome Assessment Forms/Instruments

Not applicable

Appendix E. Health Economic Forms/Instruments

Not applicable

Appendix F. Details of PK or PK/PD Methods for Modeling

This is covered in a separate analysis plan.