Statistical Analysis Plan

Protocol Title:	20170533
Short Protocol Title:	A Phase 1, First-in-Human, Open-Label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 562 in Subjects With Relapsed / Refractory Diffuse Large B Cell Lymphoma, Mantle Cell Lymphoma, or Follicular Lymphoma
Protocol Number:	20170533
Authors:	[redacted]
Sponsor:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 Tel: 805-447-1000 Fax: 805-499-9495
SAP Date:	**Document Version** — **Date** **Original (v 1.0)** — 23 April 2018 **SAP Amendment 1 (v2.0)** — 30 September 2020 **Amendment [2 (v3.0)]** — Enter Date 06 January 2022

NCT Number: NCT03571828
This NCT number has been applied to the document
for the purposes of posting on clinicaltrials.gov

Version Number	**Date (DDMMMYYYY)**	**Summary of Changes, including rationale for changes**
Original (v1.0)	23 April 2018	
Amendment 1 (v2.0)	6 July 2020	The purpose of SAP amendment 1 is to align with the Protocol Amendment 4 dated 07 August 2019 and also to limit the scope of analysis due to early discontinuation of the study. The scope of the analysis is restricted to key endpoints/ parameters, for selected parts of the study in agreement with study team to be used for the purpose of synopsis Clinical Study Report.
Amendment 2 (v3.0)	**6 January 2022**	• **Baseline section updated for overall survival** • **Efficacy section updated by adding tables for secondary efficacy endpoints**

Table of Contents

List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BLRM	Bayesian logistic regression model
B-NHL	B-cell Non-Hodgkin's Lymphoma
C_{max}	maximum concentration
C_{min}	minimum concentration
CMR	complete metabolic response
COO	cell-of-origin
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DLRM	dose level review team meeting
DLRT	dose level review team
DLT	dose limiting toxicities
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
End of Follow-up	It is defined as when the last subject completes the last protocol-specified assessment in the study
End of Study (Individual Subject)	Defined as the last day that protocol-specified procedures are conducted for an individual subject (ie, the date the subject withdraws full consent from the study, completes the safety follow-up visit or long-term follow up [whichever is later] or death).
End of Study (primary completion)	The time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis.
End of Study (end of trial)	It is defined as when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, LTFU).

Abbreviation or Term	Definition/Explanation
End of Treatment	Defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
FIH	first-in-human
ICH	International Conference on Harmonisation
INR	international normalized ratio
IPD	Important Protocol Deviation
IV	intravenous
MRD	minimal residual disease
MTD	maximum tolerated dose
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD	pharmacodynamics
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PK	pharmacokinetic
PMD	progressive metabolic disease
PMR	partial metabolic response
PR	partial response
PT	thromboplastin time
PTT	partial thromboplastin time
QTc interval	QT interval corrected for heart rate using accepted methodology
RP2D	recommended phase 2 dose
RR	respiratory rate
SD	stable disease
SFU	safety follow-up
LTFU	long-term follow-up
T_{max}	time of maximum concentration
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 **amendment 4** for study 20170533, AMG 562 dated Enter Date. **07 August 2019.** The original scope of this plan included the interim analyses, the primary analysis and the final analysis that were planned and would be executed by the Amgen Global Biostatistical Science department unless otherwise specified. **The scope of the analysis has been restricted due to the discontinuation of the study earlier than planned. The key analyses to be performed have been identified by the study team and are outlined in this revised document.**

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate the safety and tolerability of AMG 562 in adult subjects with relapsed / refractory DLBCL, MCL, or FL • Estimate the maximum tolerated dose (MTD) and/or a biologically active dose (eg, recommended phase 2 dose [RP2D])	• Incidence of dose limiting toxicities (DLTs), treatment-emergent adverse events, treatment-related adverse events, disease-related events and clinically-significant changes in vital signs, physical examinations, electrocardiograms (ECG) and clinical laboratory tests
Secondary	
• Characterize the pharmacokinetics (PK) of AMG 562	• AMG 562 PK parameters including, but not limited to, maximum concentration (C_{max}), minimum concentration (C_{min}), time of maximum concentration (T_{max}), area under the concentration-time curve (AUC), and if feasible, half-life (t1/2)
• Evaluate anti-lymphoma activity of AMG 562	• ORR according to Lugano classification • **Best** Overall response by category. [Response terminology reflects the response criteria used. The Lugano Classification response definitions for positron emission tomography-computed tomography (PET-CT) evaluations of fluorodeoxyglucose (FDG)-avid lymphomas uses the terminology complete metabolic response (CMR), partial metabolic response (PMR), no metabolic response (NMR), or progressive metabolic disease (PMD). Corresponding designations from earlier response criteria include complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD)] • Duration of response (DOR)

