## Statistical Analysis Plan

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|---|---|
| **Protocol Title:** | A Phase 1, Multicenter, Open-label, Dose Exploration and Dose Expansion Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 994 Monotherapy and Combination of AMG 994 and AMG 404 in Subjects with Advanced Solid Tumors |
| **Short Protocol Title:** | AMG 994 Monotherapy and AMG 994 and AMG 404 Combination Therapy in Patients with Advanced Solid Tumors |
| **Protocol Number:** | 20190136 |
| **NCT Number:** | TBD |
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| Version Number | Date (DDMMMYYYY) | Summary of Changes, including rationale for changes |
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| Original (v1.0) | 10MAR2021 | Not applicable for first version |
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## Table of Contents

**List of Appendices**

## List of Abbreviations

| Abbreviation or Term | Definition/Explanation |
|---|---|
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| BLRM | Bayesian Logistics Regression Model |
| BUN | blood urea nitrogen |
| $C_{max}$ | maximum concentration |
| CRF | case report form |
| CR | complete response |
| CRS | cytokine release syndrome |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DES | Amgen data element standard |
| DLRM | dose level review meeting |
| DLRT | dose level review team |
| DLT | dose-limiting toxicity |
| ECG | electrocardiogram |
| Echo | echocardiogram |
| Exposure-Response Analysis | mechanism-based modeling & simulation and statistical analyses based on individual pharmacokinetic (PK) exposure (eg, population pharmacokinetic modeling) and response, which may include biomarkers, pharmacodynamic effects, efficacy and safety endpoints. |
| End of Follow-up | defined as when the last subject completes the last protocol-specified assessment in the study |
| End of Study for Individual Subject | defined as the last day that protocol-specified procedures are conducted for an individual subject |
| End of Study (primary completion) | defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early |
| End of Study (end of trial) | defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable |
| End of Treatment | defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject |

| | |
|---|---|
| FDA | Food and Drug Administration |
| FIH | first-in-human |
| FSH | follicle stimulating hormone |
| F/U | follow-up |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IND | Investigational New Drug |
| [redacted] | |
| MRI | magnetic resonance imaging |
| MSLN | mesothelin |
| MTD/MTCD | maximum tolerated dose/maximum tolerated combination dose |
| MUGA scan | multigated acquisition scan |
| NSCLC | nonsmall-cell lung cancer |
| OR | objective response |
| OS | overall survival |
| PD | progressive disease |
| PK | Pharmacokinetics |
| PR | partial response |
| SAT | safety assessment team |
| SD | stable disease |
| Source Data | information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value. |
| Study Day 1 | defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject |
| TBL | total bilirubin |
| TMF | trial master file |
| TPI | toxicity probability interval |
| ULN | upper limit of normal |

## 1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20190136, AMG 994 and AMG 404 dated 03 December 2020. The scope of this plan includes the primary analysis and the final analysis 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/Estimands

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the safety, tolerability, and maximum tolerated dose (MTD)/maximum tolerated combination dose (MTCD) or recommended phase 2 dose (RP2D) of AMG 994 as monotherapy and AMG 994 in combination with AMG 404 in subjects with advanced solid tumors | • Dose-limiting toxicities (DLTs)<br>• Treatment-emergent and treatment related adverse events (including all adverse events, grade $\geq$ 3, serious adverse events, fatal adverse events, adverse events requiring permanent discontinuation of study treatment, and immune-related events)<br>• Changes in vital signs, electrocardiograms (ECGs), and clinical laboratory tests |
| **Secondary** | |
| • Preliminary evaluation of anti-tumor activity of AMG 994 as monotherapy and AMG 994 in combination with AMG 404 | • Objective response (OR) per modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1<br>• Duration of response (per modified RECIST 1.1)<br>• Overall survival (OS)<br>• Progression-free survival (per modified RECIST 1.1)<br>• Time to progression (per modified RECIST 1.1)<br>• Time to subsequent therapy |
| • Characterize the PK of AMG 994 monotherapy and AMG 994 in combination with AMG 404 | PK parameters<br>• Maximum serum concentration ($C_{max}$) |

| | |
|---|---|
| | • Minimum serum concentration ($C_{min}$)<br>• Area under the concentration-time curve (AUC) over the dosing interval<br>• Half-life ($t_{1/2}$), if feasible |

### 2.2 Hypotheses and/or Estimations

This is a phase 1 study and no formal statistical hypotheses will be tested.

## 3. Study Overview

### 3.1 Study Design

This is a First In Human (FIH), multicenter, non-randomized, open-label, phase 1 study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, immunogenicity, and preliminary efficacy of AMG 994 monotherapy and evaluation of AMG 994 in combination with AMG 404 in subjects with advanced solid tumors with known MSLN expression, including mesothelioma, non-small cell lung cancer (NSCLC) squamous cell carcinoma [Part 2 only] and adenocarcinoma [Part 1 and Part 2], pancreatic adenocarcinoma, and high grade serous ovarian carcinoma (platinum resistant). Study assessments will include measures of safety, tolerability, PK, and pharmacodynamics data, and preliminary anti-tumor activity.

AMG 994 will be administered by [redacted] and AMG 404 will be administered by [redacted] The study will be conducted in 2 parts: Part 1 – Dose Exploration and Part 2 – Dose Expansion. Part 1 is aimed at evaluating the safety, tolerability, PK, and pharmacodynamics of AMG 994 monotherapy and AMG 994 in combination with AMG 404 using sequential and concurrent initiation of dosing:

The maximum tolerated dose/maximum tolerated combination dose (MTD/MTCD) of the combination in subjects with advanced solid tumors will be determined using a Bayesian Logistics Regression Model (BLRM) design. Part 2 will further evaluate the safety of the MTD/MTCD and/or a biologically active dose (eg, recommended phase 2 dose [RP2D]) of the combination in specific tumor types. The dose expansion part of the study (Part 2) will be opened once the MTD/MTCD/RP2D of the combination has been determined in Part 1.

The dose exploration part of the study will consist of approximately 94 subjects and the dose expansion will consist of approximately 120 additional subjects, 30 subjects in each

of 4 tumor types (mesothelioma, NSCLC squamous cell carcinoma and adenocarcinoma [in Part 2, if upon screening found to be MSLN positive], pancreatic adenocarcinoma, and high grade serous ovarian carcinoma). Dose escalation will be conducted in subjects with metastatic or locally advanced solid tumors of types known to express MSLN for which no standard systemic therapy exists and dose expansion will be conducted in subjects with specific tumor types. The DLT evaluation period will be [redacted] for each cycle. Administration of AMG 994 (in Part 1 and Part 2) may continue until evidence of disease progression; intolerance to study medication; withdrawal of consent; or, in the absence of the above, up to 12 months if subject achieves a complete response, and up to 24 months if partial response or stable disease.

### 3.2 Sample Size

It is anticipated that approximately 214 subjects will be enrolled in this study. Approximately 94 subjects will be enrolled in the dose-exploration cohorts (Part 1). Up to 120 subjects will be enrolled in the dose-expansion cohorts (Part 2), 30 subjects in each of 4 tumor types (mesothelioma, NSCLC squamous cell carcinoma and adenocarcinoma [if upon screening found to be MSLN positive], pancreatic adenocarcinoma, and high grade serous ovarian carcinoma).

The sample size in the dose-escalation phase is based on practical consideration and is consistent with conventional oncology studies with the objective to estimate the MTD/MTCD. With 3 subjects in a cohort, there is a 27% to 70% probability of observing at least 1 DLT if the true DLT rate is 10% to 33% and with 6 subjects in a cohort, there is a 47% to 91% probability.

In the dose-expansion cohorts, a total subject sample size of 120 will provide a 91% probability of observing at least 1 adverse event with 2% incidence rate. An exact 95% binomial CI will be provided for overall response rate. With the 30 subjects in a cohort of subjects with a particular tumor type and a 20% overall response rate, the expected 95% CI would be 8% to 39%. Under certain circumstances, the sample size dose expansion will be smaller due to early stopping; see protocol section 9.4.1.1 for details.

### 3.3 Adaptive Design

Not applicable

## 4. Covariates [redacted]

### 4.1 Planned Covariates

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

[redacted]

## 5. Definitions

**Adverse Event (AE)**

An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment.

**Age at Enrollment**

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

**Area under the Curve (AUC)**

Area under the plasma concentration-time curve reflects the actual body exposure to drug after administration of a dose of the drug.

**Baseline**

For any variable, unless otherwise specified the baseline is the last non-missing assessment taken prior to the first administration of AMG 994 and for cohorts with concurrent administration of AMG 994 and AMG 404 first administration of AMG 994 and AMG 404. Where baseline measurements are taken on the same day as the study specified treatment and no times are present, it will be assumed that these measurements are taken prior to the study specified treatment being administered.

**Baseline ECG Values in Triplicate**

The mean of the triplicate ECG results should be calculated for Baseline. For all post-baseline ECG, the mean of triplicate ECG results at the same assessment will be calculated and used in the analysis. When an ECG is missing within a triplicate, all available data will be averaged for that time point.