	• Progression free survival (PFS) • Overall survival (OS)
Exploratory	
[redacted]	
• Evaluate the formation of anti-AMG 562 antibodies	• Incidence of anti-AMG 562 antibody formation

2.2 Hypotheses and/or Estimations

The maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of AMG 562 will have an acceptable safety profile and evidence of anti-lymphoma activity in patients with relapsed and/or refractory B-NHL, specifically DLBCL, MCL, or FL as measured by the overall response rate (ORR) and rate of CR. No formal hypothesis testing will be performed, and all statistical analyses are descriptive.

3. Study Overview

3.1 Study Design

This is a multicenter, Phase 1, first-in-human (FIH), non-randomized, open-label study in adult subjects with relapsed / refractory DLBCL, MCL, or FL. AMG 562 will be administered weekly as short term IV infusions (1.**5** hour).

The study will consist of up to a 21-day screening period, a treatment period, a safety follow-up (SFU) visit conducted 30 (+7) days after the last dose of AMG 562, and a long-term follow-up (LTFU) period that will begin after the SFU visit is completed. Subjects will be followed for response evaluation at week 5, week **15**, **week 25 and at end of treatment if end of treatment is at week 35 or beyond (± 3 days)** . Subjects who

stopped response evaluations will be followed every 3 months (± 2 weeks) for survival follow-up. The total duration of the LTFU will be up to 2 years from the first dose of AMG 562.

Treatment Holiday

Starting with cycle 4, a longer treatment holiday between cycles may be implemented on a per subject basis for individual treatment cycles after approval by the Amgen Medical Monitor (see Section 6.2.1.1. of protocol for details)

For subjects identified as having confirmed CR/CMR, investigators may choose to implement treatment-free intervals of 2-4 weeks ("Consolidation Phase"). For subjects remaining in CR/CMR at 12 months, treatment-free intervals may be increased to 8 weeks between cycles ("Maintenance Phase"). Treatment for these subjects can be continued until progression or at the discretion of the investigator. Treatment can be discontinued for patients remaining in CR/CMR at the discretion of the investigator.

This phase 1 study consists of two parts:

- Part 1 includes dose exploration to evaluate the safety and tolerability of AMG 562 as monotherapy in subjects with relapsed/refractory DLBCL, MCL, or FL.
- Part 2 is an evaluation of AMG 562 in a dose expansion group to gain further efficacy and safety experience with AMG 562 as monotherapy in subjects with DLBCL. Part 2 will start with a dose that is identified by the DLRT following estimation of the MTD/RP2D in Part 1.

Part 1: Dose Exploration

Up to approximately 30 subjects will be enrolled to the dose exploration cohorts to estimate the MTD, safety, tolerability, PK, and pharmacodynamics of different doses of AMG 562 in subjects with relapsed / refractory DLBCL, MCL, or FL. Dose exploration will be conducted in 2 stages using a Bayesian logistic regression model (BLRM) design to guide dose escalation. In the initial cohorts, single subjects will be enrolled at dose levels anticipated to be lower than the dose levels at which adverse events related to AMG 562 may be observed. Enrollment will proceed with multiple subject cohorts of 3 to 4 subjects per cohort when higher dose levels are open for enrollment by the Dose Level Review Team (DLRT) or if at least one subject experiences any of the three safety events below (whichever occurs earlier):

1. Non hematologic adverse event grade ≥ 2

2. Hematologic adverse event grade ≥ 3 including anemia, neutropenia, leukopenia, thrombocytopenia, and lymphopenia
3. DLT

Enrollment of subjects at each dose level in the multiple subject cohorts will be staggered by at least 3 days.