**Best Overall Response (BOR)**

The best overall response is the best response recorded from the start of the study treatment until the end of treatment or disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). Overall response assessments occurring after the start of the first subsequent anticancer therapy will not be included.

In general, the subject's best response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

BOR for a subject is the best observed disease response per modified RECIST 1.1 in the following order: Complete response (CR), Partial response (PR), Stable disease (SD), Progressive disease (PD) and Not evaluable (NE). A best overall response of CR and PR require confirmation by a repeat, consecutive scan at least 4 weeks after the first documentation of response.

A best overall response of SD requires an on-study imaging of SD or better no earlier than 7 weeks after cycle 1 day 1; otherwise the best overall response will be not evaluable (NE) unless PD is identified.

Evaluation of overall response details provided in protocol appendix 11.

**Change from Baseline**

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

Change (absolute) from Baseline = (Post-baseline Value – Baseline Value)

Change (percent) from Baseline = [(Post-baseline Value – Baseline Value)/Baseline

Value] x 100

**$C_{max}$**

Maximum observed plasma drug concentration.

**Dose Limiting Toxicity (DLT)**

DLTs are the severe toxicities during the first cycle of cancer therapy. A Dose Limiting Toxicity (DLT) is defined as any AE (meeting the criteria listed in section 6.2.1.5 of protocol) occurring during the first treatment cycle of AMG 994 [redacted] where relationship to AMG 404 cannot be ruled out.

The DLT window (DLT-evaluable period) will be the first [redacted] of AMG 994 treatment (starting cycle 1, day 1). A subject is evaluable if subject experiences a DLT or completes [redacted] of treatment. DLT window will begin from Cycle 2 through study [redacted] for combination of AMG 994 and AMG 404.

**Duration of Response (DOR)**

The duration of response is defined as time from first evidence of PR or CR to disease progression or death due to any cause. .

DOR will be calculated only for subjects who achieve a confirmed best overall response of PR or better.

*DOR (in months)* = (Earliest date of disease progression, death, censor - Date of first observation of PR or better + 1)/30.4

Dates of progression and censoring will be determined as described below in table 5.1.

**End of Study (End of Trial)**

The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (e.g., last subject last visit), following the final protocol-specified visit (e.g. SFU) or any additional parts in the study (e.g., long-term follow-up, additional antibody testing) whichever is later.

**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.

**End of Study (Primary Completion)**

It is defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s), whether the study was conducted as planned in the protocol or was terminated early.

**End of Treatment (EOT)**

Defined as the last assessment for the protocol-specified treatment of the study for an individual subject.

**Enrollment**

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria.

**Fridericia-corrected QT Interval (QTcF)**

The Fridericia correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows:

$$QTcF=QT/(RR/1000)^{1/3}$$

**Investigational Product**

The term 'Investigational product' is used in reference to AMG 994 and combination of AMG994 and AMG 404.

**Last IP Dose Date**

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

**Objective Response Rate (ORR)**

Objective response rate is defined as the proportion of patients with a Best Overall Response (BOR) of confirmed CR or PR.

**Overall Survival (OS)**

Overall survival (OS) is defined as the time from the start of treatment until event of death due to any cause. Subjects still alive will be censored at the date last known to be alive. If the date last known to be alive is after the date that triggers the analysis (i.e., the data cutoff date), the subject will be censored at the analysis trigger date.

For subjects not known to have died, their last date known to be alive will be determined as the latest date associated with clinic visits before data cutoff date including, for example, but not limited to the following:

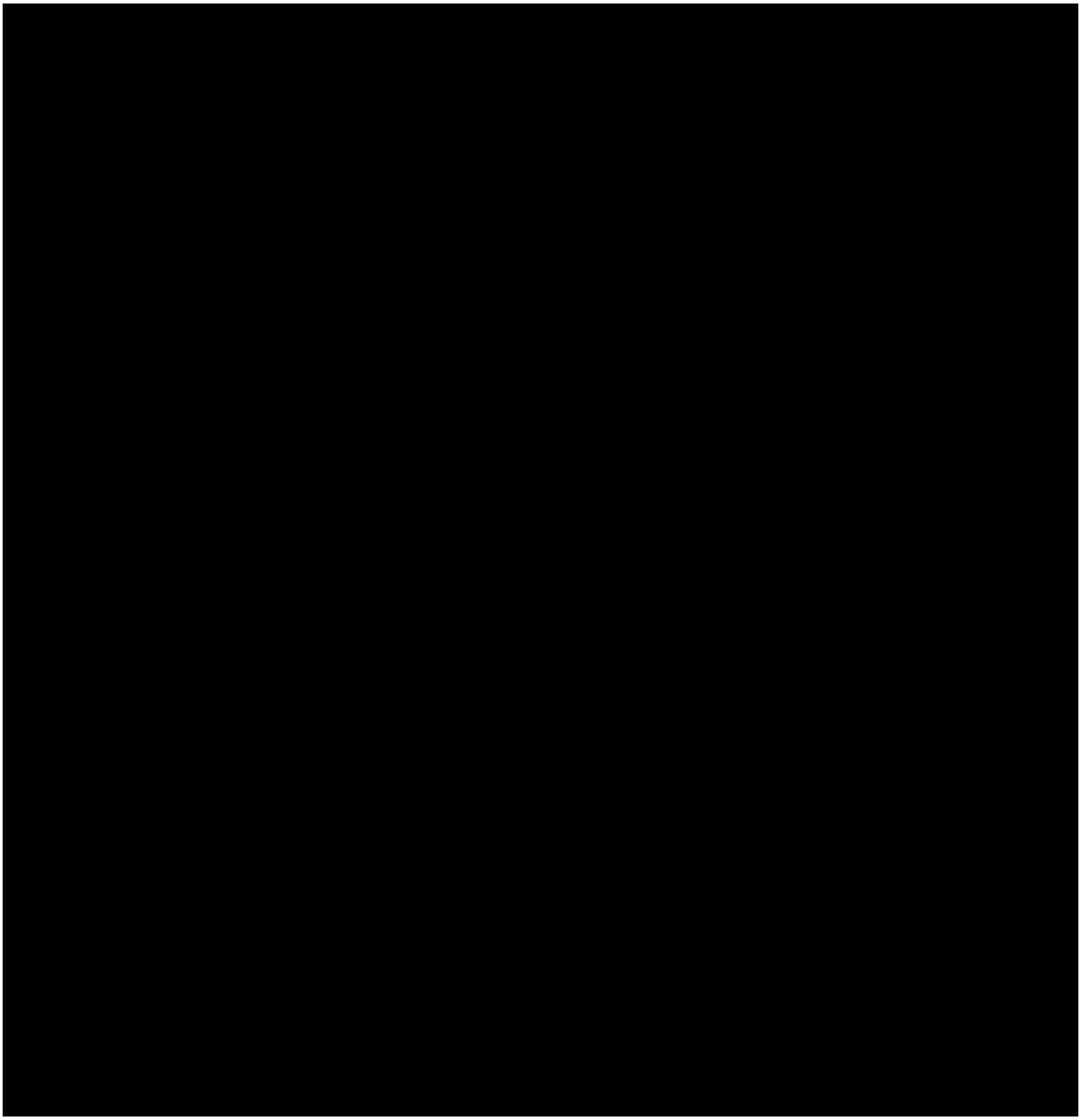
- Survival status: Last contact date if status of subject is "Alive"
- End of study date if the subject's primary reason for ending study is not "Lost to follow-up"
- Any subsequent anti-tumor therapy initialization date
- AE start or end date
- Procedure and concomitant medication start/end date
- Date of lesions assessments
- Visit date of vital signs; physical exam; ECOG; sample collection for labs
- Date of last investigational product administration

**Progression Free Survival (PFS)**

The PFS is defined as interval from the start of treatment to disease progression or death due to any cause (whichever comes first).

PFS (in months) = (Earliest date of disease progression, death, censor – Date of first dose + 1)/30.4

Subjects who are alive and have not progressed, whether on-study or lost to follow-up, will be censored at their last evaluable tumor assessment date. Censoring rules for progression-free survival analysis are given below in Table 5-1.



[redacted]

**Safety Follow-Up (SFU)**

A safety follow-up visit will be performed approximately 30 (+7) days and 140 days (±1 week) days after the end of the last dose of AMG 994 and AMG 404 combination therapy.

**Serious Adverse Event**

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:

- Results in death (fatal)
- Immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Other medically important serious event
- Is a congenital anomaly/birth defect

**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**

It is defined as the first day that investigational product is administered to the subject. The day before Day 1 is referenced as Day -1.

**Treatment-emergent Adverse Event (TEAE)**

A treatment-emergent adverse event is any adverse event starting on or after the first administration of any study drug, as determined by the flag indicating if the adverse event started prior to the first dose on the Events CRF, and 140 days (±1 week) after the last dose of AMG 994 or AMG 404 whichever is later. The severity of each adverse event will be graded using the CTCAE version 5.0. Adverse events will be coded using MedDRA v23.0 or later.

**Treatment-emergent Treatment-related Adverse Event**

A treatment-emergent 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 defined as time from the start of treatment until the disease starts to get worse or spread to other parts of the body.