AMG 562 will be administered as IV infusions at weekly intervals. If no DLTs are observed, the dose escalation will continue to the next planned dose cohort as planned. Once a subject experiences a DLT, the dose for the subsequent cohorts will be decided by the DLRT after evaluating all available safety, laboratory, and PK data as well as the recommendation from the BLRM. Subsequent dose escalation will be limited to 2-fold increases or lower after a subject experiences a DLT or ≥ 2 patients experience a grade ≥ 2 adverse event.

The DLRT may also alter the dosing schedule (dosing interval) for subsequent cohorts. The changes to the dosing schedule may also include the implementation of step-up dosing for future cohorts based on tolerability as observed in the clinical and pharmacological data.

The DLT evaluation period will be at least 28 days for all cohorts. The DLT evaluation period may also be extended to assess events starting within the DLT window. Any adverse event occurring outside the DLT window that meets the DLT definition and is determined by the investigator to be possibly related to AMG 562, and seen more frequently, or is more severe than expected, or is persistent despite appropriate management, can be determined to be a DLT upon unanimous decision by the DLRT after review of the event and all available safety data. A DLRM will be conducted after the subjects in each dose cohort have had the opportunity to complete the DLT evaluation period. The DLRT may also convene at any time to review safety data if deemed necessary.

Subjects who complete the DLT period may proceed to a higher dose level for the next dosing (intra-subject dose escalation) once this higher dose level has been deemed safe by the DLRT and after consultation with the Amgen medical monitor if:

- No DLT has been reported for this subject during or after completion of the DLT period
- The subject has not experienced any ≥ grade 2 adverse events (deemed treatment related by the investigator) during treatment

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

Dose exploration will continue until any of the following events:

- The highest planned dose level is determined to be safe and tolerable (minimum of 6 treated subjects)
- An MTD is identified where BLRM repeats the recommendation of a dose level (minimum of 6 treated subjects)
- If fewer than 6 subjects are treated at the MTD/RP2D, additional subjects may be enrolled to confirm safety and tolerability.

Further details can be found in protocol section **3**.

Step-up Dosing (Estimation of initial dose and target dose)

Step-up dosing will be explored to prevent first dose effects like CRS or neurologic events that have been observed with other BiTE antibodies. It will be introduced when two or more DLTs consistent with potential first-dose effects are observed in one cohort. Further details can be found in protocol section **3**.

Part 2: Dose Expansion

Upon completion of the dose exploration part of the study, up to approximately 55 additional subjects will be enrolled in the dose expansion part to gain further clinical experience, safety and efficacy data for AMG 562 in subjects with relapsed / refractory DLBCL. The dose to be evaluated will be at or below the MTD estimated in the dose exploration cohorts. Additional expansion cohorts may be enrolled to evaluate alternative dose levels, or biologic subsets, or other disease entities included in the dose exploration. A final estimate of the MTD and RP2D will be evaluated and confirmed utilizing all DLT-evaluable subjects from the dose exploration and the dose expansion cohorts. The DLRT will be convened in the dose expansion part of the study to review efficacy data (with recruitment ongoing). Additionally, the DLRT will review safety data in the expansion part, after the first **15** subjects were enrolled and had the opportunity to receive at least five weeks of treatment (with recruitment ongoing). The guidelines for futility due to insufficient efficacy are in Table 2 in the protocol. Ad hoc meetings may be convened at any time by the DLRT to review the safety data if deemed necessary.

3.2 Sample Size

It is anticipated that approximately 85 subjects will be enrolled in this study. Approximately 30 subjects will be enrolled in the dose escalation cohorts and up to 55 additional subjects will be enrolled in the dose expansion cohort. The sample size in the dose escalation is based on practical considerations and is consistent with conventional oncology studies with the objective to estimate the MTD. With 3 subjects per cohort, there is a 27-70% probability of observing at least one DLT if the true DLT rate is 10-33% and with 4 subjects per cohort, there is a 34-80% probability. In the dose expansion cohort, 55 subjects will provide a 43% probability of observing at least one adverse event with a true 1% incidence rate and 94% probability of observing at least one adverse event with a true 5% incidence rate. With 55 subjects and a 40% ORR, the expected 90% CI would be 29% to 52%.

3.3 Adaptive Design

A two-parameter Bayesian Logistic Regression Model (BLRM) is used to guide dose exploration. The MTD target Toxicity Probability Interval (TPI) for DLT is (0.20, 0.33] and TPIs of (0.33, 0.60] and (0.60, 1.00] are defined as excessive and unacceptable, respectively. The design seeks to identify a dose most likely to have a DLT rate in the target TPI, but with overdose control that limits the possibility the dose has an excessive or unacceptable DLT rate (Babb et al, 1998). The probability of a DLT at dose level d_i is assumed to follow a Bernoulli distribution with probability p_i where the logit of p_i increases linearly with the log of the standardized dose in the following 2-parameter logistic model:

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

where a and b are random variables and d_{ref} is 1 of the planned dose selected as the reference dose.

A bi-variate normal prior distribution (Neuenschwander et al, 2008) was selected for theta = (log a, log b) where the probability that the true DLT rate is ≤ 0.40 at the lowest planned dose is [redacted] and the probability the true DLT rate is ≤ 0.05 at the reference dose is 0.05. These values were selected such that p_i is 0.01 for the starting dose and 0.40 for the reference dose ([redacted] µg).

The operating characteristics of the two-parameter BLRM design were evaluated via simulation using EAST version 6.4.1. The cohort size was fixed to 3 or 4 subjects. All simulated studies start with the multiple subject cohorts. The initial multiple subject dose level is [redacted] µg and subsequent doses were selected based on the following rules:

After each cohort, the next dose is the one with the highest probability of the target TPI, but with a less than 0.40 probability of an excessive or unacceptable TPI.

Dose exploration will continue until any of the following events.

- The highest planned dose level is determined to be safe and tolerable (minimum of 6 treated subjects)
- An MTD is identified where BLRM repeats the recommendation of a dose level (minimum of 6 treated subjects)
- If fewer than 6 subjects are treated at the MTD/RP2D, additional subjects may be enrolled to confirm safety and tolerability.

4. Covariates and Subgroups

4.1 Planned Covariates

Not applicable.

4.2 Subgroups

No Subgroup analysis planned due to early termination of the study.

5. Definitions

Age at Enrollment

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

Baseline

Unless otherwise specified, the baseline value for parameters/assessments scheduled to be performed on the same day as the first administration of AMG 562, is the last value

measured before the first administration of AMG 562 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 562, the baseline value is the value from the screening period measured closest to the day of first administration of AMG 562. In the event that multiple assessments are done on the same day as the first administration of AMG 562 and there is no time associated with the assessments, the value associated with the last clinically planned event before the first administration of AMG 562 will be used as the baseline value

The baseline ECG is defined as the mean of all pre-dose assessments from cycle 1 day 1. The mean of the values within a triplicate will be calculated and used in the analysis. Where an ECG is missing within a triplicate, all available data will be averaged for that time point.

Body Mass Index (BMI)

Body Mass Index should be calculated using the following formula:

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

Bazett-corrected QT Interval (QTcB)

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

$QTcB=QT/(RR/1000)^{1/2}$

Change From Baseline

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

Disease-related Event (DRE)

Disease-Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease including Lymphadenopathy, Disease progression, Fatigue, Weight decreased and Night sweats.

Duration of Response (DOR)

DOR is calculated only for subjects who achieve a response (CMR or PMR). The duration will be calculated from the date a response is first achieved until the earliest date of a disease assessment indicating a disease progression or death, whichever occurs first. Subjects who do not have a relapse event will be censored on their last disease assessment date. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date.

Censoring rule for duration of response: Data for responders who are alive and without disease progression are censored at the time of last evaluable disease assessment by PET-CT scan.

Dose Limiting Toxicity (DLT)

A DLT is any of the events described in section 6.2.1.3 of the protocol, occurring in a subject during the DLT window unless clearly attributable to causes other than AMG 562 treatment.

DLT Evaluable Period

DLT evaluable period will be at least 28 days for all cohorts and may be extended to assess events starting within the DLT window.

Enrollment Date

Enrollment Date is defined as the date of enrollment collected on the CRF.

End of Treatment

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

End of Study (Individual Subject)

The end of study date for an individual subject is the last day that protocol-specified procedures are conducted for that subject. The end of study date for an individual subject is 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 analysis.

End of Study (End of Trial)

It is defined as when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, LTFU).

End of Follow-up

It is defined as when the last subject completes the last protocol-specified assessment in the study.