TTP (in months) = (Earliest date of disease progression, censor – Date of first dose + 1)/30.4

**Table 5-2. Censoring Rules for TTP**

| Situation | Date of Event or Censoring | Outcome |
|---|---|---|
| PD, no prior new anticancer therapy or prior to start of new anticancer therapy | PD | Event |
| No PD, no new anticancer treatment | Last visit; otherwise, first IP dose date | Censored |
| No PD and new anticancer therapy or PD after start of new anticancer therapy | Last visit prior to new treatment; otherwise, first IP dose date | Censored |
| No PD, but death recorded | Date of death | Censored |

**Time to Subsequent Therapy**

Time to subsequent therapy is defined as time from the start of treatment until the first subsequent therapy.

TTST (in months) = (Earliest date of subsequent therapy, censor – Date of first dose + 1)/30.4

**Table 5-3. Censoring Rules for Time to subsequent therapy**

| Situation | Date of Event or Censoring | Outcome |
|---|---|---|
| No new anti-cancer therapy | Last visit; otherwise, first IP dose date | Censored |
| New anti-cancer therapy started | Start date of new anti-cancer therapy | Event |

# 6. Analysis Sets

## 6.1 Efficacy Evaluable Analysis Set

The analysis of objective response will be conducted on the Efficacy Evaluable Analysis set defined as all subjects that are enrolled to a dose expansion cohort and receive at least 1 dose of AMG 994 or AMG 404 with at least 1 tumor lesion that is measurable in contrast-enhanced CT as defined by modified RECIST 1.1, with the following exceptions.

The following subjects will be excluded from the Efficacy Evaluable Analysis set:

1) Subjects who are lost to follow up and have no on study radiological assessments and
2) Subjects who have been on study less than 8 weeks and have no on study radiological assessments.

## 6.2 Safety Analysis Set

Safety Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 994 or AMG 404.

## 6.3 Early DLT Evaluable Analysis Set

The analysis of DLT in the initial safety review period (through [redacted]) will be conducted on the Early DLT Analysis set defined as all subjects that are enrolled and receive at least 1 dose of AMG 994 with an evaluable early DLT endpoint (evaluable in AMG 994 monotherapy cohort per Table 6.4.1).

## 6.4 Cumulative DLT Evaluable Analysis Set

The analysis of DLT in the cumulative safety review period will be conducted on the Cumulative DLT Analysis set defined as all subjects that are enrolled and receive at least 1 dose of AMG 994 or AMG 404 with an evaluable cumulative DLT endpoint (experience a DLT during monotherapy cohort or evaluable in combination therapy cohort per Table 6.4.1).

[redacted]

## 7. Planned Analyses

### 7.1 Interim Analysis and Early Stopping Guidelines

Safety data will be reviewed on an ongoing basis. Based on accumulating safety data, BLRM will be used to make dosing recommendations. In DLRMs, Amgen, in consultation with the site investigators, will review the BLRM recommended dose level and will review all available cumulative data by cohort prior to making dose escalation recommendations. As a sensitivity analysis, a 1-parameter Continual Reassessment Method model may be used to estimate the dose-toxicity relationship and in particular to estimate the dose level with a 25% DLT rate in order to help make dose escalation decisions. Adverse events, including late onset immune-mediated toxicities, and DLTs observed in all subjects will be evaluated continually and fully integrated into all DLRMs and considered in all enrollment and dosing decisions. If during the study there is any grade 5 adverse event (or any 2 of the same grade 4 adverse events) at least possibly related to AMG 994 or AMG 404, further accrual will be suspended; Amgen will conduct a safety analysis and submit to the regulatory authority for review prior to resuming enrollment.

Given that a fixed-dose administration of AMG 404 [redacted] is used as part of the AMG 994 plus AMG 404 combination, the 2-parameter BLRM for single agent AMG 994 will be used. Key details of the BLRM model as used in this study are as follows.[redacted]

[redacted]

During dose expansion, if the observed rate of responses in a particular tumor type is less than 10% after n = 10 and n = 20 subjects in that tumor type, then enrollment to that tumor type will be terminated due to futility. For purposes of assessing futility, a response is defined as an objective response per modified RECIST 1.1. The guidelines for early termination of enrollment for a tumor type due to futility are as follows:

| Number of Treated Subjects in a Tumor Type | Enrollment Stopping Rule |
|---|---|
| 10 | 0 responders |
| 20 | 1 or fewer responders |
| 30 | Enrollment complete |

If the true response rate is 5% then these termination guidelines result in a 78.7% probability of terminating tumor type enrollment at or prior to n = 20 subjects. If the true response rate is 20% then there is an 86.4% probability of continuing enrollment past n = 20 subjects.