Fridericia-corrected QT Interval (QTcF)

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

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

Long Term Follow Up (LTFU)

Following the SFU visit, there will be a LTFU period for clinical evaluation of disease status and survival. Subjects will be followed via on-site visit every 6 weeks (± 3 days) for assessments of disease status and documentation of anti-lymphoma treatment until progression of disease. From this time point onwards subjects will be followed every 3 months (± 2 weeks) for survival and anti- lymphoma treatment (on-site visits are not required, if needed also interrogation of public databases is acceptable). Subjects will be followed for a maximum of 2 years from the first dose of AMG 562, or until subject death, whichever occurs first.

Maximum Tolerated Dose (MTD)

An estimate of the MTD will be made based on a Bayesian Logistic Regression Model (BLRM) utilizing all DLT-evaluable subjects from the dose exploration and dose expansion cohorts. Based on the BLRM, the MTD is defined as the dose with the highest probability of a DLT rate between the targeted toxicity (0.2, 0.33) interval while controlling the probability of excessive and unacceptable toxicity below 40%.

Investigational Product

The term 'investigational product' is used in reference to AMG 562.

Objective Response

Objective response is defined as a tumor response assessment of either complete metabolic response or partial metabolic response determined by Lugano Classification.

Objective Response Rate

ORR is defined as the incidence rate of a confirmed CMR or PMR while on study as defined by Lugano Classification.

Overall Survival

OS is calculated as the time from the first dose of AMG 562 until death due to any cause. Subjects who are alive at the date that triggers the analysis 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, the subject will be censored at the analysis trigger date.

Last known alive date: For subjects who do not have death date available i.e. subject was alive throughout, last known alive date is defined as the latest of all the date variable in the study.

Progression Free Survival (PFS)

PFS is calculated as the time from the date of first dose of AMG 562 until the date of diagnosis of progression of lymphoma, or date of death, whichever is earliest. Subjects who are alive and did not have progression will be censored at the last date of radiographic assessment of PET-CT scans.

Study Day

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

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

Study Day 1

Defined as the first day that protocol specified investigational products are administered to the subject. The day prior to Study Day 1 is considered Day -1.

Safety Follow-up (SFU)

The SFU visit should occur approximately 30 (+7) days after the last dose of AMG 562.

Treatment-Emergent Adverse Event (TEAE)

A treatment-emergent adverse event is any adverse event **including disease related events** starting on or after the first dose of investigational product, as determined by the flag indicating if the adverse event started prior to the first dose on the Adverse Events Summary CRF, and up to and including 30 days after the end of investigational product.

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.

Toxicity Probability Interval (TPI)

Toxicity probability intervals for dose-limiting toxicity (DLT) are defined as (0.20, 0.33], (0.33, 0.60] and (0.60, 1.00] for target, excessive and unacceptable toxicity, respectively.

Half-Life ($t_{1/2}$)

The time required for the observed concentration of a drug to be reduced by one-half.

6. Analysis Sets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set.

6.1 All Enrolled Subjects

All enrolled subjects analysis set consists of the subjects who are enrolled into the study.

6.1.1 Primary Analysis Set

Not applicable to this study.

6.2 Safety Analysis Set

Safety analysis set is defined as all subjects that are enrolled and receive at least 1 dose of AMG 562.

6.3 Per Protocol Set(s)

Not applicable to this study.

6.4 DLT Analysis Set

All subjects who are DLT-evaluable (see Section 6.2.1.3 of the protocol). DLT-evaluable subjects are those who 1) experienced DLTs or 2) completed DLT observational period and did not experience DLTs.

6.5 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

The PK Analysis Set will contain all subjects who have received at least 1 dose of AMG 562 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.

6.6 Interim Analyses Set(s)

At interim analysis with cutoff determined, the DLT data will be analyzed based on DLT analysis set, and other data will be reported using safety analysis set, unless otherwise specified.

7. Planned Analyses

The following analyses are planned.

7.1 Interim Analysis and Early Stopping Guidelines

In the dose escalation part, safety data will be reviewed on an ongoing basis. Based on accumulating toxicity information, BLRM will be used to make dosing recommendations. In dose level review team meetings (DLRMs), Amgen, in consultation with the site investigators, will review the BLRM recommended dose level and will review all available cumulative data by cohort prior to making dose escalation decisions. As a sensitivity analysis, a one-parameter Continual Reassessment Method model may be used to estimate the dose-toxicity relationship to help making dose escalation decisions. Adverse events and DLTs observed in all subjects will be evaluated continually and fully integrated into all DLRMs and considered in all enrollment and dosing decisions.