During dose expansion, Amgen will conduct evaluations of the ongoing grade 4 or higher treatment-related adverse event rate to assess if the threshold for possible early trial termination has been reached. If this threshold is met, enrollment to dose expansion will be halted pending review of safety data by the DLRT. After receiving the DLRT recommendation, Amgen will choose to take 1 of the following actions.

- Terminate the trial
- Amend the protocol to potentially improve the benefit/risk for subjects (eg, increase safety monitoring, modify dose/schedule, mandate premedication)
- Continue dose expansion without any changes

The stopping rules use a Bayesian approach proposed by Thall, Simon, and Estey (1995) to terminate the study if the posterior probability that the grade 4 or higher treatment-related adverse event rate is greater than 20% is > 80%. The stopping boundaries assume a prior distribution of Beta (0.40, 1.60) are presented in Table 7.1.1 and the operating characteristics with pre-specified batch size of 10 new subjects per batch are presented in Table 7.1.2. The operating characteristics in Table 7.1.12 provide the probability of stopping the trial early for given hypothetical true rate of grade 4 or higher treatment-related adverse events, whereas the stopping criteria in Table 7.1.1 are based on situations where the empirical evidence would result in the posterior probability of ≥ 80% that the true grade 4 or higher treatment-related adverse event rate is ≥ 20%.

**Table 7.1.1. Stopping Boundary for Dose Expansion With Posterior Probability of 80% and Grade 4 or Higher Treatment-Related Adverse Event Limit of 20%**

| Number of subjects | Hold enrollment if observing this many grade 4 or higher treatment adverse events |
|---|---|
| 20 | ≥ 6 |
| 40 | ≥ 11 |
| 60 | ≥ 15 |
| 80 | ≥ 20 |
| 100 | ≥ 24 |
| 120 | Dose Expansion Complete |

**Table 7.1.2. Operating Characteristics With Batch Size of 20 Subjects**

| True grade 4 or higher treatment-related adverse event rate | Probability of early stopping of dose expansion | Average dose expansion sample size |
|---|---|---|
| 0.10 | 1.2% | 118.8 |
| 0.15 | 9.6% | 111.5 |
| 0.20 | 37.6% | 90.1 |
| 0.25 | 76.0% | 59.9 |
| 0.30 | 95.7% | 38.0 |

## 7.2 Primary Analysis

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

### 7.3 Final Analysis

The final analysis will occur when target enrollment is complete for all study parts and all subjects have ended the study. Primary and final analysis may be combined in case all subjects have ended study close to the time point of the primary analysis.

## 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. The database will be subject to edit checks outlined in the data management plan (DMP) by Amgen Clinical Data Management (CDM) department. Data inconsistencies and suspicious values will be reviewed and resolved before the database is locked

### 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 (e.g. 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

## 9. Statistical Methods of Analysis

### 9.1 General Considerations

Unless otherwise specific, all described analyses will be conducted on the Safety Analysis Set. 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.

Confidence intervals (CI) for proportions will be estimated using an exact method proposed by Clopper-Pearson (Clopper & Pearson, 1934). Kaplan-Meier methods will be used to estimate the median and percentiles for time to event endpoints with CI calculated using the Brookmeyer and Crowley method (Brookmeyer & Crowley, 1982). Kaplan-Meier methods will be used to estimate landmarks for time to event endpoints (e.g., 1-year OS) with the Greenwood formula (Kalbfleisch & Prentice, 1980) used to estimate the standard error used in CI calculation

### 9.2 Subject Accountability

The following subject disposition information will be summarized as follows

- Number of screened subjects
- Number (%) of subjects who completed IP
- Number (%) of subjects who discontinued IP
- Number (%) of subjects who discontinued IP

- Number (%) of subjects who discontinued the study
- Primary reason for ending IP
- Primary reason for study discontinuation

The percentages are based on the number of subjects enrolled in the study.

### 9.3 Important Protocol Deviations

Imported Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

### 9.4 Demographic and Baseline Characteristics

The following descriptive summaries of the demographic and baseline characteristics will be produced: Demographic (i.e., age, sex, race, ethnicity), and baseline characteristics (height, weight, Eastern Cooperative Oncology Group (ECOG) Performance Status will be summarized using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple.

### 9.5 Efficacy Analyses

#### 9.5.1 Analyses of Primary Efficacy Endpoint(s)/Estimand(s)

No efficacy parameter is considered in primary endpoints.

#### 9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Listings of secondary efficacy endpoints will be produced for all subjects in the dose-escalation cohorts and the dose-expansion cohorts.

For all subjects in the Efficacy Analysis Set, the proportion of subjects and 95% CL with an objective response (complete or partial response per modified RECIST 1.1) will be tabulated by tumor type and planned dose level and schedule.

For all subjects in the Efficacy Analysis Set, Kaplan-Meier methods will be used to estimate the time of event curve, median time to event, and percentiles with 95% CI for 1) Duration of response (DOR, per modified RECIST 1.1),

2) Overall survival (OS)

3) Progression-free survival (PFS, per modified RECIST 1.1)

4) Time to progression (TTP, per modified RECIST 1.1) and

5) Time to subsequent therapy.

Kaplan-Meier methods will be used to estimate appropriate landmarks for DOR, OS, PFS and TTP (eg, 1-year PFS)

## 9.6 Safety Analyses

### 9.6.1 Analyses of Primary Safety Endpoint(s)

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 AMG 994 or AMG 404. The analysis of early DLTs will be conducted on the Early DLT Analysis Set and the analysis of cumulative DLTs will be conducted on the Cumulative DLT Analysis Set. Subject incidence of both early and cumulative DLT will be tabulated by planned dose level. A table of both early and cumulative DLTs will be provided. The probability of a subject having an early and cumulative DLT by dose level will be estimated using a 2-parameter BLRM model.

### 9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later will be used to code all adverse events to a system organ class and a preferred term.
Where appropriate the tables will also be presented by worst grade.

Treatment-emergent adverse events will be summarized based on the number (%) of subjects experiencing events by MedDRA SOC and PT. The denominator for the percentage will be based on the number of subjects in the safety analysis set.

The subject incidence of adverse events will be summarized for

- TEAE
    - All treatment-emergent AEs
    - Grade 3 or higher treatment-emergent AEs
    - Treatment-emergent SAEs
    - Treatment-emergent AEs leading to interruption of investigational product
    - Treatment-emergent AEs leading to withdrawal of investigational product
    - Fatal treatment-emergent AEs
- Treatment-related AEs
    - All treatment-related AEs
    - Grade 3 or higher treatment-related AEs

- Treatment-related SAEs
- Treatment-related AEs leading to interruption of investigational product
- Treatment-related AEs leading to withdrawal of investigational product
- Fatal treatment-related AEs

The summaries that are displayed by SOC, PT and grade will be ordered by descending order of incidence of SOC, PT and grade with in each SOC for the total group.
The above adverse event tables will not be created if two or fewer subjects experience the adverse event.

Dose Limiting Toxicities

The analysis of the probability of DLTs will include data from DLT-evaluable subjects
The primary analysis will only include DLTs that occur during the DLT evaluation period. If DLTs occur outside the DLT evaluation period, a sensitivity analysis will be performed where DLTs occurring outside of the specified time interval are included. The number and percentage of subjects evaluated by tumor type and planned dose level.

### 9.6.3 Laboratory Test Results

Chemistry, Hematology and Coagulation

Actual values and change from baseline for selected chemistry and hematology parameters will be summarized descriptively for each scheduled visit based on the safety analysis set.

| Local Laboratory: Chemistry | Local Laboratory: Coagulation | Local Laboratory: Urinalysis | Local Laboratory: Hematology |
|---|---|---|---|
| Sodium | PT/INR | Specific gravity | RBC |
| Potassium | PTT/APTT | pH | Nucleated RBC |
| Chloride | Fibrinogen | Blood | Hemoglobin |
| Total protein | Fibrin split products | Protein | Hematocrit |
| Albumin | D-dimer | Glucose | MCV |
| Calcium | | Bilirubin | MCH |
| Glucose | | WBC | MCHC |
| BUN or Urea | | RBC | RDW |
| Creatinine | | Epithelial cells | Reticulocytes |
| Total bilirubin | | Bacteria | Platelets |
| ALP | | Casts | WBC |
| AST (SGOT) | | Crystals | Differential |
| ALT (SGPT) | | | • Total neutrophils |
| TSH | | | • Segmented neutrophils |
| Free T4 | | | • Bands/stabs |
| | | | • Eosinophils |
| | | | • Basophils |
| | | | • Lymphocytes |

| Local Laboratory: Chemistry | Local Laboratory: Coagulation | Local Laboratory: Urinalysis | Local Laboratory: Hematology |
|---|---|---|---|
| | | | • Monocytes<br>• Myeloblasts<br>• Promyelocytes<br>• Myelocytes<br>• Metamyelocytes<br>• Atypical lymphocytes |

ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MSLN = mesothelin; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TSH = thyroid stimulating hormone; WBC = white blood cell count

Shift tables will be presented for the baseline toxicity grade by the worst on-study toxicity grade in a table form for selected parameters mentioned above if applicable. CTCAE version 5.0 will be used for toxicity grading for the above mentioned parameters excluding Total bilirubin, ALT (SGPT), AST (SGOT) and Alkaline phosphatase (CTCAE version 4.03 will be used for toxicity grading).