The clinical activity of AMG 562 in the dose expansion part will be examined using a Bayesian predictive probability design. If the posterior probability is more than 85% that the ORR is 40% or less, then this is considered insufficient anti-lymphoma activity. If the ORR is too low, enrollment may be terminated early due to insufficient anti-lymphoma activity. The guidelines for futility due to insufficient efficacy assuming a prior beta distribution (0.8, 1.2) are presented in **Table 7-1**. The operating characteristics in **Table 7-2** provide the probability of stopping the trial early for given hypothetical true ORR rates.

The DLRT will be convened in the dose expansion part of the study to review efficacy data (with recruitment ongoing) after the first 15 subjects are enrolled and have had the opportunity to receive at least four weeks of treatment (with recruitment ongoing).

Table 7-1. Guideline for Insufficient Efficacy

Number of Treated Subjects	Efficacy Futility Guideline
15	4 or fewer responders
20	5 or fewer responders
25	7 or fewer responders
30	9 or fewer responders
35	11 or fewer responders
40	12 or fewer responders
45	14 or fewer responders
50	16 or fewer responders
55	Trial will stop

Table 7-2. Operating Characteristics With Batch Size of 5 Subjects

True ORR Rate	Probability of Stopping Early for Futility	Average Sample Size
0.25	**95%**	**21**
0.30	**81%**	**27**
0.35	**59%**	**36**
0.40	**36%**	**43**
0.45	**18%**	**49**
0.50	**8%**	**52**
0.55	**3%**	**54**

Additionally, the DLRT will review safety data and conduct evaluations of the ongoing DLT rate to assess if the threshold for early trial termination has been reached. The stopping rules use a Bayesian approach to terminate the study if the posterior probability that the DLT rate is greater than 33% is > 90%. The stopping boundaries assuming a prior beta distribution (0.66, 1.33) are presented in **Table 7-3**. The operating characteristics in **Table 7-4** provide the probability of stopping the trial early for given hypothetical true DLT rates. The evaluations could occur more frequently if necessary to address emerging safety concerns.

Table 7-3. Stopping Boundaries

Number of DLT Evaluable Subjects	Stop Study If Observing These Many DLTs
10	≥ 6
15	≥ 8
20	≥ 10
25	≥ 12
30	≥ 14
35	≥ 16
40	≥18
45	≥ 20
50	≥ 21
55	Trial will stop

Table 7-4. Operating Characteristics With Batch Size of 5 Subjects

True DLT Rate	Probability of Stopping Early	Average Sample Size
0.20	**1%**	**55**
0.25	**4%**	**53**
0.3	**13%**	**51**
0.33	**22%**	**48**
0.35	**31%**	**45**
0.40	**56%**	**37**
0.45	**79%**	**29**

7.2 Primary Analysis

Originally the primary analysis would occur when target enrollment is complete and each subject either completes 3 months on study or withdraws from the study. **Due to the discontinuation of the study, the primary analysis will occur at the time of study termination decision and include all required available data up to the point of that snapshot which is going to be taken for the primary analysis. This snapshot will have all data up to the LFTU for all subjects except one ongoing subject.**

7.3 Final Analysis

Originally, the final analysis would occur after all subjects have ended the study. **Due to the discontinuation of the study, the final analysis will occur when the last enrolled patient has 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. The database will be subject to edit checks outlined in the Clinical Data Management Plan (DMP). See details of this section in the DMP.

8.3 Handling of Missing and Incomplete Data

Incomplete adverse event and concomitant medication dates missing data will be imputed as described in Appendix A. For efficacy data of overall response, subjects without tumor response assessments will be considered as non-responders. Otherwise, only non-missing data will be analyzed.

Ineligible subjects and subjects enrolled in Part 1 who are not DLT evaluable may be replaced.

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. The clinical study team will identify and document the criteria for important protocol deviations.

8.5 Outliers

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. Suspected outliers will be included in all analyses unless there is sufficient scientific justification to exclude them.

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 9.3 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, and PK data by dose, dose schedule, and time as appropriate. Unless otherwise stated, the data analysis will be conducted using subjects in the Safety analysis set by cohorts and overall. 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.

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), **completed safety follow-up and long term follow-up** will be summarized by cohort and **dose**.

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

A summary noting inclusion in each analysis subset will be provided for all subjects enrolled.

9.3 Important Protocol Deviations

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

Demographic (ie, age, age groups [< 65, > = 65 and < 75, and > = 75], sex, race, ethnicity) and baseline characteristics will be summarized by cohort and dose using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple race.

The baseline characteristics to be summarized included:

- Height
- Weight
- **BMI**
- ECOG status
- Number of previous lines of treatment
- Relapse vs. refractory status
- Type of lymphoma
- **Transformed Disease (yes/no)**
- Bulky disease (yes/no)

9.5 Efficacy Analyses

Due to early discontinuation of the study, limited efficacy data will be provided as tables and listings.

The proportion of subjects by best overall response and best overall response category will be presented. Response will be determined by Lugano Classification. The Lugano Classification response definitions for PET-CT evaluations of FDG-avid lymphomas uses the terminology CMR, PMR, NMR, or PMD. Corresponding designations from earlier response criteria include CR, PR, SD, or PD. Objective response includes CMR and PMR.
Other efficacy endpoints includes duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

9.5.1 Analyses of Primary Efficacy Endpoint(s))

Not applicable for this study.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Subject listings will be provided based on the available efficacy data.

Proportion of subjects with best overall response and by best overall response category will be presented. Response will be determined by Lugano classification

which includes complete metabolic response (CMR), partial metabolic response (PMR), no metabolic response (NMR) and progressive metabolic disease (PMD).

Proportion of subjects with an objective response of CMR or PMR per Lugano classification along with corresponding 90% CI will be calculated using Clopper-Pearson method.

DOR will be calculated only for subjects who achieve a best overall response of PMR or better. Subjects will be censored following the censoring strategy described in the definition of DOR. The distribution of DOR, including the median and quartiles will be characterized using the Kaplan-Meier(KM) method based on the subjects who achieve a best response of PMR or better. The 90% CIs for the median and quartiles of DOR will be constructed using the Brookmeyer and Crowley method.

The distribution of PFS, including median, will be estimated using the Kaplan-Meier method. The 90% CIs for the median and other percentiles of PFS will be constructed using the Brookmeyer and Crowley method.

OS will be analyzed using the same method as describe for the PFS endpoints.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

Exploratory endpoints will not be analyzed with the limited scope of analysis for the discontinued study.

9.6 Safety Analyses

9.6.1 Dose Limiting Toxicities

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

9.6.2 Adverse Events and Disease-related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 19 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

The below adverse event tables will not be created if two or fewer subjects experience the adverse event.

The subject incidence of adverse events will be summarized by cohort and dose group for all treatment-emergent adverse events, treatment-emergent serious adverse events, treatment-emergent adverse events leading to interruption or withdrawal from investigational product or other protocol-required therapies, treatment-related treatment-emergent adverse events and fatal adverse events. The severity of each adverse event will be graded using CTCAE version 4.03 criteria.

Subject incidence of all treatment-emergent adverse events, treatment-emergent serious adverse events, treatment-emergent adverse events leading to interruption or withdrawal from investigational product, **treatment-emergent adverse events leading to dose reduction**, treatment-related treatment-emergent adverse events and fatal adverse events will be tabulated by system organ class and preferred term in descending order of frequency.

Subject incidence of disease-related events will be summarized for all treatment-emergent disease-related events by system organ class and preferred term.

Subject incidence of events of interest (standardized MedDRA queries and/or Amgen customized queries) when defined will also be summarized according to their categories and preferred term.

Details of each adverse event will be listed.

9.6.3 Laboratory Test Results

The selected laboratory parameters of interest include: platelets, white blood cell, hemoglobin, absolute neutrophil count, lymphocyte, AST, ALT, total bilirubin, alkaline phosphatase, PT or INR, PTT, amylase, lipase, LDH, uric acid, immunoglobulins .

Summaries of the absolute value and/or changes and percentage changes from baseline at each scheduled assessment will be provided by cohort and dose.