Potential Hy's law cases may be summarized.

### 9.6.4 Vital Signs

The analysis of vital signs systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and temperature include summary statistics over time and/or changes from baseline over time.

### 9.6.5 Electrocardiogram

The summaries over time and/or changes from baseline over time will be provided for the ECG parameters QRS, QT, QTc, RR, PR and QTcF. Subjects' maximum post baseline values will be categorized and the number and percentage of subjects in each group will be summarized for QTcF. Subjects maximum change from baseline in QTcF will be categorized and the number and percentage of subjects in each group will be summarized.

In addition, the relationship between AMG 994 exposure and change from baseline in QTcF will be explored graphically.

[redacted]

### 9.6.7 Exposure to Investigational Product

The average dose administration (μg), cumulative dose (μg), number of cycles, duration of treatment, number and percentage of subjects with dose modifications, reasons for modification will be summarized using descriptive statistics. Subject-level data may be provided instead of the summary if the subject incidence is low or single dose is given. Descriptive statistics will be produced to describe the exposure to investigational product by treatment group.

Extent of exposure to study treatments will be summarized for Safety population

- Duration of treatment (days)
  - Defined as the duration (in weeks) from the date of the first dose to the date of the last dose of study drug + 1
- Total number of treatment cycles started
  - Defined as the total number of treatment cycles in which at least one dose of study drug is administered.
- Cumulative dose received of AMG 994 and AMG 404 across all cycles, defined as the cumulative dose of AMG 994 and AMG 404.

Average dose of AMG 994 and AMG 404, defined as the total dose received divided by the number of days on treatment administered.

In addition, dose-exposure proportionality assessment will be performed for AMG994.

### 9.6.8 Exposure to Non-investigational Product

Not applicable

### 9.6.9 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term for each treatment group as coded by the World Health Organization Drug dictionary.

## 9.7 Other Analyses

The PK parameters of AMG 994 and AMG 404 including, but not limited to $C_{max}$, $C_{min}$, AUC and half-life (if feasible) will be estimated using non-compartmental methods and summarized by dose level using means, geometric means, standard deviations,

coefficients of variation, medians, minimums, and maximums. Individual concentration-time profiles will be summarized by dose level. Serum AMG 994 and AMG 404 concentrations at each time point along with PK parameter values may be listed for each subject. Summary statistics will be computed for each sampling time and parameter as appropriate. The relationship between AMG 994 exposure and efficacy/safety may be conducted.

### 9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Not applicable

### 9.7.2 Analyses of Clinical Outcome Assessments

Not applicable

### 9.7.3 Analyses of Health Economic Endpoints

Not applicable

[redacted]

## 10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

## 11. Literature Citations / References

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## 12. Prioritization of Analyses

No prioritization will be planned.

## 13. Data Not Covered by This Plan

Not applicable

## 14. Appendices

## Appendix A. Reference Values/Toxicity Grades

The Common Terminology Criteria for Adverse Events (CTCAE) v5.0 is available at the following link:

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

**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.

Imputation Rules for Partial or Missing Start Dates

| | | **Stop Date** | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **Complete: yyyymmdd** | | **Partial: yyyymm** | | **Partial: yyyy** | | **Missing** |
| **Start Date** | | **<1st Dose** | **≥1st Dose** | **<1st Dose yyyymm** | **≥1st Dose yyyymm** | **<1st Dose yyyy** | **≥1st Dose yyyy** | |
| **Partial: yyyymm** | **=1st Dose yyyymm** | N/A | 1 | **N/A** | 1 | N/A | 1 | 1 |
| | **≠ 1st Dose yyyymm** | | 2 | **2** | 2 | 2 | 2 | 2 |
| **Partial: yyyy** | **=1st Dose yyyy** | N/A | 1 | N/A | 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 day 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.

**Imputation rules for stop date:**

**For partial stop date mmyyyy, impute the last day of the month.**

**For partial stop date yyyy, impute December 31 of the year.**

**For completely missing stop date, do not impute.**

**If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.**

**If the stop date imputation leads to a stop date that is before the start date, then there is a data error and do not impute the stop date. (ie. set the stop date as missing).**

## Appendix B. Concomitant Medications

Not applicable

## Appendix C. Clinical Outcome Assessment Forms/Instruments

Not applicable

## Appendix D. Health Economic Forms/Instruments

Not applicable

## Appendix E. Details of PK or PK/PD Methods for Modeling

CPMS group will perform the modeling.