Additionally, summary of toxicity grades will be provided for laboratory analytes for which CTCAE grades are available by cohort and dose .

Potential Hy's law cases will be summarized. A Hy's Law case is defined as: AST or ALT values of ≥ 3x ULN AND with serum total bilirubin (TBIL) level of > 2x ULN or INR > 1.5 without signs of cholestasis and with no other clear alternative reason to explain the observed liver-related laboratory abnormalities

9.6.4 Vital Signs

Summary statistics for each vital sign parameter (e.g., systolic / diastolic blood pressure, heart rate, respiratory rate, temperature and pulse oximetry)will be provided for baseline and each scheduled post-baseline assessment. summaries of changes and percentage changes from baseline over time will be provided at scheduled time points as per protocol.

9.6.5 Physical Measurements

Subject's weight, height and BMI will be presented as part of baseline characteristics.

9.6.6 Electrocardiogram

Where multiple ECG measurements are taken at the same assessment the mean value will be calculated and used in the analysis. For baseline ECG, mean value of the three triplicates 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 and percentage changes from baseline over time will be provided for all ECG parameters at scheduled time points as per protocol.

9.6.7 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG 562 antibodies (binding and/or neutralizing) at any time **may** be summarized by cohort and dose. Positive anti-AMG 562 antibody data will be reviewed for each subject. Summaries of positive anti-AMG 562 antibody test results over time may be provided.

9.6.8 Exposure to Investigational Product

Details for each AMG 562 administration will be reviewed 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.

9.6.9 Exposure to Concomitant Medication

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

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

The PK analyses will be performed by CPMS group.

Serum concentrations of AMG 562 will be determined using a validated assay.

PK parameters will include, but are not limited to maximum observed concentration (C_{max}), minimum observed concentration (C_{min}) and area under the concentration-time curve over the dosing interval [AUC] and if feasible half-life ($t_{1/2}$). Pharmacokinetic parameters will be estimated using standard non-compartmental approaches based on the PK analysis set and summarized by dose level using means, standard deviations, medians, minimums, and maximums.

Serum concentrations below the lower limit of quantification 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. Individual concentration-time data will also be tabulated and presented graphically. Summary statistics will be computed for each sampling time and parameter as appropriate.

Additional PK analyses, including but not limited to analysis of the relationship between AMG 562 dose and exposure parameters (AUC and C_{max}) and dose proportionality assessments, may also be conducted.

9.7.2 Analyses of Clinical Outcome Assessments

Not applicable for this study.

9.7.3 Analyses of Health Economic Endpoints

Not applicable for this study.

9.7.4 Analyses of Biomarker Endpoints

Not applicable due to restricted scope of analysis post the discontinuation of the study.

10. Changes From Protocol-specified Analyses

To restrict the scope of analysis post the discontinuation of the study, following changes were made in the reporting of results from protocol-specified analysis:

- Primary analysis to include the reduced set of analyses at time of decision to terminate the study. Final analysis will include the follow-up for the single patient still receiving treatment.
- Analysis of exploratory endpoints will not be performed.
- Probability of each TPI and DLT will not be summarized.
- 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 will not be provided for selected laboratory parameters of interest.
- 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 not be provided for selected laboratory parameters of interest.

- The number and percentage of subjects experiencing treatment emergent laboratory toxicities with worst post dose CTCAE grades of 1, 2, 3 and 4 will not be presented.
- A listing of laboratory toxicity grade 3 or higher will not be provided.
- Vital signs listing will not be provided.
- Summary and shift table for ECOG will not be provided.
- ECG listing will not be provided.
- Analysis of biomarker endpoints will not be performed.

11. Literature Citations / References

Babb J, Rogatko A, Zacks S. Cancer Phase I Clinical Trias: Efficient Dose Escalation with Overdose Control. Statistics in Medicine 1998; 17:1103-1120

Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med. 2008 Jun 15; 27(13):2420-39

Clopper C.J. and Pearson E.S. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika Vol. 26, No. 4 (Dec., 1934): 404-413

12. Prioritization of Analyses

Not Applicable for the study.

13. Data Not Covered by This Plan

All data are covered by this plan and this section is no longer applicable post the discontinuation of the study.

14. Appendices

Appendix A. 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 concomitant medication 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.